The Natural History and Identification of Diabetes

Panel Discussion

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MODERATOR MULHOLLAND: Dr. Colwell, I believe you have made the statement in a published article that diabetes is a syndrome and not a disease. Will you explain what you mean by that term?

DR. COLWELL: From my viewpoint, Dr. Mulholland, diabetes mellitus is not a disease. It is a syndrome, characterized by relatively persistent hyperglycemia and glycosuria when untreated. In the majority of cases the cause cannot be determined or removed, but, like fever, hypertension, and tachycardia, for example, the syndrome can be due to a variety of causes, some of which can be determined and a few removed. Our habit of thinking of diabetes as a disease entity stems from the fact that in the ordinary case a cause cannot be assigned. There is good reason to believe that it is inherited like idiopathic epilepsy and migraine; however, the exact mechanism is unknown. Even so, the clinical features of this common form are indistinguishable from those less common cases which are caused by acromegaly, hypercorticoidism, pheochromocytoma, and loss of pancreatic function. Persistent hyperglycemia and glycosuria can also be caused by administration of certain hormones and drugs. It can even accompany emotional stress and hepatic disease. These syndromes must also be called diabetes by my definition.

By such criteria the treatment varies accordingly in that when a cause can be found and removed, that should be done in addition to the therapeutic methods ordinarily used.

MODERATOR MULHOLLAND: Does any other member of the panel have comments to make about Dr. Colwell's statement? Dr. Ricketts?

DR. RICKETTS: I would like to ask Dr. Colwell if he would regard the presence of glycosuria necessary. I believe his definition implied this. Would not hyperglycemia with high renal threshold be diabetes?

DR. COLWELL: Yes, I agree that persistent hyperglycemia without abnormal glycosuria should also be considered to be diabetes and treated as such.

MODERATOR MULHOLLAND: Does everyone else on the panel agree with Dr. Colwell's definition? Dr. Root, you are smiling. I don't know whether you are going to consent to it.

DR. ROOT: I think Dr. Colwell as a medical teacher will agree that the tendency during the last one hundred

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years is more and more to define clinical entities as accurately as possible. I disagree with the definition of diabetes mellitus as a syndrome because I think diabetes is basically an hereditary disease. When we say diabetes, we do not mean hyperglycemia alone; we mean a clinical disease which in given families carries with it the capacity for transmitting from one generation to another this tendency to develop diabetes under various kinds of stress. I prefer to believe that in the last fifty years the tendency has been to limit the use of the words "diabetes mellitus" to this chronic hereditary disease and to get away from using terms such as "hepatic diabetes" and "fasting diabetes." Indeed the term "fasting diabetes" is a complete error since there is no such thing as diabetes mellitus produced by fasting. It is actually a hyperglycemic response with glycosuria in a patient who has been subjected to the stress of starvation. I should like to use the word "diabetes" then only in connection with true diabetes mellitus.

DR. COLWELL: Then what would you call the hyperglycemic condition associated with pheochromocytoma and cured by its removal, Dr. Root?

DR. ROOT: If there is no hereditary element present, the hyperglycemia and glycosuria are due to pheochromocytoma and nothing else. I should say that it is hyperglycemia and glycosuria due to pheochromocytoma.

DR. COLWELL: I suppose it is a matter of semantics. I think it is easier to use one word instead of two and call it diabetes.

DR. ROOT: If it is permanently removed by that operation, then I don't think it was diabetes.

DR. COLWELL: Certainly the ordinary garden variety will not disappear, I agree.

MODERATOR MULHOLLAND: Any other comments from the panel? Dr. Root, you spoke about an hereditary tendency. Do you think all diabetes must be hereditary?

DR. ROOT: All the diabetes that I know about has an hereditary background.

MODERATOR MULHOLLAND: Can you prove that?

