brane widening can be demonstrated without use of the electron microscope. For several years we have obtained satisfactory muscle biopsies without difficulty from the vastus medialis by open biopsy or by needle biopsy using a specialized thoracotomy needle. However, any biopsy site would be expected to be suitable. These biopsies fixed in osmium, embedded in plastic and sectioned at 0.5-1μ, may be examined by phase contrast microscopy. Such preparations clearly show basement membrane abnormalities if they are present. Indeed, when we reviewed our paraffin sections stained by the periodic acid Schiff method, we were able to recognize the thick-walled interstitial muscle capillaries. However, in these preparations, one cannot distinguish the basement membrane from endothelial cytoplasm. With phase contrast microscopy this distinction can be made.

Now that morphologic studies have demonstrated the basement membrane changes, the attention of biochemists has been drawn to this problem. Recently, Lazarow[10] has shown that the glomerular capillary basement membrane contains little polysaccharide and large amounts of proline and hydroxyproline suggesting a chemical similarity to collagen.

Although the origin of the basement membrane material, its structural composition and its possible relation to the biochemical lesions of diabetes mellitus are problems for the future, this chapter in the history of the study of diabetes mellitus well illustrates that there is still much to be learned by those who are prepared to relate changes in structure with new information concerning cell physiology.

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*PREGNANCY AND DIABETES**

The combination of diabetes mellitus and pregnancy poses more controversial and provocative problems than almost any other problem appearing in gravid women. Although adverse effects of each upon the other are recognized clinically, these are poorly understood. The wide differences of opinion referable to practically every aspect of diabetic pregnancies illustrate the magnitude of the perplexities and the extensive fields for medical research.

Current studies exploring various genetic aspects of diabetes offer new concepts and the promise of solving some of the mysteries now harassing internist, obstetrician, and pediatrician alike. Causes for the frequent first appearance of diabetes during the gestation period, the alterations in insulin requirements for patients with pre-existing disease, the marked propensity toward hydramnios and toxemia, choice of the optimal time for delivery, and the route of delivery most favorable are moot issues. The most puzzling and distressing phenomenon is the profound, potentially fatal effect upon the fetus, an effect not infrequently in operation during the earliest stage of maternal disease. The type of islet cell hyperplasia observed in stillborn infants and those that die early in the neonatal period, the excessive size of these infants, and their proneness to respiratory distress are features indistinguishable in deadborn or sick infants of mothers predisposed to diabetes and those with long-established disease.

Fragments of new information are gradually accumulating from laboratories in many parts of the world. It appears certain that gaps in knowledge are narrowing as these are applied to clinical situations. Dr. Kyle, whose thought-provoking monograph accompanies this number of the *Annals* as Supplement 3, renders a valuable and needed service in his painstaking scrutiny of every angle of the problem. Unquestionably, benefits will be derived from the mustering together of all pertinent current views and the results of recent, important clinical and laboratory investigations.

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Certain aspects of the problem are heartening. When good metabolic control is achieved and cognizance is taken of changing insulin needs in otherwise uncomplicated pregnancies, as well as the hazards of hyperemesis and infection, when the importance of aggressive management of obstetric complications is appreciated, maternal mortality of diabetic mothers can be reduced almost to the vanishing point. However, this kind of record can be obtained only if physicians charged with the care of such patients are ever aware of the seriousness of coexisting pregnancy and diabetes and constantly on the alert to avoid disaster. The gloomy outlook for the offspring has shown less spectacular improvement but happily perinatal losses continue to be reduced. Over the country at large the mortality rate for diabetic progeny has dropped from approximately 30 per cent to 20 per cent during the past decade. Only a few clinics with the most experienced teams have been able to achieve a loss of less than 10 per cent, mainly because the basic deleterious maternal influences remain unknown.

The occurrence of large and stillborn infants during the totally asymptomatic phase of maternal disease has touched off an enormous number of investigations and these in great measure provide the basis for the current concept of diabetes as a failing resistance to a genetic diabetogenic influence. Specific abnormalities of chromosomal structure in patients destined to become diabetic have not yet been found. However, this field is still in infancy. Meanwhile, the work of Conn and Fajans[1] has presented convincing evidence that the genetic predisposition is present from the moment of conception, that during the "prediabetic" years the disease exists but remains compensated and therefore undetectable, and that as soon as a diminution in insulin activity can be demonstrated the hidden "prediabetic stage" has passed. It is well that Kyle, along with many others, has followed the Michigan investigators in abandoning the term "prediabetes" as a clinical diagnosis and has applied the more appropriate term *latent* or *subclinical* diabetes to temporary derangements in carbohydrate metabolism provoked by stressful conditions such as pregnancy, infection, cortisone, or emotional crises.

