CURRENT CONCEPTS OF DIABETES MELLITUS WITH SPECIAL REFERENCE TO OCULAR CHANGES

L. BENJAMIN SHEPPARD, M.D.

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Figure 1. Early Diabetic Vascular Changes. Small, dark punctate hemorrhages in a fundus that is otherwise normal.

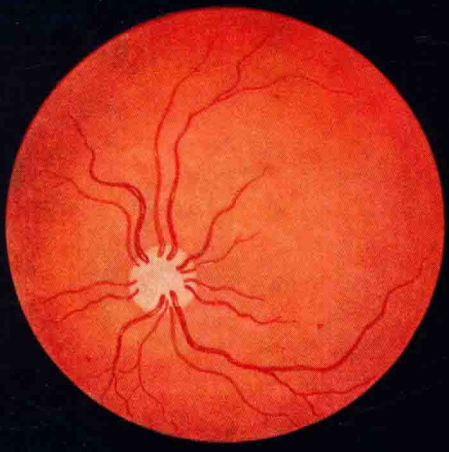
Figure 2. Diabetic Retinopathy, Mild. Minute hemorrhages and yellowish white exudates scattered at posterior pole. Uneven veins.

Figure 3. Diabetic Retinopathy, Moderate. Persistent punctate hemorrhages. Increase in the exudates, which tend to form a partial ring at the posterior pole.

Figure 4. Diabetic Retinopathy, Advanced. Vitreous hemorrhage, severe, with clouding of vitreous, so that only nerve head and surrounding sclerotic vessels can be seen.

Figure 5. Diabetic Retinopathy, Advanced. (Retinitis proliferans with and without new-formed vessels.) Thin bands of translucent scar tissue fanning out over fundus from nerve head, with interlacing new-formed vessels. Torsion of veins and perivasculitis.

Figure 6. Diabetic Retinopathy, Advanced. Torsion and sacculation of veins. New-formed vessels, retinal edema. Preretinal hemorrhages. Uneven caliber of vessels, smaller branch attenuated. Retinal detachment.



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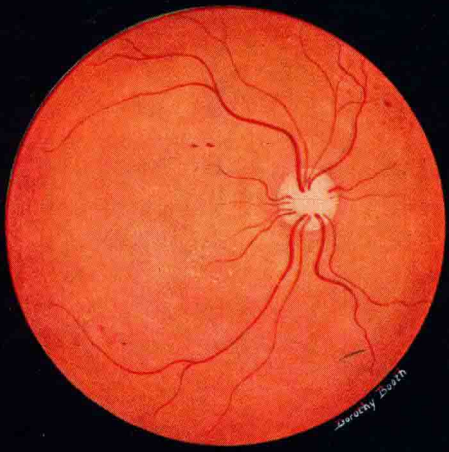

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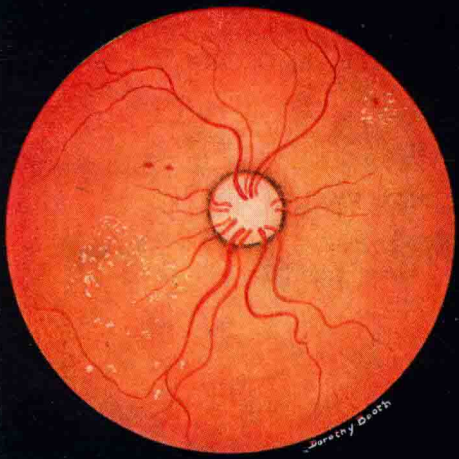

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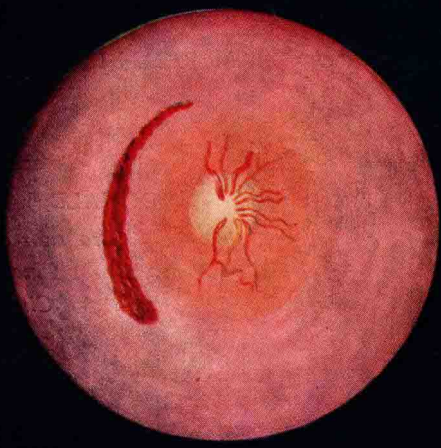

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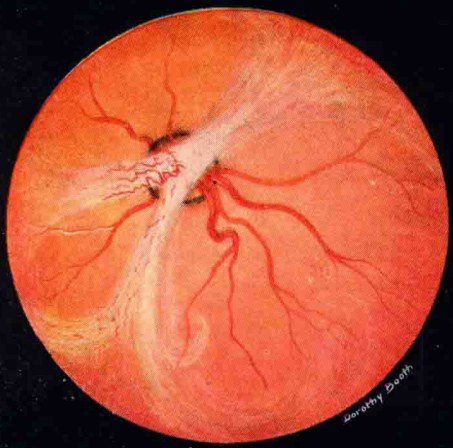