DR. ROOT: No, I cannot prove it conclusively. However, the longer diabetic patients are observed, the greater is found to be the frequency of diabetes in the relatives. In the symposium on experimental diabetes and its relation to the clinical disease organized by the Council for International Organizations of Medical Sciences (published in 1954 by Charles C Thomas) it is stated by P. Hanssen that recent investigations have completely confirmed Naunyn's view on the vital importance of heredity in the pathogenesis of early cases of diabetes. Of those the special conditions under which the disease is transmitted are uncertain. He quoted the conclusions of Harris that diabetes is not a single genetic entity. Thus cases of diabetes beginning in young persons and cases beginning late in life may have their origin in different combinations of genes. Upon this genetic background other factors may be superimposed.

DR. COLWELL: I am sure that Dr. John Howard of Baltimore thought his patient had diabetes for about two years, as I recall, before the removal of a pheochromocytoma brought about its disappearance.

DR. ROOT: Yes, I'm sure he did. The symptoms, hyperglycemia and glycosuria, are not sufficient as a definition of diabetes. Surgical removal of a pheochromocytoma would cure these symptoms unless the patient had also underlying true diabetes. I am sorry to have these people confuse the term "diabetic state" with the clinical disease that we know as diabetes mellitus.

DR. HOLCOMB: I'd like to ask Dr. Colwell to explain alimentary glycosuria.

DR. COLWELL: Alimentary glycosuria is an ill defined phenomenon, I think. A wave of hyperglycemia and glycosuria following large carbohydrate feedings should be considered to be diabetic until proved otherwise. A notable exception is its frequent appearance in persons with rapid emptying of the stomach after partial gastrectomy or gastroenterostomy. I have frequently seen glycosuria and blood sugar peaks as high as 360 mg. in such persons. Normal and even subnormal blood sugar levels are reached an hour or two later. A diabetic person should not show this, and the subsequent history in such cases proves the absence of diabetes. In other words, the hyperglycemia in such cases does not persist so that the behavior is not diabetic. It is a fairly common feature of the "dumping syndrome."

Do you agree with this definition, Dr. Holcomb?

DR. HOLCOMB: Yes, I should think so. I should like to ask another question. Do you think that the appearance of glycosuria and hyperglycemia after the administration of desiccated thyroid to an individual who has presumably had a normal carbohydrate tolerance indicates diabetes? In such a case do you think there must be a tendency to diabetes which is simply activated by the use of thyroid?

DR. COLWELL: No, I would not judge this to be inherent diabetes but a transient diabetic syndrome due directly to thyroid administration. Various substances including desiccated thyroid can cause hyperglycemia and glycosuria in normal persons persisting until their administration has been stopped.

DR. HOLCOMB: Suppose that an individual never shows glycosuria or hyperglycemia on a normal diet but does have transitory glycosuria and hyperglycemia after overeating at a banquet or after eating a lot of candy. Would you say that he has diabetes?

DR. COLWELL: Yes, I should think that if it occurred regularly he would have to be considered diabetic by definition.

DR. HOLCOMB: I should like to ask Dr. Duncan what he considers a diabetic glucose tolerance curve.

DR. DUNCAN: I consider an abnormal glucose tolerance curve one in which the blood sugar is not normal in two hours, provided the patient has been properly prepared for the test (assuming that there has been 300 gm. of carbohydrate in the daily diet at least three days in advance) and that complications such as infection, pregnancy, and thyrotoxicosis can be excluded.

I should like to add a word to Dr. Colwell's answer about the thyrotoxic patient. I wonder if hyperglycemia can be explained as in the dumping syndrome by an increased speed of absorption. An intravenous glucose tolerance test yields what we consider a normal type of curve even though the alimentary glucose tolerance test might be interpreted as being indicative of diabetes.

MODERATOR MULHOLLAND: Dr. Duncan, you spoke of the proper preparation for a glucose tolerance test, emphasizing the need for a high carbohydrate diet for at least three days in advance. I have seen a recent criticism of this recommendation. It has been claimed that no more than 100 gm. of carbohydrate daily are needed. Do you believe that?

