min A.[8] The normal level of the latter offers further evidence that the vitamin accumulates appreciably in the reticuloendothelial cells of the liver only when excessive amounts are administered.

The results described above are markedly different from those encountered in hypervitaminosis A. Blockade of the reticuloendothelial cells by India Ink is followed by an increase in protein-bound thyroid iodine, unaccompanied by changes in thyroid weight. It is obvious that if excessive amounts of vitamin A lessen hepatic destruction of thyroxine, this action cannot be due to an accumulation of the vitamin in the reticuloendothelial cells of the liver. That the effects must be explained by a different mechanism is further indicated by the lack of concomitant elevation in circulating thyroxine in the experiments discussed. The dissociation between the latter and protein-bound iodine in the thyroid is of interest because, in normal rats, the level of circulating thyroxine appears to be dependent upon the thyroxine content of the gland and is limited by the capacity of the gland to produce thyroxine.[11]

In view of the normal thyroid weight of our animals, it would seem probable that both production and storage of thyroxine is increased, although it is released in normal amounts into the circulation. Our studies on hypervitaminotic animals suggest that vitamin A may lessen hepatic destruction of thyroxine, with a consequent hyperthyroxinemia and increase in pituitary iodine; the result would be a depression of thyrotropic hormone secretion[12,13] and, eventually, a reduction in thyroid size. No explanations can be advanced as yet for the results described in the present paper. Further studies are necessary to determine the underlying mechanism producing these effects.

Summary. 1. Protein-bound iodine was decreased in the liver and increased in the thyroid after reticuloendothelial cell block; increased production and storage of thyroxine is indicated by the data presented. 2. Hepatic vitamin A was not affected by the experimental conditions, although serum vitamin A was decreased. 3. The bearing of these results on those of hypervitaminosis A is briefly considered.

11 Taurog, A., and Chaikoff, I. L., *J. Biol. Chem.*, 1946, **165**, 217.

12 Adams, A. E., and Jensen, D., *Endocrinology*, 1944, **35**, 296.

13 Sadhu, D. P., *Am. J. Physiol.*, 1948, in press.

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Ocular Refractive Changes Accompanying High Blood Sugar in Alloxan-Treated Dogs.

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Disturbances in the vision of diabetic patients are frequently observed which involve no apparent pathological changes in the eye. Since they may be remedied by a suitable correction lens, the phenomenon appears to be one of refractive change. These disturbances may be either in the direction of myopia or hypermetropia. In general, myopic changes are said to occur after the onset of diabetic conditions, but before the start of therapy; hypermetropic changes are said to occur after the start of therapy. Myopia may persist, but hypermetropia is always temporary, the average duration being 2 to 4 weeks.[1-3]

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1 Granstrom, K. O., *Acta Ophth.*, 1933, **11**, 3.

2 Duke-Elder, W. S., *Brit. J. Ophth.*, 1925, **9**, 167.

3 Hudelo, A., *Arch. d'Ophth.*, 1930, **47**, 70.

The most acceptable theories to account for these disturbances in vision are all based on the assumption that the change occurs in the lens of the eye. It is supposedly brought about by changes in the osmotic pressure of body fluids, which in turn are the effect of variations in the blood sugar from the normal level.

For example, Granstrom[1] has suggested that salt retention by the tissues and loss of tissue fluid at the time of high blood sugar might increase the refractive index of the lens and result in myopia; with decreasing glycemia and glycosuria after the application of therapeutic measures, increased fluid uptake by the lens would result in a decrease in the refractive index, *i.e.*, hypermetropia. Duke-Elder,[2] on the other hand, suggests that with high blood sugar and salt retention, the blood is so diluted by body fluids that its osmotic pressure is lowered, and with it that of the aqueous humor, the result being that the lens swells and causes myopia; with a fall in blood sugar, the lens would shrink and cause hypermetropia. He cites cases of three human patients to uphold this theory; in one myopia varied directly as the blood sugar; in another, hypermetropia developed when there was a sudden decrease in blood sugar; in a third, myopia developed with an increasing blood sugar and persisted into coma and death. Therefore he concludes that the refractive power of the eye, or the myopia, tends to vary directly as the blood sugar level.

Procedure. To test under controlled conditions the hypothesis that changes in refraction accompany changes in blood sugar, 5 dogs were rendered diabetic and their state of refraction and blood sugars were followed as long as they remained alive. Observations were carried out during this period on 2 normal dogs as controls. It is to be noted that all the dogs were of undetermined age, neither very young nor very old, and in good health at the beginning of the experiment.

Fasting blood sugar values were determined according to the Schaffer-Hartman-Somogyi method using the macro-technic.

