REVIEW OF LITERATURE

Diabetes was known to mankind from prehistoric times. As such , literature on it is very extensive and consisted of studies encompassing many fields of science. In the following review only a brief account of the works relevant to the present study have been presented. The review is not claimed to be exhaustive.

Diabetes was described by Charaka and Sushruta (**22**) more than 2000 years ago. For the past 200 years, it has featured in the history of modern medicine. Since the discovery of insulin, work on diabetes at both cellular and clinical levels have expanded fast.

The struggle for recognition of the role of pancreas in diabetes was long and arduous. The fascinating, tortuous road to this discovery involved a host of clinicians, chemists, physiologists and pathologists. The tale is filled with marvellous insights as well as egregious errors, serendipity and futile labours, triumphs and defeat.

The following masterly description of several clinical diabetes by Aretaeus of Cappadocia (about 150 A.D.) represents the sum many of our knowledge up until the second half of the seventeenth century -- "Diabetes is a remarkable disorder, and

not very common to man. It consists of a moist and cold wasting of the flesh and limbs into urine, from a cause similar to that of dropsy; the secretion passes in the usual way, by the kidneys and the bladder. The patients never cease making water, but the discharge is as incessant as a sluice let off. This disease is chronic in character, and is slowly endangered, though the patient does not survive long when it is completely established for the marasmus produced is rapid and death is speedy".

In 1674, Thomas Willis confirmed (by testing) that the urine of diabetic persons was sweet . This was actually a rediscovery, for an ancient Hindu document by Sushruta in India about 400 B.C. , has described the diabetic syndrome as characterised by a "honeyed urine". It was Mathew Dobson of Manchester - England, who in 1776 demonstrated that diabetics actually excrete sugar in the urine.

Cawley (**23**) reported in 1788 (without particular comment) that he observed a shrivelled pancreas with stones in a diabetic patient at autopsy . This may have been the first published reference to the pancreas in relation to human diabetes, but no deductions were drawn as to aetiology.

In France, Claude Bernard (**15**) was, of course, aware of the findings and speculations regarding the possible role of the pancreas in diabetes . In 1869, Paul Langerhans published a short paper on pancreatic histology in which he described a previously unknown cell type in the gland. Langerhans could assign no particular function to these cells . The paper disappeared, without ado into the literature until the 1890s. Between 1895 to 1921 experimental work developed in two directions. One was careful histology study of the islets , the other was a search for insulin itself.

In 1910, Jean de Mayer suggested that the pancreatic secretion that was lacking in the diabetic state should, when found, be called " insulin" to denote its origin from the "insulae" of Langerhans.

Frederick Banting and Charles Best (**8**) , succeeded in fulfilling all the criteria for a therapeutically active insulin and they applied for the first time the pancreatic extracts preparation for the treatment of human diabetes (**9, 10**).

The development of the radioimmunoassy for insulin in 1960 led to important insights about insulin secretion and helped to clarify some of the differences between

IDDM and NIDDM. The insulin gene was cloned in 1977 making human insulin available for clinical use.

Heterogeneity in the presentation of patients with diabetes has been recognised by Charaka and Sushruta for more than 2000 years ago **(20).** In its classic form, two common types have been recognised , the Type I or insulin dependent diabetes (IDDM),formerly called juvenile onset diabetes and the Type II or non-insulin dependent diabetes (NIDDM) ,formerly called maturity onset diabetes. These types differ in both clinical presentation and presumed aetiology **(126).** Both the forms may exist in the same family and persons irrespective of their type are subjected to long term complications albeit with somewhat different frequency.

Diabetes mellitus may be suspected or recognised clinically by the presence of characteristic symptoms such as excessive thirst, polyuria, pruritus, otherwise unexplained weight loss, or one or more of the many complications associated with or attributable to the disease. The disease represents a heterogeneous group of disorders, some of which can be characterised in terms of specific aetiology and or pathogenesis. In many cases, however, such specific pathogenic characterisation is not possible.