DR. DUNCAN: I have had no experience with that modification of the glucose tolerance test. I should expect a reduced carbohydrate intake to result in elevation of the curve obtained in the glucose tolerance test.

MODERATOR MULHOLLAND: Dr. Ricketts?

DR. RICKETTS: This has been investigated, and as I remember the results, the line of demarcation between adequate and inadequate preparation for a glucose tolerance test in terms of carbohydrate intake lies somewhere between 50 and 125 gm. per day. Above these levels you are quite sure of getting a normal curve in a normal individual. Below these levels you are quite sure of getting a diabetic curve and somewhere between, the results may be equivocal.

MODERATOR MULHOLLAND: Do you agree with this criticism or do you agree with Dr. Duncan?

DR. RICKETTS: I do what Dr. Duncan does to be safe.

MODERATOR MULHOLLAND: Do the members of the audience have any questions at this point?

QUESTIONER: I would like to ask Dr. Duncan what type of blood sugar examination he employs. He spoke of a blood sugar value of 120 two hours after glucose.

DR. DUNCAN: I was referring to a venous blood sugar determination by the Folin-Wu method. Normally the blood sugar by this method is 120 or less two hours after the 100 gm. of glucose given the usual adult patient.

MODERATOR MULHOLLAND: It has been stated that different species of animals show considerable difference in the way they react to removal of the pancreas. Dr. Ricketts, do you think that a depancreatized human being is a true example of a case of diabetes mellitus?

DR. RICKETTS: I think that he is, Dr. Mulholland, in every respect that I can think of.

MODERATOR MULHOLLAND: Is it a fact that the diabetes is generally mild with requirement of only a small amount of insulin?

DR. RICKETTS: Yes, it is true that in none of these cases is the usual insulin requirement more than 40 to 50 units. I should say, of course, that since the external secretion of the pancreas is obviously lacking they certainly differ from patients with spontaneous diabetes in this respect. But in respect to their ability to get along without insulin the diabetes is just as severe as in any case of spontaneous diabetes. It seems that with the single exception of the small insulin requirement there is very little difference between artificially produced diabetes and the naturally occurring diabetes in man.

DR. ROOT: Dr. Ricketts, I understand that there have been cases in which the diabetes following complete pancreatectomy could not be controlled with 30 to 40 units of insulin and that the insulin requirement had risen to at least 80 units.

DR. RICKETTS: This matter was reviewed recently in a short editorial in the Journal DIABETES. My attention was called to it by Dr. Frank Allan. There have appeared in the literature two or three accounts of totally depancreatized human beings whose insulin requirement on occasion would rise above the 40 or 50 unit level. These occasions represented periods of stress, and it is no surprise to me to learn that a period of stress in a depancreatized man will cause an increased requirement for insulin just as it may in a depancreatized animal. What we were talking about in our earlier conversation was the habitual state of the depancreatized man; under these circumstances my first remark is still true.

DR. COLWELL: Mr. Chairman, to revive our previous dispute, I should like to ask Dr. Root if he would call this "pancreatectomy diabetes" or "pancreatectomy hy-

perglycemia and glycosuria."

DR. ROOT: I think the hyperglycemia thus produced is due to hypoinsulinism and not due to diabetes mellitus. I think the condition shows little resemblance to clinical diabetes mellitus as we see it among patients we treat.

DR. COLWELL: How is it different?

DR. ROOT: The patients we see with diabetes mellitus have an hereditary condition with pancreatic inferiority where the person who has only suffered pancreatectomy does not have an hereditary diabetic tendency. By the operative removal of the pancreas you do not produce diabetes mellitus but merely hypoinsulinism. You have not conferred upon that person the capacity for transmitting any hereditary tendency into the next generation.

DR. COLWELL: We can be in complete agreement if you want to call the idiopathic or perhaps hereditary condition "diabetes mellitus" and other varieties "diabetic states or syndromes."