Refractive errors were determined by retinoscopy while the animals were under nembutal anesthesia and atropine cycloplegia. The refractive errors were denoted in the customary manner; positive values indicating the degree of hypermetropia and negative values, the degree of myopia. The visual axis had to be estimated in relation to the optic disc, but this was facilitated by the characteristic color of various portions of the dog's retina. Atropine (1% solution) was instilled into the conjunctival sac at 20-minute intervals, and retinoscopy was performed only at a minimum of 90 minutes after the initial installation, or 45 minutes after cessation of the pupillary response to bright light. Care was taken to keep the cornea moist with normal saline during the tests. Repeated observations have shown that retinoscopic findings on dogs under these conditions, like those on man, agree to within $\pm$ 0.25 D. Therefore it was assumed that changes of 0.25 D have no significance; changes of 0.50 have borderline significance; and changes of 0.75 D are definitely significant. The control dogs showed no significant changes during the 4 months they were kept under observation.

The 5 dogs were rendered diabetic by intravenous injection of alloxan (10% solution) in the proportion of 50 to 100 mg per kilo body weight. In some cases more than one injection was necessary to maintain a high

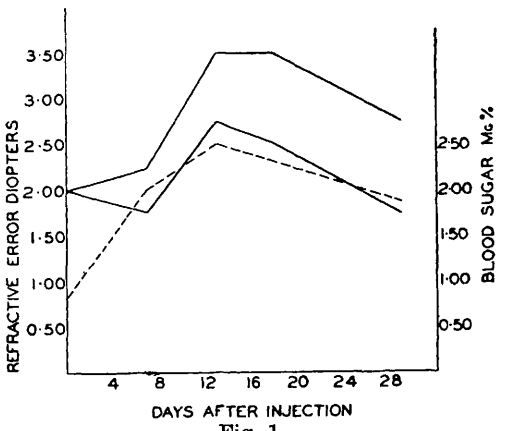

Fig. 1.

Results obtained on Dog No. 2 during the month following injection of alloxan. The broken line represents blood sugar. The unbroken lines represent the refractive error in the meridians of highest and lowest refractive power; therefore the vertical distance between these lines represents the degree of astigmatism.

blood sugar. The animals were fed twice daily a meal consisting of 200 g meat and 50 g sugar, which was more than ample for maintenance of weight. Water intake was unrestricted.

Results. The most striking of our results is shown in Fig. 1. The refractive change is in the direction of hypermetropia, not myopia, the change parallels the course of the blood sugar, and there are astigmatic changes as well. Such a definite refractive change, however, occurred in only 3 of the 5 dogs; the greatest refractive changes, in diopters, being in the 5 dogs, +1, +4, +.5, +1, and +.5, and the corresponding highest blood sugar values, in mg %, 340, 286, 440, 750, 500. No definitely significant change in two of the alloxan-treated dogs was observed, despite a very high level of blood sugar having been reached. No myopic changes whatever were observed in any of the 5 treated dogs.

In 1 dog an attempt was made to determine whether an alteration of the sympathetic-parasympathetic equilibrium would affect the refractive change. A sterile operation was performed in which the right superior sympathetic nerve was divided in the neck. In order to avoid the possibility of regeneration, the free ends of the nerve were sutured into the tissues some 3 inches apart. The only difference between the behavior of the 2 eyes of this dog after injection of alloxan was that the onset of the refractive change in the right eye appeared 2 days later than that in the left; the magnitude of the change was the same for both eyes.

Discussion. The significant observation in this set of experiments is that hypermetropic changes may occur at the time of acute or increasing hyperglycemia. This is in contradiction to the opinion of many investigators who state that in diabetic human patients hypermetropic changes occur only after the start of therapy.

It should be borne in mind that the alloxan-induced diabetes may differ from normally occurring diabetes or pancreatectomy diabetes. Thorogood and Zimmerman[4] state that coma is not common even in severe alloxan diabetes, and there is a lesser degree of acidosis and ketonuria. An increase in osmotic pressure within the lens might be the result of acidosis, in which state Krause[5] has suggested that certain proteolytic enzymes may act on the lens substance, producing fragmentation of protein with consequent increase of osmotic pressure. The entrance of water into the lens would represent the incipient cataractous state. Reports of transient diabetic cataract by Alt[6] and others suggest that myopic changes might be early cataractous changes which are reversible, and which do not progress to the point of opacification. Bellows and Chinn,[7] from their studies on swelling of the lens *in vitro*, conclude that there is a gradation of osmotic pressures ranging from external to internal layers, and water entering the lens tends to collect subcapsularly. Finally, there is evidence that myopic changes can be produced by lens swelling as in the transient myopia during sulfanilamide therapy. If myopia is the result of an acidosis, this factor may possibly be inoperative in alloxan diabetes.

Summary. Hypermetropic refractive changes may occur in the eyes of alloxan diabetic dogs at a time when the blood sugar level is rising or has reached a high level. Changes in the direction of myopia were not observed.

4 Thorogood, E., and Zimmerman, B., *Endocrin.*, 1945, **37**, 191.

5 Krause, A. C., *Biochemistry of the Eye*, Johns Hopkins Press, 1934.

6 Alt, A., *Amer. J. Ophth.*, 1906, **23**, 294.

7 Bellows, J. G., and Chinn, H., *Amer. J. Ophth.*, 1941, **24**, 979.