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Hyperinsulinemia: A Merging History with Idiopathic Tinnitus, Vertigo, and Hearing Loss

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Abstract: The history of neurootology and the history of diabetes mellitus have their earliest but separate recognition in ancient Egyptian medicine. Both the polyuric condition resembling diabetes and "humming in the ear" now known as *tinnitus* were described. Yallow's refinement of a radioimmunoassay for insulin demonstrated increased insulin (hyperinsulinemia) in known diabetics. Glucose-insulin tolerances corroborated Yallow's findings. Specific hyperinsulinemia patterns of non-insulin-dependent diabetes mellitus, type II (NIDDM) have been identified. Hyperinsulinemia precedes hyperglycemia. Hyperinsulinemia with normal glucose tolerance is the earliest identifier of NIDDM.

In 1977, Updegraff identified hyperinsulinemia with idiopathic Menière's disease. Sustained clinical response was achieved in all who maintained nutritional management. This finding was the first major impact of hyperinsulinemia in the clinical arena. Subsequently, Updegraff's studies were substantiated by others. As a result, the clinical pathology of hyperinsulinemia has become a major factor in multiple medical disciplines. The hyperinsulinemia associated with idiopathic tinnitus, vertigo, and hearing loss and the hyperinsulinemia of NIDDM, without regard for glycemia status, are one and the same entity. The merging relationship preceded the clinical recognition of both entities. A retrospective relationship to ancient Egyptian medicine and before is considered to be most probable.

Keywords: Hippocrates, hyperglycemia, hyperinsulinemia, in situ diabetes, tinnitus

EARLIEST HISTORY

To gain an appreciation of hyperinsulinemia and its merging relationship with idiopathic neurootology—mainly tinnitus, vertigo, and hearing loss—one must begin with an awareness of the history of neurootology and the history of diabetes mellitus. Both received earliest recognition by the ancient Egyptians, as noted in the Ebers papyrus dating back to the seventeenth dynasty B.C. (1650–1532) [1]. The polyuric states clinically resembling diabetes mellitus and "humming in the ear" now known as *tinnitus* were described [2].

In general, the purpose of the Egyptian papyri was to provide physicians with instructions of methods to be applied in curing disease and in preparing medicine, with no particular emphasis on or discussion of differential diagnosis or etiology. It remained for the ancient Greeks to initiate this gigantic step and to endeavor to establish a theoretical basis for treatment [3].

The first instance of medicine deserving of the adjective *scientific* was seen in ancient Greece and was connected with the name of Hippocrates [3]. The Alexandrian accounts of the life of Hippocrates are rich in detail, noting that he was born in the year 460 B.C., descended from Hercules as well as from Asclepios. He studied medicine and philosophy with famous teachers and traveled over the entire Greek world. He died at an advance age (at dates ranging from 375 to 351 B.C.). His tomb still could be seen in the second century A.D., according to Celsus Cornelius (circa A.D. 30) [3].

A medical writer of renown, Hippocrates was as eminent for his eloquence as for his knowledge. One saying of Hippocrates has achieved universal use. Only a few who quote it today are aware that originally it referred to the art of the physician and was referenced as the first of his aphorisms [4]: "Life is short; and the art is long; the occasion fleeting: experience fallacious, and judgment difficult." The Hippocrates figure as the legendary Father of Medicine soon replaced the histori-

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cal Hippocrates. More than 60 books or manuscripts assumed to originate from Hippocrates' time (i.e., fourth and fifth century B.C.) presumably were compiled in the second century A.D. as *Corpus Hippocraticum* and now go by the name of the *Hippocratic Collection* [3].

Although all writings were attributed to Hippocrates, it is not known definitely whether he was the author of all of them. Nevertheless, the *Hippocratic Collection* is an outstanding compendium of medical science in antiquity and has retained importance up to the present time. According to Feldman [2], tinnitus is mentioned six times, and three different words describe tinnitus. Specific symptoms of diabetes are not identified.

On the subject of physician behavior, the writings are exceptional. The Hippocratic Oath is the known document associated most widely with the name Hippocrates [3]. This famous testament contained both affirmations and prohibitions targeted for the physicians of his time, when abortion and assisted suicide prevailed. The earliest reference to the oath occurs in the first century A.D. Later, it was adapted to Christianity by substituting God, Christ, and the saints for the names of Asclepios and his family [5]:

> **I will neither give a deadly drug to anybody if asked for it, nor will I make a suggestion to this effect. Similarly I will not give a woman an abortive remedy. In purity and holiness I will guard my life and my art.**

Graduating medical students for centuries have stood to swear to the provisions of this oath. Self-evident today in the practice of medicine is the present worldwide need for a continuous renewal of moral and virtuous principles.