DR. DUNCAN: I wonder if we shouldn't look upon a pancreatectomy type of diabetes as experimental diabetes, as being quite different from clinical diabetes in which we use hyperglycemia and glycosuria as the criteria to make the diagnosis. Certainly we see patients with evidence of clinical diabetes long before these criteria appear, such as the birth of a big baby, the mother of whom does not develop the diabetes which we predict until probably five or ten years later. Occasionally we see typical diabetic retinitis or diabetic neuropathy, and if diabetes exists in the family we predict that probably this patient will develop diabetes later. I am just wondering if there is not an underlying process influenced by the genes, let us say, which goes along and eventually destroys the efficiency of the pancreas, and eventually hyperglycemia and glycosuria occur. Hemochromatosis is another type of disorder which eventually causes a form of diabetes. Ordinarily clinical diabetes is quite different from the diabetes caused by pancreatectomy.

MODERATOR MULHOLLAND: That is an interesting observation. I think Dr. Root might give you some support on that.

QUESTIONER: Given an intact circulation, is there any difference in the utilization or in the effect of insulin when given intravenously or hypodermically?

DR. DUNCAN: For a great number of years I taught students not to depend on insulin given intravenously. Dr. Barclay Biedleman when he was with us tested the administration of insulin intravenously and subcutaneously and invariably it is more effective more promptly when given intravenously than when given subcutaneously, but I am not at all sure that that proves that it would act in the same way in the presence of ketosis or sepsis. I avoid the intravenous administration of insulin except in the case of the initial dose in the treatment of diabetic coma when I want that chance of a very rapid action, or when poor absorption might be present as occurs in peripheral vascular collapse.

MODERATOR MULHOLLAND: Dr. Lukens, perhaps you can contribute to these discussions.

DR. LUKENS: I should like to make one comment in connection with the discussion of pancreatectomy in man. For the very obvious reason that it is difficult, physicians have not applied to the depancreatized man the standard criteria set up by Minkowski in 1889. If we would measure the excretion of glucose and nitrogen during fasting as Dr. Ricketts tried to do to the best of his ability, we would then see quite clearly that pancreatectomy in man is the most severe form of diabetes with which we have ever come in contact. Dr. Ricketts stated that this was so and I wish to echo it. I think it is very important to realize that the severity of diabetes is measured by multiple criteria. What is the severity of the mildest type of diabetes? It is an abnormal glucose tolerance test, and there may be little or no glycosuria. What is the severity of the moderately severe case of diabetes? It is likely to be in the proportion of the available glucose in the diet excreted in the urine. Then you go up to severe diabetes, and the fasting glucose and nitrogen excretion are your best measurements. It is very difficult for those of us who live in one room to be fully cognizant of what is going on in the next room.

MODERATOR MULHOLLAND: Thank you, Dr. Lukens. I see that another member of the audience would like to ask a question.

QUESTIONER: Dr. Duncan, what happens to the blood sugar in shock?

DR. DUNCAN: I'm not sure what kind of shock you are referring to—if it is the kind a woman receives in a telephone message that her husband has been shot, or if it is the type which occurs in myocardial infarction. Ordinarily there is an increase in the blood sugar for a short period. I suppose that the effect is similar to the injection of epinephrine.

MODERATOR MULHOLLAND: Is that the kind of shock you have in mind—surgical shock?

QUESTIONER: Yes, sir, surgical shock.

MODERATOR MULHOLLAND: Would anyone else wish to comment on this?

DR. COLWELL: Yes, I think it is generally agreed

that there is hyperglycemia during shock. In fact, in any condition in which there is diminished blood supply to the liver with anoxia, there is an increased glucose supply and hyperglycemia, assuming the presence of adequate glycogen.

QUESTIONER: I should like to ask Dr. Root if he agrees with Dr. Duncan that the peak of glucose tolerance tests has little diagnostic significance.