The disease as a syndrome rather than a single disease was recognised by Bouchardat (**18**). In 1936, Himsworth characterised diabetes as an "insulin sensitive" or "insulin resistant" syndrome which includes a group of disorders differing in their clinical features, biochemistry and causes (**57**). Lawrence RD 1951 ; further identified two main classes of diabetic patients, those who were insulin-deficient and those who were not ; he further distinguished secondary forms due to primary pancreatic destruction and disorders of fat storage (**85**). Lawrence's classification was supported by Harris , who suggested that insulin deficient types tended to run separately in families and may be due to separate genetic influences (**52**). Hugh-Jones , distinguished Type I and Type II diabetes by clinical criteria (**59**).

In I976, the late Andrew Gudrew recognised that diabetes is a clinically heterogeneous disorder and suggested discarding the rigid terms "Juvenile-onset" and "maturity-onset" in favour of " Type 1" and " Type 2" diabetes respectively (**28,29**). He justified the classification by pointing out that insulin dependent (Type I) patients were distinguished by the then recently established HLA associations (**29**) and by the occurrence of islet-cell antibodies, implying a specific aetiology (**17**) which supported Cudworths classification. By 1978, the frequent association of

insulin dependent diabetes mellitus (IDDM) with certain HLA antigens and islet-cell antibodies was widely recognised.

The National Diabetes Data Group **(95)** in the USA published a provisional consensus classification in 1979, which became the basis for that recommended by the World Health Organisation (WHO) Expert Committee on Diabetes in 1980.

The WHO classification represented a landmark by providing standardised diagnostic criteria for diabetes and a uniform terminology suitable for clinical and epidemiological research, which have now been widely adopted **(3, 153)**.

Important progress has also been made in understanding NIDDM **(92)**. Although there has been interesting debate about the relative roles of insulin resistance and insulin deficiency, there is now general agreement that both are important. Furthermore, consequences of the possible substantial effect of genetic factors **(97, 98, 99)** to the development of NIDDM has been suggested by the finding of a concordance rate of about 90 percent in identical twins. The specific genetic basis for most cases of NIDDM is not yet known, but search for the contributing genes has become very intense.

There have been great advances in the understanding of the pathogenesis and genetics **(118,123)** of IDDM. The finding of strong genetic linkage to the major histocompatibility antigens has provided important insight into the genetic basis of IDDM. Some potentially useful linkage markers in HLA, for IDDM, have recently been identified **(44, 86, 91, 104, 105, 129, 138, 142).**

EPIDEMIOLOGY

Any hypothesis put forward regarding the aetiology of IDDM must account for the characteristics of its distribution in human populations. The accumulated data on the incidence of IDDM during the last 20 years demonstrate that IDDM occurs in most human groups and that the risk is the highest **(107)** among populations of European origin (PEO). While these differences among populations may be determined in part by genes, the range of variation within the PEO is almost as great as the range among populations **(37,143)** . Prevalence rates are slightly higher in several countries in Northern Europe but significantly lower from Sweden and Finland **(107)** . In India, epidemiological data on IDDM in an urban area of South India is 0.26 / 1000 **(1, 114) .**

In contrast to IDDM, incidence data on NIDDM are scarce, and thus we depend on prevalence data as estimates of cumulative incidence to describe the occurrence of NIDDM in human populations.

The prevalence of NIDDM was 7.7 percent among some populations in Europe and 11.1 percent among populations of African origin (**53**) settled in USA. The prevalence in Hispanic minorities was even higher but did not approach that among Pima Indians of Arizona (**75**).

The prevalence of NIDDM in PEO is rather low compared with the prevalence in American populations (**53**) . In several populations in Europe, the combined prevalence of diagnosed and undiagnosed diabetes is less than half that in American populations even through less stringent diagnostic criteria (WHO) were used. The prevalence in Saudi Arabia was similar to that in the United States (**53**) , while in Central Asia the prevalence among men is quite similar to that in European men surveyed at a slightly younger age. The substantial difference in the occurrence of diabetes among PEO, particularly between those in Europe and North America, points to an environmental component in the development of diabetes. Moreover, an important role of environment in the development of NIDDM in Asian populations

is suggested by data on the Chinese living outside Asia (**26,39**) . The prevalence of NIDDM is high (20.8 percent) among Chinese living on the Island of Mauritius in the Indian Ocean (**39**) . The NIDDM is more common and the prevalence being high in the migrant Japanese living in Hawii - USA than in those living in Hirosima - Japan (**50, 65**) .