Not to be overlooked was the emphasis Hippocrates placed on nutrition. In the oath, he states, **"I will apply dietetic measures for the benefit of the sick according to my ability and judgement."** As an early proponent and innovator of dietetics as a method of treatment, Hippocrates has been credited also as the Father of Dietetics [6].

For many succeeding generations, Hippocrates was the ideal physician. Several hundred years later, Galen, a Roman physician of note, venerated Hippocrates as one "who with purity and holiness lived his life and practiced his art" [5]. Hippocrates was truly a man of virtue.

Another Greek important in the history of medicine is Aristotle (384–322 B.C.), who was the teacher of Alexander the Great, not a practicing physician as was Hippocrates. Aristotle was a philosopher and scientist concerned with problems of anatomy and physiology. He is credited as the innovator of the biological sciences. Aristotle's papers related to tinnitus are limited, but masking of tinnitus by an external acoustic stimulus is, according to Feldmann [2], plainly described and reasonably explained for the first time. Aristotle's writings note no identifiable reference to symptoms credited to diabetes.

Scripts by Aulus Cornelius Celsus (circa A.D. 30) gave detailed insights into the state of the medical arts in the ancient Roman Empire. Although not a physician but a writer, Celsus compiled everything about medicine that was known in his time, which included commentaries regarding tinnitus [7].

Claudius Galenus (Galen; A.D. 125–199), a distinguished physician, noted varying treatments for tinnitus. They included opium and *Mandragora* to dull the sensitivity of the brain so that the tinnitus would be less annoying. Early in his career, Galen was physician to gladiators, an early form of "sports medicine." Later, Galen became the personal physician to Emperor Marcus Aurelius [8]. A contemporary of Galen, Aretaeus of Cappadocia initiated the term *diabetes*, which is an Ionian Greek term meaning "to run through" or "a siphon" [9]. This generic description referred to conditions causing increased urine output. Both Aretaeus and Galen considered diabetes to be a rare disease. Galen employed alternative terms for diabetes, including *diarrhea urinosa* and *dipsakos*, the latter emphasizing the cardinal symptoms of excessive thirst and drinking [9].

RENAISSANCE THROUGH THE EIGHTEENTH CENTURY

The period of the Renaissance through the fifteenth and sixteenth centuries brought about a revolutionary new approach in medical science and a turning away from ancient authorities in all spheres, including the natural sciences and medicine.

In medicine, physicians and scientists began to dissect human bodies. Universities were founded in Europe. Chairs were established in anatomy, physiology, physics, and (later) pathology and chemistry, which became the basic sciences of practical medicine [10].

In 1683, a new approach to the diseases of the ear was highlighted in a monograph by DuVerney (1648–1730), which was devoted entirely to the anatomy, physiology, and diseases of the ear. Some time later (1821), Jean-Marie Itard published his monograph highlighting his clinical experience and marking the beginning of modern otology. Itard's text was the beginning also of audiological medicine [2]. It included the first clear description of external noise deliberately applied to mask tinnitus.

The association of polyuria with a sweet-tasting substance in the urine was first reported in the Sanskrit lit-

erature dating from the fifth and sixth centuries A.D. [11]. Not until the seventeenth century was the sugar content of diabetic urine first demonstrated by Thomas Willis of England [9]. In the eighteenth century, Matthew Dobson, also of England, identified sugar in diabetic serum [9]. This finding was the first evidence that diabetes might be a generalized disorder.

NINETEENTH AND TWENTIETH CENTURIES

In Germany in the early nineteenth century, otology was influenced greatly by Itard. As cited by Shulman [2], the first comprehensive books about otology in this period were written by German authors Martell Frank in Würzburg (1845) and Edward Schmalz in Dresden (1846). The defining of otology as a clinical specialty has its historical origin at the University of Würzburg, where the otoscope using mirror lighting first was developed.

The nineteenth century is termed *the experimental period*, during which science and the practice of medicine gained more than they had during all the previous centuries together. Claude Bernard (France, 1813–1878) demonstrated that glucose was stored as hepatic glycogen. In 1869, while working on his doctoral degree in Berlin, Paul Langerhans (1847–1888) had noted small clusters of cells in teased preparations of pancreas. They were separable from the surrounding exocrine and ductal tissue. Langerhans simply described these structures, without speculation as to their possible function. In 1889, Oskair Minkowski (1858–1931) and Josef Von Mering (1849–1908) in Strasbourg removed the pancreas from a dog to determine whether the organ was essential to life. After the operation, the animal unexpectedly displayed the typical signs of severe diabetes. The dog also was hyperglycemic and glycosuric. This study firmly established the role of the pancreas in causing diabetes [12].