DR. ROOT: I once thought that peaks in a glucose tolerance test were of little diagnostic value. Then in Vienna I encountered in a medical journal a description of a remarkable child. The child was described as having hepatic diabetes because after glucose had been discovered in the urine the glucose tolerance test was made. The blood sugar rose to 400 mg. per 100 cc. at the peak, but at the end of two hours the blood sugar had returned to normal. This case was reported as an extraordinary case of a child with a liver disorder. Some nine months later the doctor who had reported the case arrived in Boston and the first thing he said to me was, "Dr. Root, I am sorry to have to tell you that there was an error in that case report. Only a few months later that child had true diabetes mellitus and is now taking insulin." At present Dr. Hugh Wilkerson is conducting an investigation of pregnancy in diabetic women. He and his group of advisors which includes Dr. Lukens and Dr. Ricketts are applying a standard which makes use of both the peak and the two hour value in interpreting the glucose tolerance test in a large series of pregnancies. Their results will be awaited with great interest.

In our own series of cases I can say that as we follow patients over the years we find that many who have had a single hour blood sugar value exceeding 170 mg. have shown the development of true diabetes mellitus with classical symptoms in the course of a ten-year period. We have therefore come to regard a high peak in a glucose tolerance curve (exceeding 170, using venous blood in the Folin-Wu method), as not perhaps proving diabetes but at least indicating that the patient has an abnormality and that he needs repeated follow-up examinations for life.

DR. HOLCOMB: I should like to present this question. A diabetic patient is treated with diet and insulin for a period of one year. During this time his weight is reduced forty pounds to a normal figure. Treatment with insulin is discontinued. In a few months he is able to take a diet with a liberal amount of carbohydrate without glycosuria or hyperglycemia. A glucose tolerance test at the end of one year is normal. Three years later under stress, hyperglycemia and glycosuria return and treatment with insulin is again needed. A situation like this makes me wonder if a glucose tolerance test is a sufficiently sensitive method of detecting diabetes of very mild degree.

MODERATOR MULHOLLAND: That is a good question. Do you wish to answer it, Dr. Lukens?

DR. LUKENS: I have said for some time that an infection with fever brings about more stress than 100 gm. of glucose. This is illustrated by your case.

Fajans and Conn have attempted to make the glucose tolerance test more sensitive by administering cortisone in advance of the glucose. Among the relatives of diabetics a fairly high incidence of positive tests was found with this technic. Further efforts to use more sensitive tests may be made in this direction.

DR. HOLCOMB: What do you think about the obese diabetics who have been shown to have a normal glucose tolerance test after weight reduction?

DR. LUKENS: If they were once diabetic I think that diabetes is still present as in the case that you cited.

DR. RICKETTS: I can answer that question of Dr. Holcomb's a little more specifically. Dr. Conn told me that not long ago when he followed up these cases which he and Dr. Newburgh originally reported, I think more than fifteen years ago, he found that a good many who had apparently lost their diabetes after reduction of excess weight had subsequent development of true diabetes mellitus. This substantiates Dr. Lukens' guess on the subject.

MODERATOR MULHOLLAND: All of us are interested in the fact that diabetics generally have a high incidence of vascular disease of all types. Dr. Ricketts, do you believe that vascular disease is part and parcel of the natural history of diabetes?

DR. RICKETTS: It seems to me we have to say it is, in the vast majority of cases. One of the most informative studies I know of on the subject was undertaken by Dr. Root and I think he ought to talk about it instead of me. I merely want to say that in the experience of Dr. Root and his colleagues there was high incidence of retinopathy and nephropathy in cases of long-term diabetes, and in most of these cases the diabetes had been poorly controlled. There were however a few cases of severe diabetes in which these complications did not develop in spite of poor control. On the contrary, these complications were absent in most of the cases of mild diabetes generally well controlled, but they did occur in a few such cases. All of this adds up in my way of thinking to the statement that most of the vascular degeneration occurring in diabetes is seen in cases in which the disease has been

present for a long time and with glycosuria poorly controlled. There are a few exceptions, and these exceptions form almost the most intriguing part of the problem.

