WORLDWIDE AND LOCAL EPIDEMIOLOGY OF DIABETES MELLITUS

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Diabetes mellitus is a disorder of metabolism characterised by hyperglycaemia due to deficiency or diminished effectiveness of insulin. The disease is a chronic one affecting carbohydrate, protein, fat, water and electrolyte metabolism. In its fully developed form it is characterised by fasting hyperglycaemia, atherosclerosis, microangiopathy and neuropathy. Hyperglycaemia may become manifest years before the clinical recognition of vascular disease or neuropathy.

The great majority of investigators now agree that diabetes mellitus (DM) may present clinically in a mild or asymetric form without a fasting hyperglycaemia; and that this is the most recognisable form of the disease. The typical vascular and neuropathic manifestations of DM may occur in patients with relatively mild carbohydrate intolerance and with normal fasting blood glucose levels.

DM is the most common of the endocrine disorders. Only a rough estimate as regards its incidence which varies from place to place can be made. When a population survey is conducted, previously undiagnosed cases are discovered and they are approximately as numerous as known cases. Most of the undiagnosed cases are discover among the older age group, ie. over 50 years. Undiagnosed diabetics often admit to symptoms which they may have endured for considerable periods without consulting a doctor. In some, however, there are no symptoms.

DM is commoner in middle and late life than in the younger ages; thus although the overall prevalance of known cases is about 1 in 200, the proportion is much lower in children and much higher in older persons.

Glycosuria in a population is more common than the disease entity. Glycosuria is frequent if urine samples are collected after a meal, or still more relevant after taking an oral glucose load of 50g. Using Clinistix, glycosuria may be detected in approximately 6% of males and 3% of females. It is slightly commoner in old people.

The significance of glycosuria varies greatly with age. In the young it is usually due to a low renal threshold for glucose and not due to hyperglycaemia. For glycosuric patients in their twenties, less than 10% have diabetes mellitus. In the old, however, glycosuria is usually significant and particularly in females indicates diabetes mellitus.

When population screening includes blood sugar estimations, problems in interpretation are again encountered due to a general variation of blood sugar values with age. After the age of 60 years, it may be difficult to decide what is diabetic and what is normal. The mean blood glucose value 1 hour after the ingestion of 50g glucose, rises by approximately 1 mg per 100 mls blood for each year of age. The 2-hour value for women aged over 70 years is just approximately 120 mg per 100 mls, a figure which is often taken as the dividing point between DM and normality. Hence, it is important to remember that although values above 120 mg per 100 mls are considered in the diabetic range, this value is only an arbitrary one.

It has been found that apparenly minor abnormalities of glucose tolerance are common but it is impossible to predict the course of events in an individual whose Glucose Tolerance Test (GTT) is mildly abnormal. In fact in a retrospective study of borderline cases it was shown that some patients with a mildly abnormal GTT may progress to frank DM whilst others may remain static or even regress (Schliak, V. et al 1975). In view of this observation, it is probably wise to regard a person with a mildly abnormal GTT as having an increased risk of developing frank DM and therefore needing periodic retesting, while remembering that there may be improvement or no further deterioration.

Diabetes mellitus has a multifactorial aetiology, on the basis of which two main types of diabetes are recognised:

1. PRIMARY or IDIOPATHIC DM includes the great majority of cases (99%). Unlike the secondary group, this is a treatable but not curable condition.
   a) Juvenile onset DM usually develops in the first 40 years of life in patients of normal or subnormal weight. Administration of insulin is necessary for their survival, hence the term insulin dependant DM.

b) Adult or maturity onset DM usually appears in middle aged or elderly patients who are often obese, and in whom hyperglycaemia can usually be controlled by dietary means alone or supplemented by oral hypoglycaemic compounds.

