

I. Arthur Mirsky

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I. Arthur Mirsky's contributions to the store of human knowledge are recorded in 292 publications that include original papers, abstracts, lectures presented at scientific meetings, and reviews. Although trained as a physician and psychoanalyst, Arthur Mirsky's greatest love was laboratory research in physiology and biochemistry, and he worked at the laboratory bench throughout his professional career. The laboratory was his love, and he turned it into a powerful workshop in which to test critically his own hypotheses as well as those of others. His writings were clear, to the point, critical with data, and honest and straightforward. The design of experiments included adequate controls, accurate observation, and meaningful conclusions. Speculations were clearly separated from experimental facts. Mirsky was a man who moved with the times, and he continually tested new concepts as they became available and related them to his own fields of interest. He remained scientifically young throughout his career and was, as Dr. Grinker showed in his memorial address in Pittsburgh, "a man ahead of his time."

It is impossible to do justice to Mirsky's scientific legacy within the space available, and only two of his numerous contributions to medical science can be highlighted, viz. his early studies in diabetes mellitus and his pioneering investigation of the humoral secretions of the stomach.

His association with Samuel Soskin at the Metabolic Laboratory at Michael Reese Hospital in Chicago stimulated the young man's fertile mind to explore metabolic diseases in general and diabetes mellitus in particular. Arthur Mirsky then maintained an intense interest in diabetes during the rest of his life. He systematically explored the effects of pancreatotomy on the metabolism of carbohydrate, fat, and protein in many species, including the dog, rat,



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owl, duck, and goose. The effects of insulin on intermediary metabolism under a great variety of conditions were defined in a multitude of studies. The diabetogenic action of anterior pituitary extracts was another problem addressed by him. However, it was the observation that certain diabetics who lost their lives in accidents displayed normal island tissue at autopsy that produced Mirsky's concept that the tissues of such patients may exhibit a pathologic capacity to destroy insulin. This led him to investigate the ability of various tissues to inactivate insulin during *in vitro* incubation. In the course of these he observed that incubation of insulin with liver extracts destroyed

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its physiologic activity. The system at work in this process was termed "insulinase." A heat-stable substance, also derived from liver, having the ability to inhibit "insulinase" activity was also recognized and named "insulinase inhibitor." Mirsky then explored the effect of fasting on the "insulinase" content of liver in rats and found it markedly lowered. Feeding of a balanced diet restored "insulinase" activity to normal levels. However, refeeding of fasted rats with a diet high in carbohydrate produced a greater increase in "insulinase" than did the refeeding with a high-fat or balanced stock diet. Hypoglycemic sulfonamides were found to inhibit "insulinase" via a noncompetitive mechanism. In the course of these many investigations and at a time when diabetes was universally viewed as a simple pancreatic deficiency of insulin, Mirsky formulated the innovative concept that "the insulin insufficiency of diabetes mellitus can be due to an increased rate of insulin destruction."

The insulinase-anti-insulinase concept redirected the stream of speculation concerning the origins of diabetes a full 180°. His formulation offered one possible solution to a dilemma, viz. a shortage of insulin effect in a sea of apparent insulin plenty. This was the beginning of subsequent and current views regarding insulin antibodies, instantaneous delays in insulin release as causes of subsequent deficits, counter-regulatory responses to insulin effects, etc.

Arthur Mirsky's work on the etiology of peptic ulcer and his attempts to develop diagnostic tools to pinpoint individuals who may be ulcer-prone make fascinating reading. The first paper on this subject appeared in the *Journal of Clinical Investigation* in 1948 under the title "Uropepsin Excretion by Man. I. The Source, Properties, and Assay of Uropepsin." Based on the earlier observations of Brucke (1946), it had been established by several investigators that human urine contains proteolytic activity with an acid pH optimum. The enzyme responsible was named uropepsin. Mirsky reasoned that since uropepsin is not found in the urine of gastrectomized dogs, gastrectomized cats, and humans or in patients with achylia gastrica of pernicious anemia, "some correlation might be found to exist between gastric activity and the amount of uropepsin in the urine." He developed a reliable procedure for the estimation of uropepsin, delineated certain properties of the enzyme with this technic, and suggested that uropepsin "originates as the result of the peptic activity of the gastric mucosa." Intravenous administration of pepsinogen to dogs resulted in increased uropepsin excretion in the urine,

and this Mirsky interpreted to mean that pepsinogen and uropepsin may be identical. He stated "If the above hypothesis is true, uropepsin may be regarded in the light of an excretion product of an endocrine rather than an exocrine secretion since in this case, the product of glandular activity is being secreted directly into the blood stream rather than into the lumen of a gland. The endocrine activity of the peptic glands may be regarded somewhat analogous to a similar activity of the pancreatic acinar tissue. Although it is true that such cells secrete most of their enzyme products into the pancreatic ducts, some of these products (amylase, lipase) gain access directly into the blood and, in certain conditions, the amounts so absorbed become markedly increased." The concept of an endocrine function of the stomach is thus clearly stated by Mirsky. Several years later such a role of the stomach was firmly established by the studies of Gregory on the antral hormone gastrin.

