wastes. The exact part exercise plays in protecting or predisposing to excess wear and tear on body tissues, especially of the vascular system, is not known. The sedentary individual who is continually feeding into his blood stream a concentrated caloric flow must, thereby, expose the vascular walls to greater strain than if the blood stream is speeded up by physical activity. Exercise may exert an influence as a catalyst by shortening the time period during which a high caloric concentrate is bathing the vascular walls. The sense of well being experienced following exercise may be the result of speeding up the blood stream, improving the tonicity of the vascular walls and shortening the danger period of exposure to metabolic concentrates which are commonly found in the walls of diseased blood vessels.

Diet, insulin, and exercise with the avoidance of prolonged exhaustion are the requirements upon which diabetes control is established. The exact level of the blood sugar is but one measure of control. For a physician interested in maintaining control of the diabetic state, the available evidence emphasizes the importance of maintaining the level of the blood sugar not over 200 mg. for any prolonged period of time. Granted many individuals may carry on apparently in satisfactory fashion with blood sugar levels over 400 mg. and more or less constant glycosuria for a variable period of time. Acceptance of such distortion of normal body chemistry as a condition compatible with well being is a dangerous practice. There are still many angles of the diabetic problem for which no answers are yet available. Nevertheless, the more clearly the metabolites and electrolytes of the blood fall within the accepted normal range, the closer will the diabetic come to satisfactory control.

EDWARD L. BORTZ, M.D.

DIABETIC RETINOPATHY.

The characteristic vascular lesion of diabetic retinopathy consists of the presence of great numbers of minute saccular aneurysms in the retinal capillaries. Hemorrhages and exudates commonly surround the aneurysms, indicating that these are loci of weakness in the vascular wall. The aneurysms are often hyalinized. Capillary aneurysms in the retina are also seen in a variety of other retinal lesions involving tissue damage, venous occlusion, etc. but in these conditions the aneurysms are mainly fusiform or varicose, while in the diabetic they are mainly saccular.

The retinal lesions of the diabetic are closely related to the renal lesions described by Kimmelstiel and Wilson. The latter are often associated with capillary aneurysms in the kidney glomerulus, and the typical globular hyalin, glomerular nodule of Kimmelstiel and Wilson may, in fact, be a hyalinized saccular capillary aneurysm. Kimmelstiel[1] believes that the hyaline material in the glomerular lesion is laid down outside the capillary basement membrane, while I have suggested[2] that the hyalinization occurs inside the aneurysmal sac in the retina, but it is agreed that the retinal and renal lesions are joint manifestations of the same vascular disease. Neither these retinal nor these renal lesions, characteristic of the diabetic, are direct consequences of atherosclerosis or malignant hypertension. They are almost never seen in atherosclerotic or hypertensive nondiabetics and may occur in diabetics in the absence of both athero- and arteriolosclerosis. Patients with diabetic retinopathy and nephropathy commonly show increased capillary fragility suggesting the presence of a generalized capillary disease, but microaneurysms have so far not been demonstrated in significant numbers in organs other than retina and kidney.

The characteristic capillary lesion is most frequently seen in diabetics of long standing, but it is not directly related to the severity of the diabetes in terms of insulin requirement. Many patients show a decline in insulin requirement associated with the onset of the retinopathy. The relative frequency of episodes of acidosis in patients with and without retinopathy is disputed. Zubrode, Eversole and Dana[3] found a lower frequency of acidosis in adult diabetics with than without retinopathy and nephropathy. Wilson, Root and Marble[4] found a higher frequency of acidosis in juvenile diabetics with than without retinopathy. In extremely rare instances, retinopathy or nephropathy morphologically identical with those of the diabetic have been found in nondiabetics.

Rich, Berthrong and Bennett[5] discovered that renal lesions resembling those of the Kimmelstiel-Wilson nephropathy could be produced in rabbits in a period of 2 to 3 weeks by the administration of 7.5 mg. of cortisone in daily intramuscular injections. Rich[6] found typical Kimmelstiel-Wilson nephropathy in a nondiabetic patient who had been subjected to very prolonged corticotrophin (ACTH) therapy. Naquin[7] has noted the appearance of retinal capillary aneurysms in nondiabetics under corticotropin treatment. Friedenwald and Becker have found that alloxan diabetes in rabbits predisposes these animals to the capillary lesions elicited by cortisone and corticotropin. They have,[8] therefore, suggested that the retinopthy and nephropathy of the diabetic may be the consequence of an increased secretion of cortisone

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(or related substances) by the adrenals of these patients.

Clinical estimates of adrenal activity with respect to glucocorticoids are extremely tenuous. Thorn,[9] using as an index the fall in eosinophile count following corticotropin administration, concluded that about half of all diabetics tested showed deficient adrenal function. Thorn's patients were unclassified with respect to the presence or absence of retinopathy. Hoover, Becker and Winter, in a similar study, found that all the diabetics exhibiting adrenal hypofunction by this test were free of retinopathy. Within the limits of reliability of this test, diabetics with retinopthy exhibit more adrenal activity than the average diabetic without retinopathy. Shadaksharappa[10] studied the urinary steroid excretion in a small group of diabetics. Those with and without retinopathy showed diminished output of ketosteroids, but diabetics with retinopathy excreted more oxysteroids than did those without retinopathy.