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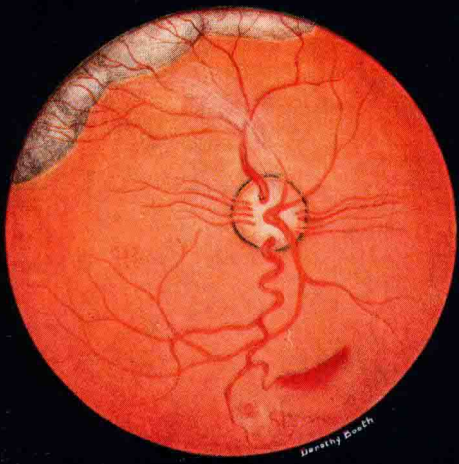

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INTRODUCTION

Diabetes, for the ophthalmologist, has a special and a constantly increasing interest. It is in the eye, particularly in the retina, that the complications of diabetes may appear first, and it is there that they can be studied better than anywhere else in the body, even more readily than in the kidney. Diabetes is a chronic disease, frequently involving the eye in varying degrees. The present study will review not only the clinical and experimental changes found in diabetes with special reference to the eye but also findings in a number of closely related fields. All the retinal changes in the diabetic will be included in the term *retinopathy*.

Diabetes is an insidious, progressive, and degenerative metabolic disease that may affect any part of the body. Best [29] concisely defined diabetes as a disturbance of carbohydrate, protein and fat metabolism due to an imbalance of the glands of internal secretion. In order to interpret the retinal findings in a diabetic intelligently it is necessary to know how diabetes affects other parts of the body, so that the patient may receive maximum benefit from the correlation of the diversified information contributed by many investigators.

INCIDENCE OF DIABETES

TODAY THERE are approximately two million diabetics in the United States.[197] This group is a public health problem as well as a medical one and constitutes a fair percentage of a physician's practice, whether he is a general practitioner or an ophthalmologist. Diabetes ranks sixth among the chronic diseases when rated according to the number of days lost from work and other usual activities. The increased incidence is due to early diagnosis and to the prolongation of life.[140] Through education in the control of diabetes and various surveys, our population is becoming more diabetes-conscious.

We are now able to discover diabetic cases sooner and encourage them to start with a specific therapy. Usually the diagnosis is considered correct if there is a repeated positive urinary sugar, a fasting blood sugar above 129 mg. per cent, or a blood sugar above 164 mg. per cent following an average meal.

Diabetes is a chronic disease, commonly developed in middle life, although it occurs in all age-groups, even in infancy. Statistics [58, 109, 140] show that there is an increasing chance that the non-diabetic may become diabetic as he approaches 50 years of age. This is especially true if he is overweight, for such individuals have a low tolerance for carbohydrates. The obese person at the onset of diabetes usually tends to develop an improved carbohydrate tolerance as he loses weight and becomes a controlled diabetic.

ETIOLOGY OF DIABETES

DIABETES MELLITUS may be an hereditary disease.[105, 109] In John's [98] series of 500 diabetic children, an hereditary factor was found in 31.5 per cent. Burnstein [35] presented observations of one diabetic family and showed the hereditary tendency through five generations. In 107 diabetics, in my own practice, the relative incidence of the hereditary factor was 31.76 per cent (34 patients).

Diabetes may also be a metabolic disturbance, due to various hormonal [42] and neurovegetative influences.[49, 82, 180] It is now apparent that dysfunction of several endocrine organs may account for the impaired carbohydrate metabolism.[57, 125, 199] Soskin [169] has demonstrated the endocrine relationship and established the significance of an adequately functioning liver in intermediary metabolism of carbohydrates and related substances. Contemporary medical thought regarding endocrinology is very different from that which prevailed 20 years ago. The hypothalamus, though small anatomically, has come to assume much importance in regard to functional activity. Harvey Cushing held it to be the base of elemental life—vegetative, reproductive and emotional—over which man has superimposed a layer of inhibitions. A recent concept is the establishment of a functional unity of the endocrine system, wherein the pituitary is considered its center. The pituitary functions appear to be greatly under the control of the hypothalamus. The present trend of investigation appears to indicate an increasing importance of the hypo-

thalamic centers in the regulation of carbohydrate metabolism.[49, 63, 95, 180] Most of our knowledge concerning the imbalance of the endocrine glands in diabetes has been gained in the experimental field. An insufficient supply of pancreatic insulin in the diabetic does not always explain glycosuria and hyperglycemia.[176] A large number of patients require more insulin than is produced by the normal pancreas. The insulin requirement of the depancreatized human suggests that other factors must be at work.[80] This would indicate an endogenous wasting of the body insulin (in a manner not as yet known), which may be caused by a neutralization of insulin by certain enzymes, by an inhibition of the insulin, or by a combination of such influences.[58] The investigation of the pancreatic alpha cell hormone, by Heard,[89] indicated that a hormone antagonistic to insulin is produced by these cells and might explain the presence of hyperglycemia where a mildly deficient supply of insulin may exist.