MODERATOR MULHOLLAND: Dr. Root, do you wish to say something about this question? You have been interested in it for many years.

DR. ROOT: In our study of some 450 cases of diabetes selected because of onset of the diabetes early in life before the age of twenty-five years, we made use of X-ray examination of the arteries in the legs, the aorta, and the pelvic vessels, examinations of the eye grounds, and tests of the urine and blood for evidence of kidney complications. We classified these cases according to the type of control of diabetes over the period of ten to twenty years. Actually the percentage of patients in the group labeled as having been in "poor control," (that is, with hyperglycemia, glycosuria, and only occasional medical examinations) and who developed serious lesions in the arteries in the eyes was very high. The percentage of those who escaped lesions in this group at the end of twenty years was very low. On the other hand among patients who had been kept under very good control, a large majority escaped any of the severe retinal and renal complications. Indeed, none in the group of "good control" had developed the typical diabetic nephropathy. Unfortunately, there is still a group of physicians—some of them opthalmologists—who quote statements to the effect that there is no relation between the severity of diabetes and the retinitis of diabetes. In our group of patients the facts are exactly reversed. We have now studied nearly 500 cases of retinitis proliferans, and it is obvious that the frequency of retinitis proliferans of the malignant sort is many times greater in severe diabetes which begins early in life as contrasted with the mild diabetes which begins late in life. There is in our group a very direct relationship between the severity of diabetes and the severity of the eye lesions.

DR. HOLCOMB: I have a suspicion that the development of vascular complications in cases of diabetes may be related in part to an inherited susceptibility to cardiovascular defects.

QUESTIONER: I am wondering if exercise may be a factor in the cases in which there is freedom from the development of arteriosclerosis.

DR. COLWELL: I don't have any reason for thinking that exercise might prevent vascular disease in diabetes. All we can do is speculate about the cause. Certainly vascular disease is a most intriguing and important question about which the evidence is just beginning to accumulate.

DR. DUNCAN: In regard to the question about exercise, I am not entirely in accord with Dr. Colwell. I believe that exercise has a rather definite effect and that those who earn their living through muscular activity are less likely to develop diabetes than those with sedentary occupations.

Changing the subject, I am wondering if we haven't been feeding our diabetic patients too much fat in view of Dr. Ancel Keys' observations. Should we not raise the carbohydrate, provided it doesn't increase the difficulty in controlling the diabetes? I have given more and more carbohydrate up to the limit or a little short of it, where it might cause difficulty in controlling the diabetes. I wonder if Dr. Root would like to comment on these points—the amount of fat in the diet, and exercise.

DR. ROOT: I quite agree. Certainly our practice in recent years has been to give more carbohydrate and less fat in the dietary prescription. We rarely prescribe over 250 gm. of carbohydrate per day, and indeed our prescriptions are more nearly in the area of 150 to 200 gm. per day. My experience has been that if you try to force diabetic patients to take 300 to 400 gm. of carbohydrate by the addition of syrup and sugar, the diabetes is not merely more difficult to control but there may also be a tendency for conversion of what was at first relatively mild diabetes into more severe diabetes.

MODERATOR MULHOLLAND: There are some disagreements—I see that some of the members of the panel are shaking their heads.

DR. DUNCAN: We give more carbohydrate than does Dr. Root, and we draw the line where there is difficulty in controlling the diabetes. I have been very much impressed with Keys' surveys of the amount of fat in the diets of various groups, and I wonder if more fat can be tolerated by individuals who have a great deal of exercise. The possible favorable effect of exercise in relation to the development of vascular disease, it seems to me, has been largely overlooked in the investigations in this field.

