The Concept of Metabolism : A Historical Perspective

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Indian medical science, even from ancient times, had identified the metabolic and genetic basis of diseases. According to Charaka, the great master of Indian Medicine, in his treatise (circa 400BC) "health and disease are not predetermined and life may be prolonged by human effort. The middle path should be the aim of anyone desiring a life in harmony with oneself and with the world outside" (Charaka Samhitha, 8, 3). He observed that *madhumeha* (diabetes mellitus) is produced by the alterations in the metabolism of carbohydrates and fats; and the statement still holds good. "Obesity have many handicaps; shortened life, difficulty in movement, tiredness, body odour, sweating, ravenous hunger and severe thirst. Obesity is the result of over-eating, when the individual takes rich, sweet, fatty food, enjoys sleeping during the day, refrains from mental work or suffers from genetic disorders."(Charaka, 21, 4).

Although the term "metabolism" or an apt equivalent Sanskrit word may not be seen in ancient literature, our forefathers were well aware of the concept. According to Charaka, "As food and drinks are burnt by digestive fire, they give rise to two products; absorptive matter (*aahaara rasa*) and waste matter (*kitta*). The '*aahaara rasa*' in turn gives rise to substances like blood, muscle, fat, bone, marrow etc. When the vital force of organ falls or rises, the corresponding supply of *aahaara rasa* increases or decreases to restore equilibrium. If the healthy body is a product of wholesome food, it follows that ill health must result from unwholesome food" (Charaka Samhitha, Sutra 28, 3-5).

Even before the time of Charaka, during the early Vedic period itself the acharyas had the concept of 'metabolism'. They knew that the food is ultimately converted into parts of the body; and finally excreted. This whole phenomenon was considered to be the function of '*Prana*'. In Bhagavad-Gita (Canto 15, verse 14), Bhagavan Krishna states that "the '*Vaiswanara*' fire abides in the body of beings, and associated with '*Prana*' and '*Apana*', digest the food". The '*Prana*' sustains every attributes of the living body such as strength, health, growth, resistance to illness etc. As long as '*Prana*' flows correctly, a person lives long in good health; when it is weakened, he falls ill; and when it goes out, the person dies. The attributes of '*Prana*' is subdivided into various aspects; they are called '*vaayu*', inappropriately translated as 'winds'. Thus, the fire that digests the food is said to have most important, and its rise and fall determines the level of all other activities. The work of digestion of food is done by '*Udaana vaayu*', and subsequent absorption into blood and transporting the '*aahaara rasa*' into all parts of the body are done by the '*Vyaana*'. It keeps the blood in motion everywhere in the body. Further, '*Samaana*' equalizes, assimilates and converts the '*rasa*' into various '*dhaathus*' (constituents of body organs). Finally the excretion is effected by the '*Apaana vaayu*'. These

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'winds' or more appropriately translated as 'fires' burn constantly and account for the never-ending transformation of '*rasa*' (digested particles) into '*dhaathus*' (constituents of body organs) and finally into impurities.

Later workers have further developed the idea. By 4th century, Charaka reviews and condenses all the previous knowledge in his Samhitha. Thus Charaka writes "Food which supplies nutrients is digested and turned acidic by the digestive fire. In the absence of this process, food cannot be transformed into constituents of organs or their attributes such as strength. The '*Prana*' transports the ingested food to the stomach, where it is broken down by the digestive fire. This is reminiscent of rice grains in a pot being cooked by fire and being turned into soft boiled rice" (Charaka, 15, 3-19). "The food gets digested in the *aamaasaya* (stomach) before reaching all the other parts through *dhamani* (channels)" (Charaka, 2,15).

The essence of food or '*aahaara rasa*' then enters the blood. Charaka continues to state further metabolic process: "The channels of blood originate from the heart and its great vessles" – (Charaka Samhita, 30, 3-14.) "Vessels as *dhamanis* (arteries) pulsate; while *siras* (veins) are non-pulsatile; both act as channels, remain conduits and transport substances swiftly" (Charaka, 5, 3). "When purity of blood is disturbed, many disorders occur". (Charaka, 24, 4-10).

The essence of food that is entering into the blood is then reaching all the tissues. According to Charaka " The '*rasa*' reaching the organs become the '*dhaathus*', such as muscle, fat, bone, marrow and semen. These '*dhaathus*' (constituents) in turn give rise to '*upadhaathus*' (subsidiary constituents). Thus blood becomes blood vessels. Muscle gives rise to fat and skin. Fat in turn changes into ligaments."

Excretion, according to Charaka, is due to the work of '*Apaana*'; and the excretory products are many. Thus the waste from food gives rise to feces and urine; waste from '*rasa*' is phlegm; sweat is the waste originating from fat.