The preponderance of evidence shows that human diabetes is a pancreatic disease which is caused by a specific hormone deficiency.[24, 29, 43, 58, 109, 190] In addition to the pancreatic factors,[37, 71, 95, 97, 190] the pituitary, the adrenal, the thyroid, and the liver [121, 169] may play an important role. The anterior pituitary growth hormone influences carbohydrate metabolism by interfering with the utilization of carbohydrates in the peripheral tissues [47] and greatly increasing the demand for insulin. ACTH stimulates the formation of compound F-like hormones, which causes the conversion of proteins into carbohydrates (gluconeogenesis).[97, 163]

The adrenal cortical response may increase the demand for insulin, either as a result of a primary disturbance, such as a tumor, by the production of compound F or by a secondary disturbance due to a stimulation by excessive

ACTH.[170] Whether or not diabetes will develop in patients with a prolonged ACTH therapy or a relative excess of adrenal cortical hormones depends upon the ability of the islets of Langerhans to meet the increased insulin demand. The results of the experiments of Houssay[95] and of Becker,[19] in certain groups of diabetics, strongly support the theory that the lesion causing diabetes may be the consequence of a metabolic hormonal disorder.

The importance of the adrenal cortical hormones and the anterior pituitary hormones in the metabolism of carbohydrate, fat, and protein is well demonstrated by the experiments and discussions of Talbot,[178] Thorn[180] and Houssay.[95] From their findings it is apparent that the anterior pituitary hormones and the adrenal cortical hormones play an important role in increasing the formation of carbohydrates from noncarbohydrate sources (a condition known as gluconeogenesis).[125]

We shall go a long way toward understanding our patients if we are constantly aware of the possible hereditary factors in diabetes mellitus and how these may be affected by stress.

When man is exposed to disease, or circumstances upset his individual stability quotient, he may be said to be under stress. His ability to readjust his physiologic processes to these adversities might be called individual resistance (or adaptability). It has been suspected for a long time (since Addison's classic description of adrenal cortical insufficiency in man) that the adrenal glands have an important function in the control of this individual resistance to stress and strain. The anterior pituitary gland also plays a major role in the stress mechanism.[97] The body as a whole enters into the response to the stress, whether it is acute or chronic. Material pertaining to stress is found in the discussions of Selye,[163] under "Adaptation Syn-

drome." During the stage of resistance following the "alarm reaction," most of the morphologic changes regress. If stress continues unabated, eventually there is exhaustion of the mechanism of resistance; the organ affected can no longer compensate and the organism dies. Experimental data have been accumulated to show the important role in the stress mechanism, not only of the adrenal cortex but also of the entire related endocrine system.[19, 95, 164, 167, 169, 174] The co-existence of diabetes with other endocrine disorders is uncommon.[58, 138]

An increase or a decrease in a thyroid hormone in a diabetic produces, respectively, an increase or a decrease in the insulin need. The thyroid hormone is not a diabetogenic hormone like the pituitary.[58]

The liver probably maintains the key position in the control of the body metabolism.[58, 121, 155, 169] The normal liver is adjusted to supply the amount of sugar required by the tissues and ceases production as soon as the blood sugar rises above this level.[169] After the liver and the pancreas, the anterior pituitary gland is next in importance in the regulation of carbohydrate metabolism.[95] It is short sighted to consider diabetes as a disorder of carbohydrate metabolism alone or to imply that the lack of insulin is the only hormone deficiency involved. The uncontrolled diabetic uses carbohydrates at a hyperglycemic level, at the same time spilling large amounts of sugar, which points to the over-production of glucose. The secondary changes associated with diabetes and the problems arising from disturbed metabolism are undoubtedly inter-related, not only in the field of endocrinology [169] but also in that of nutrition.[116] More emphasis should be placed upon the impaired response to endogenous insulin associated with nutritional deficiency.[31]

In diabetes mellitus in humans, changes are found in

pancreatic islets in from 40 to 45 per cent of the cases. They are more common if the disease has been long standing and, in our laboratory experience, are especially prone to develop if there is hypertension. Similar pathology may be observed in the development of nodular glomerulosclerosis. These changes consist of hydropic degeneration, fibrosis and hyalinization and thickening of the islet capillaries. Since these changes are absent in a large proportion of cases, it would seem that damage to the islets does not always accompany diabetes mellitus. On the other hand similar but not identical states may be produced by damage to the islets such as in the alloxan animal. The possible relationship of pituitary, thyrotoxic and adrenal diabetes to the pancreatic type deserves further study. Warren [191] has observed that it makes no difference whether this is a hydropic or hyaline change; it is a selective pancreatic destruction. Hyalinization is a slow process, associated with periods of recurrences and recessions that eventually lead to destruction of the functioning islet cells, with a proportionate reduction in the insulin. The characteristic early lesions are cellular degranulation, followed by hydropic degeneration (glycogen infiltration) of the beta cells.[24, 25] Experimental work indicates that exhaustion and finally functional death of the beta cells are due to over-feeding the partially depancreatized animal,[7, 8] by the injection of anterior pituitary extract,[37, 51, 199] or by prolonged intra-peritoneal injections of glucose.[52] The latter experiment suggests that the hydropic change is associated with or possibly caused by hyperglycemia. Experimentally, diabetes can be produced by the injection of alloxan. Further research will be needed before we can prove a definite parallalism between the experimental studies and the pathogenesis of human diabetes.[19, 153] Mitotic figures at the periphery of the islet clusters indicate that regeneration follows hydropic degen-