Pregnancy is normally associated with increased adrenal function and might be expected, therefore, to exacerbate diabetic retinopathy. This has been found to be the case by Lawrence (1948),[11] and Becker (1952).[12] Green (1951)[13] reported the disappearance of retionopathy in one diabetic patient following surgical removal of the adrenals. A spontaneous disappearance of the retinopathy has been recorded in a diabetic who developed Simmonds' disease.[14] Saskin[15] and coworkers have reported improvement in the retinopathy of some diabetics treated with testosterone. The administration of testosterone has been shown to produce atrophy of the hypophysis and diminish adrenal activity in animals.[16] It has been used effectively in some cases in the treatment of Cushing's disease.[17] Many of the diabetics treated with testosterone show diminished daily insulin requirement as would be expected if they were experiencing diminished adrenal activity.

The clinical evidence summarized above is tenuous and indirect. The best that can be said about it is that, so far, no clinical findings contradict the hypothesis of Becker and Friedenwald of relative adrenal hyperfunction in diabetics with retinopathy. In the experimental animal, the interaction of alloxan diabetes and cortisone or corticotropin in the production of retinal and renal capillary lesions is unequivocal. What, then, are the possible metabolic and biochemical pathways of this interaction? Exploration of this problem has just been begun but some possible clues may be enumerated.

Both insulin and cortisone seem to be involved in mucoid metabolism. Jacobs[18] found that the glucosamine fraction of plasma mucoid rose and fell with the plasma glucose of diabetics in response to insulin withdrawal and administration. Glick[19] finds that the hyaluronidase inhibitor of the plasma increases after administration of cortisone, and diminishes after adrenalectomy. Layton[20] found that cortisone inhibited the synthesis of mucoid sulfates. McManus[21] has suggested on morphologic grounds that the retinal and renal capillary lesion of the diabetic might be the result of a disturbance in mucoid metabolism. It seems possible that some defect in the basement membrane of the capillary may be the immediate cause of the aneurysms.

Both pancreas and adrenal dysfunction have large effects on the utilization of several of the B vitamins. Many diabetics show evidence of deficiency in some B factors and some B deficiencies can be demonstrated in alloxan diabetic animals. The association of diabetic neuritis with diabetic retinopathy is by no means infrequent. The vitamin deficiency of the diabetic probably is not generally to be accounted for by his restricted diet, but it may be noted that a severe increase in diabetic retinopathy was observed in Denmark[22] during the period of war time food restriction. The reason for the apparently enhanced vitamin requirement of the diabetic is obscure, but insulin is required for the formation of high energy phosphate compounds, and hence indirectly for the conversion of most of the B vitamins into their phosphorylated functionally active forms. Even the parenteral administration of insulin with adequate control of the blood sugar level may not fully replace the diabetic's insulin deficiency in the portal circulation.

Deficiencies of pantothenic acid, pyridoxine, and thiamine have each been shown in experimental animals to cause depletion of lipoids in the adrenal cortex. The interpretation of these findings is equivocal since lipoid depletion in the adrenal may result from stress, that is adrenal hyperactivity, or from an incapacity to synthesize the adrenal lipoids. In regard to these B vitamin deficiencies, a choice between these two possible interpretations cannot in each case be made on the basis of currently available data. However, it has been shown that deficiency of pantothenic acid is associated with adrenal hypofunction.[23] Moreover, the body can synthesize its steroids from acetate and the biochemical production of active acetyl groups requires the presence of coenzyme A of which pantothenic acid is an integral part.

As was noted above, some diabetics without retinopathy show adrenal insufficiency in terms of a defective eosinopenic response to corticotropin. Winter[24] has recently tested the possibility that this defective response might be due to pantothenic acid deficiency, and has

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found that the response in these patients becomes normal after administration of pantothenic acid alone or with pyridoxin. The pantothenic acid deficiency in these cases appears to be quite marginal, and is not associated with a grossly deficient capacity in acetylation.[25] In experimental animals on a pantothenic acid deficient diet, it has been found that diminished adrenal function develops before gross evidence of insufficiency in other organs.[26]

The relation of adrenal function to vitamin B_{12} is very different from the pantothenate-adrenal interrelation. B_{12} deficiency in contrast to pantothenate deficiency has not been shown to be associated with adrenal lipoid depletion or adrenal hypofunction. Symptoms of B_{12} deficiency are markedly exacerbated by cortisone[27] and the turnover of this vitamin is greatly accelerated in adrenal hyperfunction. Chow and Becker found that cortisone treated animals and humans excrete far larger fractions of a test dose of B_{12} than do normals. Some of the symptoms of cortisone intoxication, for instance, thymus atrophy,[28] are reversed by administration of B_{12}. Chow and Becker[29] have tested the capacity of diabetics with and without retinopathy to retain a test dose of B_{12}. They found that diabetics without retinopathy excreted in their urine a smaller fraction of the test dose than did normals. They interpreted this as indicating B_{12} deficiency in this group of patients.