How does red blood evolve from *rasa* which is devoid of red colour? How does blood, which is liquid, give rise to muscle that is solid? These, and many such questions have been raised in those ancient times. According to Charaka, the '*aahaara rasa*', the essence of food, imbibes the red colour of blood from '*pittha*', which has fire like properties. "When blood is worked upon by air (modern oxygen?), water, and fire (modern cellular oxidation?), it becomes constituents of muscle and other '*dhaathus*' of the body." (Charaka Samhitha, 15, 20). When Charaka says that "the essence of food which turns into body constituents, and finally as excrements; all these are resulted from the same process"; he speaks parallel to the concept of metabolic process of the modern medicine. When Charaka adds that "the transformation process in body constituents takes place in gradual but never-ending cycles", we are sure that he is very near to the "metabolic cycles" of modern times.

Charaka was very much aware of the inborn metabolic diseases.

"Diseases are of three types; Inborn, Exogenous and Psychological...." "The child is the product of the Mother, Father, Self and Nutrition" (Charaka Samhitha, 3, 1). "Fetal anomalies are resulted from disorders of the mother, father or environment" (Charaka, 4, 27-31). "The proper management of pregnancy is no less precarious than carrying a cup filled to the brim without spilling the oil" (Charaka, 8, 14).

Coming to more recent times, the earliest treatises in biochemistry, the "Book of Organic Chemistry and its Applications to Physiology and Pathology", published in 1842 by Justus von Liebig (1803-73), who introduced the concept of metabolism. The term "Biochemistry" was coined by Neuberg in 1903 from Greek words, bios (life) and chymos (juice).

In the Western literature, the first controlled experiments in human metabolism were published by Santorio Santorio (1561- 1633). He received his medical degree at the age of 21. His great achievement was the introduction of quantitative experimentation into biological science. In 1611 he was appointed to the chair of theoretical medicine at the University of Padua. He continued to teach there until his retirement in 1624. Santorio spent the remainder of his life in Venice. In his book *Ars de statica medecina* (Concerning Static Medicine) (1614), he describes a series of experiments in which he weighed himself in a chair suspended from a steel balance, before and after eating, sleeping, working, fasting, and excreting. For thirty years, Santorio slept, ate and worked, in the weighing contraption. His work was a radical break with traditional medical theory. While the central metaphor of Aristotelian natural philosophy and Galenic medicine had been organic (elements and qualities), Santorio made it mathematical (number, position and form). Santorio inspired later researchers in metabolism.

In the early 1800's the belief prevailed that the composition of the human body and indeed, of all living things, was a result of a 'vital force' and it is impossible to experimentally synthesize constituent compounds of the human body. Friedrich Woehler (1800-1882) born in Frankfort, was a student of Berzelius. In attempting to prepare ammonium cyanate from silver cyanide and ammonium chloride, he synthesized urea in 1828. He sent a note to Berzelius "I can prepare urea without requiring a kidney of an animal, either man or dog". This was the first organic synthesis, which shattered the vitalism theory. This was a true 'paradigm shift' and led to revised thinking on what chemists could accomplish with regards to 'organic' compounds.

The first human metabolism study was performed in 1841 by Alexander Ure, who observed the conversion of benzoic acid to hippuric acid. W.Keller, in Woehler's laboratory provided the confirmation of Ure's experiments. In Keller's words: "In the evening, I ingested 2 grams of benzoic acid in a sugar syrup. During the night I started sweating, which could be an effect of this acid. I experienced no other obvious effect. In the urine eliminated the next morning was found to be unusually acidic. After the residue was mixed with hydrochloric acid and allowed to stand, a large amount of long prismatic brown crystals was formed, which did look like benzoic acid. Another portion, which had been concentrated to a syrupy thickness, formed a magma of crystalline plates after being mixed with hydrochloric acid. Long, colorless prismatic crystals were then isolated. These crystals consisted of pure hippuric acid."

The postulated oxidation of cinnamic acid to benzoic acid was confirmed by Woehler and Frerichs in dogs where they isolated hippuric acid in the urine after administration of cinnamic acid. When these authors administered benzaldehyde to dogs and rabbits they also were able to isolate hippuric acid in the urine.

In the early part of the 20th century, numerous studies of human basal metabolism were conducted at the Nutrition Laboratory of the Carnegie Institution of Washington in Boston, under the direction of Francis G. Benedict. Prediction equations for basal energy expenditure (BEE) were developed from these studies. The Harris-Benedict equations remain the most common method for calculating BEE for clinical and research purposes.