What are the factors at work during the incubation period or the "diabetes premellitus" years? Are there harmful agents other than transient hyperglycemia in operation during the latent phase? Probably in no other situation is the image of diabetes as a straightforward deficiency disease characterized by hyperglycemia and glycosuria and controlled by administration of insulin more open to question than in its association with pregnancy. That perinatal losses of large sturdy-appearing babies occur when maternal hyperglycemia is minimal or only temporary during periods of stress and long before the tendency to ketoacidosis appears suggests that diabetes is a far more generalized process than was formerly supposed. It is likely that unfavorable intrauterine effects upon the fetus may be one of its first manifestations and that loss of carbohydrate tolerance may be a relatively late event. When the final answers are in, the definition of the disease process must explain what the lethal factors are and the mechanism by which they operate to destroy the fetus in spite of what is presently considered good control. It must also explain the inconsistencies found between the onset of premature vascular aging, nephropathy or retinopathy, and the duration of diabetes or its severity as judged by the amount of insulin required.

The attention directed by Kyle to the precipitating or diabetogenic effects of pregnancy is well advised. As far as the mother is concerned, end results of gestational influences are threefold: (1) a genetic predisposition to diabetes may be temporarily unmasked; (2) permanent diabetes may be precipitated; and (3) pre-existing disease is usually aggravated but only during the course of gestation. When the pregnancy is over, the patient with established diabetes is not made worse as a rule nor is her resistance to insulin increased. It is not yet clear which of the women showing a transient abnormality in carbohydrate metabolism during gestation will ultimately develop overt diabetes or whether all of them would if they lived long enough. O'Sullivan's observations[2] revealed that of gravid women in whom this type of temporary reduction in carbohydrate tolerance was discovered, 28.5 per cent progressed to permanent diabetes within five and one-half years. Studies of much longer duration than are presently available will be necessary before this problem can claim a firm scientific solution.

The difficulty in distinguishing a diabetic diathesis from metabolic alterations due to pregnancy is rightly emphasized in this review. The sections on extrapancreatic factors and placental function point out the direction of present interest and the rapidity with which scientific research in this field is moving. The inclusion of apparently conflicting reports in these same areas illustrates the need for gathering together and sorting out the results of current work. The physiologic changes brought on by pregnancy are incredibly complex. Some exert an anti-insulin action and some appear to be designed to prevent an overshoot of

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anti-insulin effect. Good evidence can be found to suggest that increases in growth hormone and adrenocorticotropin-like activity, in adrenal cortical steroids, and in thyroxin occur during pregnancy. In addition, circulating insulin may be inactivated by an antagonist present in the albumin fraction of plasma protein or it may undergo degradation or trapping by the placenta. Each of these factors singly and certainly in combination militates to diminish insulin activity. On the other hand, protein-binding of cortisol and thyroxin is increased during gestation, an alteration which is enhanced in the presence of the high levels of estrogen normally found particularly in the last half of pregnancy. Curiously, the effect of ACTH-like activity appears to be potentially bilateral. As a counterpart to its influence in stimulating adrenal hormone output, Freinkel and Goodner[3] showed that large amounts of ACTH could block insulin destruction attributable to an enzymatic substance which they isolated from human placentas. It is conceivable that the provisional appearance of diabetes during pregnancy represents an unfavorable balance between the sum of biologic activity of insulin and its synergists on the one hand and its antagonists on the other and that exhaustion of pancreatic insulin secretion is only one of several mechanisms for decompensation.

Factors in human pregnancy other than the complex hormonal changes create difficulty in diagnosis, particularly the alterations in gastrointestinal and renal functions. These are aptly discussed in the supplement. The widely varying results of different investigators using the same tools for diagnosis indicate the need for a more specific testing method and perhaps an even greater need for the establishment of firm grounds for interpretation. Advantages and disadvantages of the oral versus the intravenous glucose tolerance tests are considered impartially, although in summary the author indicates his own reliance upon the results of the oral test. We are thoroughly in accord with this view and, along with Kyle, we recognize the difficulty in judging borderline cases when this method is used. From the standpoint of fetal welfare, the penalty for failure to detect latent diabetes at this opportune time can be inordinately high and therefore the most sensitive and as nearly accurate a method as possible should be used. The cortisone modified glucose tolerance test performed several months postpartum provides the best means of confirming the results obtained by the standard oral test during pregnancy[4] and should be used more widely in borderline cases. However, the cortisone glucose tolerance test should not be used for diagnosis during the course of pregnancy. It is probably safest to follow the general precept stated by W. P. U. Jackson[5] that "during pregnancy the ordinary glucose tolerance test is not worsened but the added stress of cortisone seems to overcome pancreatic reserve in some apparently normal women" irrespective of whether one considers the decompensation to reside in the pancreas or in some other system.