Diabetics with retinopathy excreted as much or more of the test dose than do normals. This might indicate that these patients were saturated with B_{12} or that they were unable to retain the test dose because of adrenal hyperfunction. To test this, these patients were treated with testosterone and retested for B_{12} excretion. In every case greater retention of B_{12} was found after testosterone than before. The increased retention was most marked in those patients who showed increased insulin sensitivity after the testosterone, that is, evidence of diminished adrenal function.

Becker, Winter and Friedenwald then tested the influence of B_{12} deficiency in rabbits on the renal lesions produced by cortisone. Nondiabetic animals on a B_{12} deficient diet, given 7.5 mg. of cortisone daily for two weeks, showed a much higher incidence of renal lesions resembling the Kimmelstiel-Wilson nephropathy than did animals on a normal diet containing aureomycin and vitamin B_{12} subjected to the same cortisone treatment. The lesions were, in fact, more severe and abundant than those produced in alloxan diabetic animals on a B_{12} supplemented diet given the same cortisone treatment. It would appear, therefore, that one of the convergent metabolic pathways leading to the production of the vascular lesion may be B_{12} deficiency induced by diabetes and exacerbated by adrenal hyperfunction.

In general, the diabetic shows an increase in plasma lipids. Lipemia is common in alloxan diabetic rabbits. Increased blood lipids can also be produced by cortisone and this effect is found in experimental rabbits. In rats, on the other hand, lipemia is not readily elicited either by alloxan diabetes or by cortisone administration, and this species does not develop retinal or renal capillary aneurysms under the experimental conditions that produce these lesions in rabbits. It would seem possible, therefore, that a disturbance of the fat metabloism may be related to diabetic retinopathy and nephropathy. A recent issue of DIABETES was devoted to reports from several clinics on the blood lipids of diabetics with and without retinopathy.[30]

The possible clues as to the locus of metabolic interaction between the diabetic state and adrenal hyperfunction lead in many diverging directions. The brief list enumerated above by no means covers all of the possibilities. Somewhere in this perplexing nexus the immediate cause of the retinopathy may one day be found. Root has said that it makes no sense to consider diabetes as unrelated to pancreatic dysfunction. With this, I am in full agreement, but it would be fatuous to assume that the whole complex of symptoms, complications and sequelae of diabetes are simply and directly related to hypo-insulinism.

JONAS S. FRIEDENWALD, M.D.

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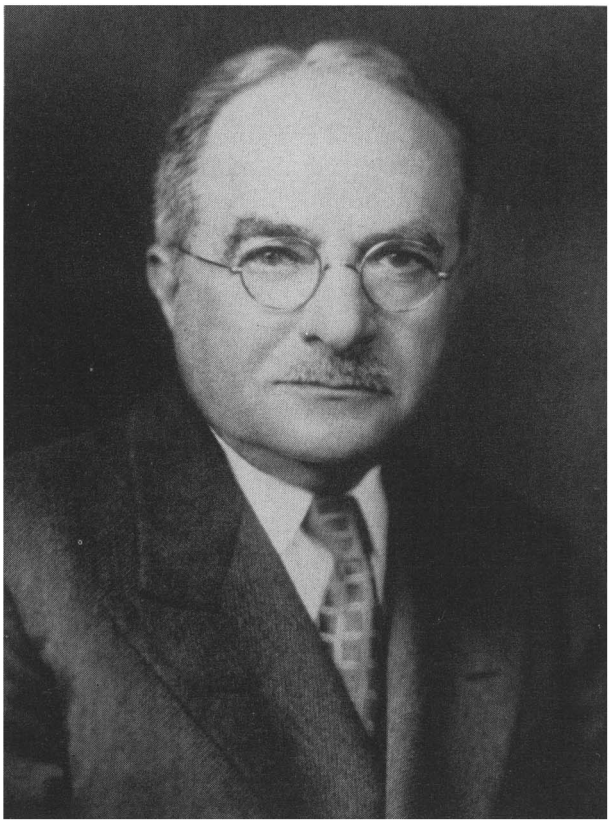
LOUIS I. DUBLIN, MEDICAL STATISTICIAN

News of the retirement of Louis I. Dublin, Ph.D., from his post as Statistician and Second Vice President of the Metropolitan Life Insurance Company, recalls not only his distinguished personal career but also the growing significance of studies of statistics in relation to medical problems. Progress in medicine long depended chiefly on clinical observation. In recent generations, great advances have been aided by laboratory investigation. The increasing recognition of the value of medical statistics is in great measure due to Doctor Dublin's work.



Louis I. Dublin

Doctor Dublin organized the Statistical Bureau of the Metropolitan Life in 1911, and was its chief until his retirement at the close of 1952 when he completed 44 years service with that company. He continually focused attention on the social and economic losses suffered by the country as a result of preventable sickness and pre-

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