Maupertuis described in 1752 an autosomal dominant postaxial polydactyly in four generations of one family. This may be the first case report of an inherited genetic disorder. In 1814, Joseph Adams published "A Treatise on the Supposed Hereditary Properties of Diseases". Adams recognized the difference between autosomal recessive and autosomal dominant conditions (although he did not use this terminology). He also recognized that hereditary diseases can

express later in life; that some hereditary diseases require an environmental exposure in order to be expressed; and that the reproductive fitness of individuals with hereditary disease is diminished. In 1866, Gregor Mendel published "Experiments in Plant-Hybridization," which proposed the principles of heredity and introduced the concept of dominant and recessive genes to explain how a characteristic can be repressed in one generation, but appear in the next. Today, he is widely considered the founding father of modern genetics.

Inherited biochemical disorders were first described in 1902 by Sir Archibald E. Garrod (1857-1936) in his landmark paper "The incidence of alkaptonuria: a study in chemical individuality", published in Lancet (ii, 1616-1620, 1902). Garrod reported that patients complain that their underwears are getting blackened. He concluded that the disease is inherited and it is due to the deficiency of the enzyme required for further metabolism of homogentisic acid. Garrod later learnt of Mendel's work, and this led him to describe alkaptonuria and several additional disorders in his book "Inborn Errors of Metabolism", published by Oxford University Press in 1909. He coined the term "Inborn Errors of Metabolism". Due to this work, Garrod is now considered the founder of biochemical genetics. The famous 'Garrod's tetrads is Alkaptonuria, Albinism, Pentosuria and Cystinuria.

Otto Conrad von Gierke (1877-1945) received his medical doctorate at Heidelberg in 1901. He reported the case of the association of liver enlargement and disturbed glycogen metabolism in 1929. Simon van Creveld gave further details of the same disorder in 1932. According to some authors, the disease that carries von Gierke's name is not the one that he described in 1929 and, von Gierke's patient probably had a deficiency of the glycogen debranching enzyme. In 1929, Richard Schönheimer studied a patient with hepatomegaly due to massive glycogen storage and suggested that this disorder may be due to an enzyme deficiency. In 1952 Cori and Cori found glucose-6-phosphatase to be deficient in 'von Gierke disease' (glycogen storage disease type I). This observation marks the first time that an inborn error of metabolism was attributed to a specific enzyme deficiency.

In 1934 Norwegian physician Ivar Asbjorn Folling reported a few cases of Phenylketonuria. He noticed that hyperphenylalaninemia was associated with mental retardation. In Norway this disorder is still known as Følling's disease. Dr. Følling was one of the first physicians to apply detailed chemical analysis to the study of disease. His careful analysis of the urine of two retarded siblings led him to request many physicians near Oslo to test the urine of other retarded patients. This led to the discovery of the same substance that he had found in eight other patients. He discovered that the substance in urine is phenyl pyruvic acid. The development of a treatment strategy for phenylketonuria in the early 1950s by the provision of a phenylalanine low diet was another hallmark in the history of metabolism and biochemical genetics. Robert Guthrie (1916-1995) developed a cost-effective screening method for phenylketonuria in 1961, using small blood spots dried on filter paper collected from newborns.

Philippe Gaucher described the disease in his doctoral thesis in 1882. Brady et al elucidated the biochemical basis for the disease in 1965.

Michael Lesch was a medical student at Johns Hopkins Hospital, where pediatrician William Leo Nyhan was a faculty member. These two identified Lesch-Nyhan Syndrome and its associated hyperuricemia in two affected brothers (aged four and eight), and published their findings. After the initial description of the syndrome in their 1964 paper, it took only three years until the metabolic cause was identified by Seegmiller *et al*.

Homocystinuria, first described in 1962, is the latest identified inborn error of metabolism. It was discovered independently by Gerritsen in Madison, Wisconsin, and by Carson and Neill in Belfast, Northern Ireland. The patients of both groups were studied because of mental retardation.

Following this, several groups around the globe have taken to bench work in the research of Inborn Metabolic Disorders (IMD's). The discovery of defective enzymes/proteins/ metabolites has been fuelled with the discovery of several separation techniques contemporarily. The Human Genome project has contributed to it too.

With the advent of molecular biology techniques, defective genes have been identified. Most IMD's being single gene disorders have been voted the best candidates for gene therapy. Several mutations characteristic of a given ethnic population, geographical region or individuals have been typed and it has been proposed the mutations define degree of response to cofactor therapy (Eg. PHA gene). Our understanding of the human genome and protein complement has led us to the era of genomics and proteomics and thus the study of metabolism has been now termed as "Metabolomics", the future of metabolism studies.