Several practical observations deserve emphasis because the magnitude of the problem continues to increase with every successful pregnancy and the number of physicians called upon to care for the diabetic mother and her infant increases accordingly. Cases of diabetes in the United States today exceed three million, with at least one undetected for every known case.[6] The importance of vigilant medical teamwork can hardly be overstressed. Although meticulous metabolic control will not yet guarantee a successful outcome for the fetus, poor control will result in fetal losses of approximately 45 per cent even in this, the "insulin era."[7]

The susceptibility of diabetic mothers to fluid retention has not been satisfactorily explained. Most of these have some degree of hydramnios with significant accumulation in 10 per cent, or twenty times the expected incidence. It should be made clear that hydramnios has different implications in diabetic and nondiabetic subjects. In the latter it is frequently associated with erythroblastosis or with fetal congenital malformations particularly of the central nervous system and the gastrointestinal tract. In diabetic mothers progressive hydramnios is often an unfavorable sign as far as fetal health is concerned and may serve as an indication to proceed with delivery if the gestation period warrants intervention. However, the increased occurrence of congenital malformations in infants of diabetic mothers is unrelated to hydramnios. Instead, some other factor in intrauterine environment of diabetic women appears to be responsible. This is probably not a sublethal effect of the same factor that destroys the fetus late in pregnancy because perinatal deaths are increased for many years before diabetes becomes manifested, whereas congenital anomalies are not more frequent at this stage of the disease. In our experience, the development of maternal ketoacidosis during early pregnancy seems to bear the closest relationship to defective fetal development. It is important that the diabetic woman present herself for prenatal care as soon after conception as possible and that ketosis be avoided at all times.

The comprehensive evaluation recommended for this early stage is essential for future management. However, issue will be taken with the use of X ray for

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evidence of vascular calcification and with the choice of the phenolsulfonphthalein excretion as a measure of renal function during pregnancy. Whenever possible, methods other than those permitting even small amounts of irradiation should be used for estimating vascular status in the first trimester. Results of the phenolsulfonphthalein test are often misleading in gravid women because the rate of urinary flow from kidney to bladder is reduced due to dilatation of the renal pelvis and ureter and diminished ureteral peristalsis. This relative stasis of urinary flow also contributes to the development of infection. Because pyelitis is so significant and far more frequent in diabetic pregnancies as compared with normal pregnancies, special attention to diagnosis and longer period of treatment is necessary.

It is ironic that diabetes makes the need for proper timing of delivery so critical and at the same time makes estimation of the expected date of confinement so difficult. Menstrual cycles are frequently irregular. Excessive size of the fetus or the presence of hydramnios suggests a more advanced pregnancy but in the patient with hypertension the fetus may actually be smaller than average for gestational age. Thus, estimation on the basis of fundal height alone may lead to delivery too early in a less critical situation and too late in the most threatening. X ray for distal fetal femoral epiphysis may be warranted this late in pregnancy but failure to see the epiphysis does not indicate immaturity unequivocally. The recent work of Greene and Touchstone,[8] using estriol determinations as an index of placental function, appears to offer a promising means of judging fetal welfare objectively. These authors have established values for normal pregnancy and have demonstrated that when these remain sufficiently elevated the pregnancy can safely continue to greater maturity. On the contrary, when low or rapidly falling values are found in complicated pregnancies, including diabetic, fetal life is in jeopardy and in all probability the infant stands a better chance outside the uterus than inside the uterus, if the gestation period exceeds thirty-three weeks. Technicalities of the method have limited its use but so far there is no other laboratory test that can claim to provide this information.

From the standpoint of the puzzling fetal disturbance, the works of Vallance-Owen and Lilley[9] and of Lowy, Blanshard and Phear[10] have opened entirely new areas of investigation. Their studies have shown that an insulin antagonist, polypeptide in nature, linked with the albumin fraction of plasma protein is capable of inhibiting the uptake of glucose by muscle but not by adipose tissue. These questions need answers. Does this antagonist cross the placental barrier? If so, can it account for the weak condition and fat habitus of the infant of a diabetic or subclinical diabetic mother? Is there any way of inhibiting or neutralizing the antagonist?

These problems and many others posed in Kyle's comprehensive review await elucidation before the next notable advance will be made. Until then, detection of the genetic predisposition, strict management of the metabolic and obstetric conditions, optimal timing of delivery which must be individualized, and skillful pediatric care of the newborn will surely continue to give the best chance for a successful outcome. Hopefully, some of the many current studies of carbohydrate metabolism and insulin activity in pregnant subjects will provide clues to basic etiologic factors in the genesis of the disease.

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