In 1893, Edward Laguesse (1861–1927) suggested that the clumps of cells described by Langerhans be named the *islets of Langerhans* and that they might constitute the endocrine tissue of the pancreas. This concept was continued by Jean de Mayer, a Belgian physician who, in 1909, gave the name *insulin* (Latin *insula*, or "island") to the glucose-lowering hormone, the existence of which at that time still was hypothetical. de Mayer postulated that this hormone was produced by the islet tissues. Various workers isolated active but impure hypoglycemic extracts from the pancreas before the discovery of insulin by Banting et al. in 1921 [12].

The year 1918 is also significant for the establishment of the 100-g, 3-hour glucose tolerance test for diabetes mellitus identification. The insulin work at the University of Toronto was a collaborative effort. Banting initiated the study in the summer of 1921, supervised by Macleod and using Best as a student assistant. Collip joined the team in late 1921 and developed an extraction procedure that yielded more potent and purer preparations suitable for clinical use. The first diabetic patient treated by insulin in January 1922 was a 14-year-old boy, Leonard Thompson [12]. The Nobel Committee awarded Banting and Macleod the 1923 prize in medicine for the discovery of insulin, the prize money being shared equally with Best and Collip.

DISCUSSION

Shulman traced tinnitus from its very first recognition [2]. The early history of diabetes mellitus revealed no relationship per se to neurootology. In 1951, Bornstein's use of bioassay to demonstrate insulin in diabetic patients received little attention [13].

Yallow's refinement of a radioimmunoassay (RIA) for insulin (1960) demonstrated increased insulin (hyperinsulinemia) in known diabetes after a 100-g glucose load [14]. This technology introduced a new analytical chemistry technique to clinical medicine, for which a Nobel prize was awarded to Yallow.

In our laboratories, the RIA of insulin applied to the 100-g glucose tolerance (1972) not only corroborated Yallow's findings of increased insulin (hyperinsulinemia) but identified specific hyperinsulinemia patterns of non-insulin-dependent diabetes mellitus (NIDDM). Our database of more than 16,000 glucose-insulin tolerances statistically has confirmed standards for euinsulinemia, hypoinsulinemia, and hyperinsulinemia [15]. It has confirmed also that hyperinsulinemia precedes hyperglycemia. **Thereby, hyperinsulinemia with normal glucose tolerance is the earliest identification of glucose intolerance** [15]. This condition was identified as *diabetes mellitus in situ* (occult diabetes) [16].

The first major impact of hyperinsulinemia in the clinical arena was in the discipline of neurootology. In 1977, Updegraff [17] identified hyperinsulinemia with idiopathic Menière's disease. The cases were an intermix of normal, impaired, and diabetic (NIDDM) glucose tolerance. **All who had maintained nutritional management compliance experienced sustained clinical response** [18]. Updegraffs studies subsequently were substantiated by others. Mangabeira-Albernaz, Fukuda, Proctor, and Brookler independently identified hyperinsulinemia as the major diagnostic factor in their cases of idiopathic dizziness and tinnitus [18]. The relationship of hyperinsulinemia and subjective idiopathic tinnitus was addressed specifically by Proctor and Proctor [19]. The limited use of RIA technology and the poten-

tial for greater availability of enzymatic immunoassay presents a practical and precise alternative to RIA hyperinsulinemia identification [20]. The clinical pathology of hyperinsulinemia, especially that associated with euglycemic glucose tolerances, has been identified as an etiological factor in essential hypertension, atherosclerosis (mainly coronary artery disease), primordial follicle dysfunction, gestational diabetes, and idiopathic peripheral neuropathy, in addition to the pioneer identification of associated idiopathic tinnitus, vertigo, and hearing loss [15,20].

CONCLUSION

The merging relationship of hyperinsulinemia with idiopathic neurootology—mainly tinnitus, vertigo, and hearing loss—has been established. The first clinical impact of hyperinsulinemia was in the arena of neurootology; this condition has since become a major factor in multiple medical disciplines.

The hyperinsulinemia of NIDDM and the hyperinsulinemia associated with idiopathic neurootology, with-out regard for glycemia status, are the same entity. The merging relationship of hyperinsulinemia and its associated pathology existed before the clinical recognition of tinnitus, vertigo, hearing loss, and diabetes mellitus. Although undetected, a retrospective presence of hyperinsulinemia in ancient Egyptian medicine and before is judged to be most probable.

Solomon, the wisest of men, said it so well in Ecclesiastes 1:10:

> **Is there anything of which it may be said "See, this is new?" It has already been in ancient times before us.**

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