The epidemiology of non-insulin dependent diabetes mellitus (NIDDM) has provided a lot of valuable information on several aspects of the disease, which include the natural history, prevalence, incidence, morbidity and mortality in several populations around the world (**67, 113, 115, 139, 152, 159**) .

There is a need to obtain epidemiological data on the prevalence of diabetes in the Indian subcontinent, to study magnitude of the problem due to its wide geographic variations. Hence, the data published on PEO and Asian migrant populations are not directly comparable to those from Indian populations (**1, 39, 58, 60, 65, 66, 67, 83, 75, 113,114, 115, 116, 158, 159**) .

There are some interesting data showing high prevalence of diabetes in migrant Asians, Japanese and Chinese population settled in different countries (**16, 39,**

87,131). The data from epidemiological studies are lacking on Indian populations until the early seventies. Even those studies that were published during the early seventies had adopted a non - standardised method, based on questionnaires to obtain data and the acceptability of those data are open to question **(147) .**

The overall prevalence of diabetes when adjusted to the age distribution of the Indians living in Southall - London and Fiji are 10 percent and 9 percent **(87).** The age adjusted prevalence of diabetes was 8.2 percent in the urban and 2.4 percent in the rural population in Madras - India , highlighted the urban / rural difference in the prevalence rate and further substantiated the high prevalence rate in urban India **(1, 58, 60, 113, 114, 147, 150) .** In eastern India, more so in West Bengal, extreme paucity of data is noticeable.

GENETIC MARKER ASSOCIATION

The search for genetic marker associations has a long history in human genetics. These studies examine the frequency of polymorphic traits, such as blood group antigens and blood proteins, in individuals with and without a given disease. The occurrence of disease and particular marker type in the same person, more often than expected by chance, is called association. The association can be caused by a number

of mechanisms including (1) Pleiotropic action of a gene, that is, the multiple effects of a single gene; (2) Epistatic interaction in which penetrance is suppressed as a result of one non-allelic gene having an influence on another; (3) Gene selection, as in the case of resistance to malaria in certain areas of the Mediterranean ; (4) Linkage disequilibrium or non-random association of genes arising from one of two causes: (a) either two populations, homozygous or having very different frequencies for different haplotypes have mixed relatively recently such that subsequent recombination has not been sufficient to lead to a random distribution of the alleles, or (b) certain combinations of alleles at closely linked loci (i.e. haplotypes) are selectively advantageous for their bearers and have therefore been preserved in high frequency by epistasis.

Linkage refers to the physical position of two or more loci on a chromosome and has frequently been confused with association. Genes are said to be linked when they are located on the same chromosome and do not assort independently in families. The closer the loci, the tighter the linkage which results in fewer recombination events. Linked genes need not be related to the same physiological process. Linkage between a gene for a disease and another gene does not imply any causal relationship, but segregation of a disease consistent with linkage to a known genetic marker is good

evidence that the disease in question has a genetic component. Association usually implies that there is some relationship between the two factors, but does not imply linkage. Similarly, closely linked genes associated because of lack of recombination will cause any linkage induced associations to dissipate over time **(11, 13, 22, 41,48, 52, 69, 70, 71, 88, 101, 123, 128,133, 137, 138, 142, 150).**

In the early 1970s, certain HLA antigens **(100)** determined by serologic typing methods were shown to be positively associated with IDDM but not with NIDDM. A review of the investigation of HLA and IDDM has been presented **(137)** . In all the populations studied, IDDM has been confirmed largely to occur in individuals who carry HLA -DR3 and / or HLA -DR4. Although the risk of IDDM is profoundly influenced by HLA - DR antigens, only a small percentage of individuals carrying HLA -DR3 and / or HLA -DR4 ever develop IDDM. A variation of this hypothesis is that IDDM susceptibility is determined by more than one locus in the HLA region, e.g., DR and the closely linked DQ locus. The HLA - linked gene that conveys susceptibility to IDDM might not be distinguishable by the available serologic methods. Application of nucleotide sequence polymorphism by means of polymerase chain reaction (PCR) amplification and oligo-nucleotide probes, has identified specific DE - 4 haplotypes defined by DQB1 alleles that are strongly associated

with IDDM **(44)**. So far, it has not been possible to subdivide DR -3 haplotypes. In addition, certain DQ -B1 alleles have been found to confer protection against IDDM **(6)**.