Mirsky continued with his investigations of the peptic ulcer problem. He observed that the ingestion of food, which raises gastric secretion, has little effect on the uropepsin level in healthy subjects. Similarly, the administration of histamine fails to raise uropepsin levels. A comparison of healthy subjects with peptic ulcer patients indicated that the latter excrete uropepsin at approximately twice the rate of the former. The plasma pepsinogen levels paralleled the levels of uropepsin and were considerably higher in duodenal ulcer patients. Mirsky suggested that high plasma levels of pepsinogen may pinpoint those members of the population who are ulcer-prone. Throughout his studies, Mirsky clearly recognized the complexity of the peptic ulcer problem and published a lucid account of his views in the *Archives of Digestive Diseases* 3:285 (1958) entitled "Physiologic, Psychologic, and Social Determinants in the Etiology of Duodenal Ulcer."

The above-cited studies in diabetes mellitus and in peptic ulcer were intermingled with other published reports that indicate the broad scope of his interests and intellectual abilities. These included data dealing with blood flow, skin, sweat, menses, respiration, and oxidation reduction. He also published findings in various disorders including convulsions, hypertension, hepatitis, cholelithiasis, hyperthyroidism, uremia, malaria, syphilis, rheumatic fever, alcoholism, myasthenia gravis, poliomyelitis, anaphylaxis, and circulatory shock. He became strenuously involved in defining in primates important aspects of conditioning, adaptive behavior, fear,

avoidance, and communication. Yet these lists, despite their length, fail to identify all of the elements in his wide-ranging studies.

As with his scientific contributions, no brief memorial can justly portray the many facets of this man. However, several of them—his perceptiveness, hypersensitivity, love-hate, and loyalty traits—constantly recur in a review of Arthur Mirsky's life.

Mirsky was an extremely perceptive man. His in-born wish for the well-being of his fellow man, sharpened by years of psychoanalytic training and practice, made him acutely aware of inner problems and feelings in others before they were externally manifest and, indeed, before they were recognized by the person himself. He was at his best in identifying the earliest manifestations of reactive depression in colleagues and those about him and discreetly or overtly achieving a resolution of their problems. His tangential and discreet maneuvers took the form of notes, phone calls, requests for reprints, references, or information that he already had, or laudatory comments on a lecture, publication, or election to office. The motivation for such moves was often well-concealed because recognition of the works of his fellow men was an ingrained trait in Mirsky.

His perceptiveness for the inner feelings of others mirrored his own personal hypersensitivity. He was acutely aware of this trait in himself and often cited the mental hygiene approach to seeming or unintentional slights.

Both his loves and his hates were intense. His devotion to a wide circle of professional colleagues and others within his circle of influence stemmed from

love. Genuine hate motivated his rejection of the few. Judging by specific examples, such rejection was rooted in Mirsky's hatred of deceit.

His relationship to his wife, Eleanor, was legendary. He constantly acknowledged by word and behavior his love for and dependence on her. He turned to her in accomplishment and failure, joy and distress, success and defeat. In this relationship she was more than a celebrant and consoler. She served as a modulator, storehouse, and balance wheel of the positive and negative forces of his personal and professional life and released them in judicious proportions to add momentum to or to stay the course of his prodigious drive. The strength and depth of these forces were clearly evident during their entire life together, but never more so than during his prolonged illness.

Loyalty was a two-way street to Mirsky. He was intensely loyal to his colleagues, dean, chancellor, and university, and he expected no less from them. He manifested this loyalty with a protagonistic spirit and was usually the first to fight in behalf of a threatened colleague and demand his or her rights. His loyalty led him to pay homage to the officials both as icons and as persons but did not interfere with his outspoken criticism of any of their actions that violated Mirsky's well-grounded belief of that which is right and proper. He expected—nay, demanded—the same loyalty from them. In his decades at Pittsburgh, Mirsky by forthright and outspoken loyalty resolved enervating dilemmas brought about by inadequate confrontation and by compromise.

The scientific community and mankind are both diminished by his death.