DR. HOLCOMB: We began using diets relatively high in carbohydrate and low in fat in 1926, but the amount of carbohydrate prescribed varies considerably. Some patients cannot take more than 150 gm. of carbohydrate a day. They don't want more than that. On the other hand the lean laborer may need 330 gm. of carbohydrate, 150 gm. of fat, and 160 gm. of protein to maintain his weight. Thus the amount of carbohydrate, protein, and fat should depend on the individual

and his activities.

When we find that a patient has difficulty in controlling his diabetes despite fidelity to his diet, we have recently gone back to the old practice of using 100 gm. of carbohydrate, raising the fat to keep the diet isocaloric. Thus we have kept the diabetes under good control, and tolerance has been regained. Diabetes may be much more stable with such a diet than when a high carbohydrate diet is used.

DR. COLWELL: I should like to present the other side of the question. My custom has been to be less liberal with carbohydrate than this. My reasons have been three: First, I have yet to be persuaded that high fat diets can cause atherosclerosis. Second, even though blood cholesterol levels are a factor, good control of the diabetes is more important than the amount of fat in the diet in encouraging normal blood lipid levels. Finally, it is much easier to control abnormally high blood and urine sugar in diabetes when the carbohydrate eaten is moderate in amount. Like many others, I believe that we should maintain normal levels as well as possible in an effort to avoid vascular complications unless and until it is proved that it is unnecessary. For these reasons I prefer not to be extravagant with carbohydrate.

MODERATOR MULHOLLAND: Some believe that the vascular lesions in the eyes and in the kidneys are peculiar to diabetes. Are they different from vascular lesions in nondiabetics, Dr. Ricketts?

DR. RICKETTS: The fact is that in both the retina and the kidney the lesions which we regard as characteristic of diabetes have been described in nondiabetic states, but only under rare circumstances. Certainly the overwhelming number of such lesions found by the pathologist and the ophthalmologist occur in cases of diabetes and particularly in cases of diabetes of long duration.

Becker and Friedenwald in post-mortem studies have found that patients with diabetic retinopathy have shown in practically all instances the presence of the Kimmelsteil-Wilson type of lesion in the kidneys. The association between these lesions in the two parts of the body seems to be very close indeed.

MODERATOR MULHOLLAND: What do you think about the relationship between the development of these lesions and function of the adrenals, the metabolism of vitamin B_{12} and pantothenic acid? I have heard a good deal about these factors in recent years.

DR. RICKETTS: I don't know what to think, Mr. Chairman. It is too early for me to say.

MODERATOR MULHOLLAND: Do you think that this problem is entirely in the experimental stage?

DR. RICKETTS: Yes, sir.

MODERATOR MULHOLLAND: Can you express an opinion about the significance of these factors?

DR. RICKETTS: No, except to cite what facts are known. The facts are that two different groups (in Baltimore and in Columbus, Ohio) have succeeded in producing both renal and retinal lesions in diabetic rabbits by the use of cortisone and/or corticotropin. This has been confirmed and probably has some significance. What that significance is for man I can't say at this point.

Perhaps Dr. Lukens would like to comment about his pituitary diabetic dog which apparently developed Kimmelsteil-Wilson lesions.

DR. LUKENS: That was a single animal—it was an odd occurrence. It suggests the possibility that in the next few years these lesions may perhaps be studied in the laboratory.

Far more important observations have come from South America on the one hand and from Boston on the other. Rats made diabetic have developed a high percentage of renal lesions in as short a time as two or three months. These rats were untreated. Any form of treatment or absence of diabetes appeared to prevent the lesions.

Our hopes for laboratory investigation of this problem must be guarded since it may take ten to twenty years for these lesions to develop in man. It is quite clear that the laboratory worker is going to take a long time to solve the problem.

DR. RICKETTS: Dr. Lukens, are you convinced that these experimental lesions in the rats are reasonably identical to the lesions occurring in man?