Thus, possibility of other genetic non -HLA or non-genetic factors are involved in determining who will and who have a susceptible HLA type . There have been great advances in the understanding of the pathogenesis of IDDM in western countries. The finding of a strong genetic linkage to the major histocompatibility antigens has provided important insight into the genetic basis of IDDM. Some potentially useful linkage marker for diabetes have been identified **(43, 86, 104, 128, 129, 142)**.

These HLA -DR associations are not the same throughout the world. In south India, although there is an increased prevalence of either DR 3 or DR 4 in IDDM patients, there is no additional susceptibility in those with both DR3 and DR 4 **(100, 128, 129, 137, 138)**.

The whole genome linkage analysis of type 1 (IDDM) diabetes using affected sib pair families and semi-automated genotyping and data capture procedures has shown that type 1 (IDDM) diabetes is inherited. A major proportion of clustering of the

disease in families can be accounted for by sharing of alleles at susceptibility loci in the major histocompatibility complex (MHC) on chromosome 6 for IDDM 1 and at a minimum of 11 other loci on nine chromosomes. Primary aetiological components of IDDM 1, the HLA -DQB1 and - DRB1 class II immune response genes, and of IDDM 2, the minisatellite repeat sequence in the 5' regulatory region of the insulin gene on chromosome 11 p 15, have been identified **(142).**

Susceptibility to autoimmune insulin-dependent (type 1) diabetes mellitus is determined by a combination of environmental and genetic factors, which include variation in MHC genes on chromosome 6 p 21 (IDDM 1) and the insulin gene in chromosome 11 p 15 (IDDM 2). Linkage to IDDM 1 and IDDM 2 cannot explain the clustering of type 1 diabetes (IDDM) in families **(101).**

In Asian Indian, HLA -DRB1, DQA1 and DQB1 allelic association was found in IDDM patients **(90, 138).**

A cluster of genes important in glycide metabolism **(135)** which include phosphoglucomutase (PGM_1), glucose dehydrogenase (GDH), 6-phosphogluconate dehydrogenase (PGD), UDP-galactose-4-epimerase (GALE),and glucose transport

protein - GLUT-1, **(64)** ; is located in the short arm of chromosome 1 near Rh locus **(89,151)** . This gene proximity suggests that the association with diabetes may be due to the action of genes located near the Rh locus and are linkage disequilibrium with it. Therefore, this area of the chromosome 1 appears to be a promising candidate for clarifying the genetic basis of heterogeneity of diabetes and its clinical variability **(86)** . Therefore, this gene proximity appears to be a promising candidate for clarifying the genetic basis of heterogeneity of diabetes in Indian context **(86)** .

Another genetic marker - known as Glyoxalase I (**54, 69, 77, 79, 90, 106, 109**) is situated on the human chromosome 6. There is a close linkage between loci for GLO and the human major histocompatibility gene complex (HLA). Hence, the genetic marker - GLO I appears to be a promising candidate for clarifying the genetic basis of heterogeneity of diabetes and its clinical variability **(12, 13, 22, 30, 31, 88, 103)** .

Several genes have been suggested as markers for NIDDM but to date , apart from evidence for association in the adenosine deaminase **(11)** and glucokinase **(48)** in some families affected by maturity-onset diabetes of young, no other consistent association has yet been found.

The choice of genetic marker selection for association study in diabetes requires special consideration with respect to study populations and their backgrounds **(127).** In the present study the biochemical genetic markers chosen for association, are Phosphoglucomutase (PGM_1) on chromosome 1 and Glyoxalase - GLO I marker on the chromosome 6 of human, both appear to be promising candidate for clarifying the genetic basis of heterogeneity of diabetes in Indian scenario.