2. SECONDARY DM includes only a minority of cases which are a result of recognisable pathological process process or secondary to the treatment of some condition.

a) Those due to demonstrable pancreatic disease, where the pathological process causes the destruction of the pancreas and leads to impaired secretion and release of insulin. This group includes conditions such as pancreatitis, haemochromatosis, pancreatectomy and rarely tumours.

b) DM may also occur in relation to other endocrine disorders with abnormal concentrations of hormones which are insulin antagonists. Examples include growth hormone (acromegaly); adrenocortical hormones (Cushing's); adrenaline (phaeochromocytoma) and thyroid hormones (hyperthyroidism).

c) Drugs which block any step in the metabolism of insulin such as Alloxan and Streptozotocin; and those which block its secretion including thiazide diuretics, diphenyl hydratin and L-asparaquinase may be a cause of DM. Peripheral insulin antagonism occurs with glucocorticoids and ovulatory suppresant drugs.

d) DM can also be related to non-endocrine disease, particularly liver disease such as cirrhosis and hepatitis.

GEOGRAPHICAL AND RACIAL VARIATIONS (Pyke, D.A. 1969): Prevalance of DM is not known with certainty. Differences in testing procedures and criteria used to establish DM have led to variations in reported results. Nevertheless, crude estimations of prevalence can be made on different population samples by measurements of blood sugar levels, by interview, or by medical history.

DM occurs everywhere, no nation or race is immune, but in some it is rare. The total number of cases in Britain, diagnosed and undiagnosed, stands at roughly 6% with the highest incidence being in the seventh to eight decade of life.

Among the Eskimos of Alaska and Greenland, DM is very uncommon, and when it does occur it is mild. Insulin requiring diabetes is almost unknown.

In North American Indians there are wide differences. Among a tribe which lives in Alaska, DM as in the Eskimos is rare. However, it seems that among tribes in USA it is unusually common. Among the Pima Indians of Arizona, half of those over 30 years have blood glucose levels suggestive of DM. This tribe is notably obese and their diet is heavy with carbohydrate and fat. However, this does not wholly explain their remarkable frequency of DM. It seems to be due, at least in part, to a resistance to insulin, rather than a lack of it. Moreover the DM is clinically mild. Marriage outside the tribe seems to be too common for inheritance alone to account for the increased prevalance.

A high incidence of abnormal glucose tolerance has also been described in the Cherokee Indians of North Carolina.

There are also racial differences in the diabetes prevalance. In the West Indies, where the disease is common, DM seems to be twice as common in those of Indian descent as in negroes. The sex ratio is also different being the same in Indians, but having a higher rate in female negros. A similar racial difference is seen in South Africans. Obesity, poverty and diet have been considered but none fully explain the racial difference.

Diabetics number at least 1% of the population in Israel. It was suggested that the rate was low in new immigrants but rose to normal levels in those who had been settled for more than 25 years. Environmental, social or economic factors may have played a part in the incidence.

DM in Japan is about as common as in the Western countries. Juvenile onset diabetes and diabetic coma are rare, and the disease is considered more common in men than in woman.

Diabetes mellitus is one disease which in the mind of many Maltese physicians and doctors appears to be commoner on the Maltese Islands than elsewhere. Very few documented studies have been carried out regarding the incidence and epidemiology on the disease in the Maltese population.

A survey on blindness carried out in 1958 showed that of 638 blind persons, 92 (15.9%)

of these had in fact lost their eyesight because of DM (Damato, F.J. 1960). Diabetic retinopathy now accounts for about 10% of new cases of blindness at all ages. In addition, because it is associated with a much higher mortality than most other causes of blindness, these proportions are halved if persons who are blind from diabetic retinopathy are compared to the total existing blind poulation (Khan & Heller 1974). The apparent discrepancy in the figures from Malta can only be interpreted with some reservations, since besides being due to a possible increased local prevalence, it may be due to inadequately treated diabetes locally. In addition, the study population is not a representative one suitable for the prevalence study of diabetes in the Maltese population.

