

## INSULINASE

The metabolic derangement of diabetes mellitus is due to an insufficiency of insulin. The cause of the insufficiency in man remains unknown. Whereas the classical studies of von Mehring and Minkowski<sup>1</sup> and of Banting and Best<sup>2</sup> suggested that a decrease in the production of insulin by the  $\beta$  cells of the pancreas could account for the insulin insufficiency, later studies made it apparent that some extrapancreatic factor must be involved in the majority of patients with diabetes mellitus. Thus, whereas the metabolic derangement occurs in the susceptible experimental animal only after the removal or destruction of from 80 to 90 per cent of the islet tissue of the pancreas, such extensive damage is relatively rare in human diabetes.<sup>3</sup> Further, although the syndrome becomes apparent in the alloxanized rat or the growth-hormone treated dog when the amount of extractable insulin in the pancreas falls to between 10 and 20 per cent of that found in normal animals,<sup>4</sup> the quantity of extractable insulin from the pancreas of nearly all patients who develop diabetes after the age of twenty years ("maturity-onset" diabetes) exceeds that concentration.<sup>5</sup> In accord are the relatively recent observations that almost 90 per cent of patients who develop the diabetic syndrome after the age of forty years respond to the arylsulfonyleureas with a decrease in the blood sugar. Since these agents are hypoglycemic only in the presence of insulin-producing islet tissue, their effectiveness in patients with diabetes reveals that many such patients do produce insulin.

An insufficiency of insulin can result from the excessive activity of some mechanism which prevents the peripheral action of the hormone. All definitive evidence suggests that the known contra-insulin factors such as adrenocorticotropin, somatotropin, corticosteroids and glucagon are not involved in the usual diabetic syndrome. Likewise the presence of inhibitors of insulin in the circulation cannot account for the insulin insufficiency even though they may play a role in the development of insulin resistance. Accordingly, it was proposed that an increase in the rate of destruction of insulin by the extrapancreatic tissues, rather than a decrease in the production of insulin by the pancreas, is responsible for the insulin insufficiency in the majority of patients with diabetes mellitus.<sup>6</sup>

The demonstration that insulin is inactivated and destroyed by homogenates, extracts and slices of liver and other tissues<sup>7, 8</sup> as well as by the intact animal<sup>9</sup> is in accord with the above hypothesis. This destruction of insulin is dependent upon the presence of a heat-

labile system, insulinase, which catalyzes the hydrolysis of insulin and exhibits all the characteristics of an enzyme system with a Michaelis-Menton constant of about  $8.5 \times 10^{-8}$  M/liter and a maximum velocity of degradation of  $2.5 \times 10^{-8}$  M/min.<sup>10, 11</sup> (Molecular weight of insulin assumed = 12,000)

Although the absolute specificity of insulinase cannot be determined until it has been purified to a greater degree than has been accomplished to date, its relative specificity has been demonstrated. Thus the action of insulinase on insulin as well as on synthetic polypeptides differs from that of trypsin, chymotrypsin, carboxypeptidase and other known proteinases and peptidases. Further, fresh liver extracts which are active in catalyzing the hydrolysis of somatotropin, adrenocorticotropin, glucagon, and other proteins as well as insulin, lose their insulinase activity on dialysis, aging, and even relatively mild heating while retaining their capacity to hydrolyze the other proteins.<sup>12</sup> Factors which increase the activity of insulinase in vitro do not influence the systems responsible for the hydrolysis of other proteins by liver extracts. Likewise, the insulinase activity of a relatively pure preparation from pancreatic extracts<sup>13</sup> has been found to differ from the systems responsible for the hydrolysis of other proteins.

Definitive evidence that the activity of insulinase is increased in patients with diabetes mellitus must await the development of methods which will permit the assay of this enzyme in man. Indirect evidence, however, is available in the demonstration that indole-3-acetic acid, which inhibits the action of insulinase in the experimental animal, is effective in reducing the blood sugar of many patients with "maturity onset" diabetes.<sup>14</sup>

The possibility that an increase in the rate of the activity of insulinase with a consequent increase in the destruction of insulin may play a role in the insulin insufficiency of diabetes mellitus in man suggests new approaches to both prophylaxis and treatment.

### REFERENCES

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## Seale Harris

### 1870-1957

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Almost a century has gone by since the War between the States, and one by one the medical leaders who attained eminence during the Reconstruction Era have passed away. Most recent of these was Seale Harris, who died on May 16, 1957, of a cerebral vascular lesion three days after his eighty-seventh birthday. Seale Harris had the distinctive qualities of the great physicians of his period—doctor, teacher, medical investigator and writer. Dr. Harris combined a deep concern for the health needs of each patient with a penetrating insight into the disturbances of disease. He blended what today is called psychosomatic and scientific medicine. He sought always to disseminate knowledge as a teacher and writer. An outstanding internist, he was particularly recognized for his therapy of diabetes mellitus and his discovery of its antithesis—hyperinsulinism.

Dr. Harris did more than treat patients well. He had a deep desire to better medical practice in all its phases. He engaged in a never-ending education of physicians in the fundamentals of physiology and biochemistry. In many talks to the public he advocated the free choice of one's physician to replace company-paid doctors. He strongly emphasized sound nutrition and strongly denounced the use of alcohol. Unshakable in his convictions, Seale Harris promulgated his beliefs forcefully and fearlessly, and lived to see them gain acceptance.

Dr. Harris was proud of his forebears. Descended from sturdy Scotch-Irish planters and soldiers, Seale Harris' father was a country surgeon in northwest Georgia, with a great love for classic literature and music. His mother was valedictorian of her class at college and had a serene and happy disposition. From these parents, whose wealth perished with the ante-

bellum South, came five sons who achieved distinguished careers respectively as the leading educator of Georgia; as Adjutant General of the Army during World War I; as United States Senator from Georgia for three terms; as career officer of the United States Army, and as an eminent physician.

With the financial aid of his elder brothers, and by his earnings carrying the rod for the crew that surveyed the route of the Seaboard Railroad from Rome, Georgia, to Chattanooga, Seale Harris obtained his Bachelor of Arts degree from the University of Georgia and his M.D. from the University of Virginia in 1894. As a medical student, Harris occupied the dormitory room earlier used by Edgar Allen Poe.

After graduation, Harris engaged in general practice with his uncle in Union Springs, Alabama, from 1894 to 1906. There he also served as County Health Officer. In 1897 he married Stella Rainer, daughter of the town's banker. To them were born Josephine Harris Keegan and Seale Harris, Jr. His son who was associated with his father in practice died in 1944 in Australia while in military service.

In the agricultural community of southeastern Alabama, Seale Harris established a reputation for diagnostic and professional acumen. In 1906 he became Professor of the Practice of Medicine of the University of Alabama at Mobile. He prepared for this appointment by a year of postgraduate work at Johns Hopkins University, the Polyclinic Hospital in New York, and various medical centers in France and Germany. Dr. Harris held this Professorship until 1913 when the demands of practice and his duties as Secretary-Treasurer of the Southern Medical Association and Editor of the