COMPLICATIONS IN DIABETES

The complications that occur commonly in diabetes include retinopathy, nephropathy and neuropathy. Patients with all forms of diabetes for sufficient duration, including insulin dependent diabetes mellitus (IDDM) and non insulin dependent diabetes mellitus (NIDDM), are vulnerable to these complications, which cause serious morbidity **(2, 19, 21, 32, 40, 61, 63, 93, 94, 96, 108, 112, 117, 121, 120, 125, 144, 145, 146, 148, 149, 155).**

RETINOPATHY

The Wisconsin epidemiologiy study of diabetes retinopathy , have defined the natural history **(111)** of retinopathy in IDDM and NIDDM by stereoscopic fundus photography **(154)** . As with all diabetic - specific complications, the development of retinopathy depends on the duration of the disease **(2 , 47, 51, 71, 72, 73, 82, 94, 110, 111, 112, 117, 121, 141, 157)** . Micro aneurysms, dot and blot hemorrhages and hard exudates are described as "background" retinopathy or, preferable, nonproliferative retinopathy. With increasing severe retinopathy, these abnormal vessels can become occluded, leading to retinal ischaemia with infarctions in the nerve layer of the retina, seen as soft or "cotton wool" exudates (pre - proliferative retinopathy). Proliferative retinopathy is clinically divided into neovascularisation of the disc and elsewhere, on the basis of the differential risk for loss of vision associated **(2, 34, 51, 83, 96, 121, 141).** As noted, no studies have unequivocally demonstrated a salutary effect of intensive therapy on diabetes retinopathy.

NEPHROPATHY

Although intensive therapy of diabetes may decrease the rate of progression from microalbuminuria to overt proteinuria, the ultimate effect on the development of end-stage renal disease (ESRD) is unknown **(33, 46, 93, 119,124) .** Intensive diabetes therapy does not appear to affect the progression of nephropathy in its later stages **(148).** The majority of intervention studies have been of short duration. No intervention has been demonstrated to halt the progression of the disease as such **(19, 36, 49, 61, 125, 144) .**

NEUROPATHY

Intensive therapy, to a limited degree, helps the slowing of nerve conduction and other electro-physiologic abnormalities associated with diabetes **(21, 40, 49, 108, 130, 132, 149, 155) .** The clinical improvement in nerve function, such as sensory function, or in painful neuropathy has been moderate at best **(4, 7, 84) .**

MANAGEMENT

There is no doubt that diabetes affects several aspects of life and ideally requires the patients to make several changes. It affects all aspects - diet, life style, physical well-being , mental state, economic condition, sexual and marital life. Hence arose the concept of diabetic education for prevention (**56, 62**) . The methodologically appropriate studies (**45, 78, 122**) demonstrated that, in itself diabetic patient education did not improve diabetes management. There are some reports that demonstrated better management with improvement in the health care delivery system (**140**) . Diabetic education becomes useful only when self glucose monitoring skills are imparted with it (**5, 140**) . Satisfactory diabetic control was achieved through care and control (**25**) . The St.Vincent declaration is an important document with the aim of improving both the clinical care as well as the social conditions of the diabetes population in Europe (80) . The Diabetes control and complication trial and United Kingdom prospective diabetes study groups are well designed study for a good metabolic control, showing of various treatment modalities and management of co-morbid conditions (24) .

Diabetes mellitus is accompanied by characteristic long term complication **(102,136).** The nature and extent of these complications are universal in occurrence, commonly include retinopathy, nephropathy and neuropathy. Diabetes of sufficient duration are vulnerable to these complications, which cause serious morbidity. In West Bengal, sufficient data on the progression of the disease are sadly lacking.

In India, at present there is very little information on epidemiology, genetics, long term complications and management ; except some sporadic reports **(1, 29, 30, 60, 81, 113, 115, 116, 134, 138, 150) .**

As is clear from the foregoing literature survey, there is a severe lack of appropriate data as far as India (particularly West Bengal) is concerned. So, meticulous endeavour for proper and comprehensive understanding of the disease process in this State - West Bengal, is felt necessary.

In view of the above mentioned review, there seems to be little doubt as to the profound usefulness of probing into some aspects of diabetes in West Bengal, India.