DR. LUKENS: I cannot answer the question about the identity in the case of the rat. In the case of the dog, we thought it was close enough to make the suggestion.

DR. RICKETTS: I agree with you about the dog.

DR. LUKENS: I do think this. These lesions whether they are identical or not are the result of diabetes in the rat; that seems to be fairly clear, and with that little bit of a stepping stone we might move on.

DR. RICKETTS: Unless they are the result of alloxan.

DR. LUKENS: No, because four years of experiments with partial pancreatectomy eliminate that.

DR. COLWELL: Yes, alloxanized animals which do not become diabetic do not develop the lesions.

MODERATOR MULHOLLAND: A question has been asked in regard to the basic difference between juvenile and adult diabetes mellitus.

DR. RICKETTS: I will start if you like. It seems to me Wrenshall made a most notable contribution to this problem by showing that diabetes beginning in childhood is accompanied by the almost total absence of extractable insulin in the pancreas. However, diabetes beginning in adulthood is characterized in some cases by a marked diminution of insulin, in other cases by very little diminution, and on the average by about 50 per cent of the insulin content of the normal pancreas. For the want of a better explanation for the unstable and labile behavior of the juvenile diabetic, my thinking is now running along this line. This individual is totally dependent on injected insulin. There is no injectable insulin which has the homeostatic control over the blood sugar that a normal pancreas has. There is no preparation of insulin put under the skin which can close down its insulin output when the demand decreases and increase that output when food is taken or when stress is experienced. It seems to me that with the information we have available this is the best explanation for the instability of the juvenile diabetic, and if one follows that line of reasoning it is easier to see why the adult diabetic who has some pancreatic reserve left, some ability to vary his insulin secretion with the coming and going of need, is better able to achieve a reasonable degree of homeostasis.

DR. COLWELL: It should be added that when diabetes begins in the first two decades of life, almost always it becomes severe very rapidly. Rarely is there any exception to the rule that it progresses into a severe form totally dependent upon insulin for life. By all criteria this is total diabetes—the most severe form seen in humans. In older people severe diabetes such as this is less common, but when it does occur in my experience those people tend to be thin and diabetes has been present a long time. Older people are more often fat, however, and have milder, less rapidly progressive forms of the disease. Clinical experience suggests that the diabetes now thought by physiologists to be an insulin-deficient variety is the kind present in most juveniles, whereas in the older people with milder forms of the disease the mechanism may be quite different. Certainly they are less dependent upon insulin as a rule.

QUESTIONER: In performing an autopsy on a twenty-six-year-old man who had had diabetes for twenty years, I noted marked sclerosis of the coronary arteries and typical Kimmelsteil-Wilson changes in the kidneys. The major arteries, however, showed no change. How can this be explained?

DR. ROOT: The number of young diabetic patients who begin to show clinical evidence of coronary artery disease in the early twenties is certainly increasing. We have seen a good many cases in which the amount of coronary atherosclerosis was advanced far beyond any change noted in the aorta or other arteries. In most cases, coming to post-mortem between the ages of twenty and forty with a history of diabetes for twelve to fifteen years there is not only coronary atherosclerosis but a good deal of atherosclerosis in the other arteries as well.

DR. HOLCOMB: I have recently seen a boy of fifteen with diabetes of two months' duration who died in coma; at the post-mortem examination atherosclerosis was found in the coronary arteries and in the aorta.

MODERATOR MULHOLLAND: Have patients with total pancreatectomy been followed long enough for observation of the development of vascular lesions as seen in cases of idiopathic diabetes? Does anyone know of such a case or cases?

DR. RICKETTS: This is a very good question. I don't know of any such cases. This much I can say. Dr. Lawrence has reported the development of premature atherosclerosis in patients who became diabetic by reason of pancreatic disease such as fibrosis, calculi, and so on. Although this is not thoroughly documented, there seem to be, in the human being, examples of premature vascular disease coming on as a result of induced diabetes presumably without relation to any hereditary factor.