A similar prevalence was found in another population survey carried out on 5,757 individuals living in rural and urban areas (Zammit Maempel, J.V. 1965). Glycosuria after a high carbohydrate diet was found in 8.9% (9% males and 8.8% females) of the sample population, with a prevailing peak age of 70-79 years (29.3% males and 30% females). Glucose tolerance tests were carried out on glycosurics and non-glycosurics. The GTT's showed that 70.1% of glycosurics and 15.0% of non-glycosurics were diabetic. This gave an overall prevalence rate of 19.9% and also indicated that 1 in 6 of non-glycosurics had diabetes mellitus. Since Zammit Maempel defined diabetics as those whose GTT showed a fasting or 2-hour blood glucose level of 100 mg per 100 mls, he later corrected the prevalence rate to 17.2% taking the dividing point as 120 mg per 100 mls. This survey also indicated that the prevailing form of diabetes was the maturity onset diabetes in the peak ages of 50-54; the juvenile onset diabetes being uncommon.

URINE TESTING

Population — rural & urban
(n=5757)

No glcosuria	Glycosuria
91.1%	8.9%

GLUCOSE TOLERANCE TEST
(dividing line 100 mg%)

	Normal	Diabetic	Renal glycosuria	Lag storage curve
Non-glycosuric (n = 392)	67.8%	15.0%	1.5%	15.7%
Glycosuric (n = 324)	15.1%	70.1%	7.4%	7.4%

AGE DISTRIBUAION OF DIABETICS
(n=140)

0—9	10—19	20—29	30—39	40—49	50—59	60—69	70—79	80+	Age
0.0%	0.7%	2.1%	12.1%	25.7%	40.0%	17.1%	2.1%	0.0%	Diabetics

Fig. I: Prevalence of diabetes in the Maltese Population
(Zammit Maempel, J.V. 1965)

When compared with figures for Oxford, Massachusetts — 4.7% (Wilkerson & Krall, 1947); for Bedford — 12% (Butterfield, 1974); and the United States — 1.45% (McDonald, 1964), it would appear that there is a definite increased prevalence rate for the Maltese Islands. This higher prevalence could be attributed to obesity and diet coupled to a genetic influence, however it could have also been contributed to by the emigration drive which affected

predominantly the young. The 1921 census report for the Maltese Islands shows that no less than 11860 males emigrated to the U.S., Canada and Australia between 1911 and 1921. In the fifteen years from 1947 to 1962 permanent emigration was substantial. Its effects on the population may be gauged from the fact that had there been no emigration since 1947, the population of the islands fifteen years ago would have been greater by some 80,000 persons, less a number of returned emigrants estimated at 11,000 and plus the children who would have been born here had their parents not emigrated (Anonym. 1963b).

Diabetes mellitus in the Maltese Islands has an average proportional mortality rate of 64.33 per 1000 (1963-1972). Mortality statistics in the case of diabetes are imperfect indicators of disease incidence for a number of other variables may be coexistent causes for the death of the patients. A yearly mortality rate graph for the period 1896 to 1972 (Anonym., 1963a updated) shows two characteristic trends culminating in two peaks in 1942 and 1971. There is previous to these peaks mild upward trends with the yearly figures exhibiting wide irregular divergences from the trend. The peak of 1942 coencides with the Second World War period. Insufficiency of hypoglycaemic drug stores may in part explain the high mortality of this period. However, an increase in the mortality rates is not unique to the islands and can be compared with figures given by McDonald (1968) for the period 1957 to 1966. This increase may be attributed to (1) increased efforts at detection, (2) a general increase in life expectancy, and (3) an increased awareness of the disease.

URBAN-RURAL DIFFERENCES: Zammit Maempel (1965) also showed that there existed a definite higher incidence of glycosuria in the rural prevalentiy agricultural area studied (11.5%) as compared that in the urban area (8%), giving a ratio of 1:1.44. This ratio is directly opposite to that given for the United States for the years 1961-1963, which are given as 1.7:2. Zammit Maempel suggests that the difference was due to the fact that up to about 40 years ago, the rural areas in Malta were, unlike the urban areas, practically isolated from the more thickly populated part of Malta because of poor means of communication. This gave rise to a greater degree of intermarrage, with a corresponding increase in a genetically transmitted tendency. Other variables may include diet habits and different modes of life.

Another variable which the author recorded was the relation of physical activity and the disease. He found that heavy manual activities were less frequently encountered in diabetics (10.1%) than in non-glycosuria and glycosuric non-diabetes (42.7%). It was not determined whether this observation was a causal factor or the result of the disease. It may, however, be related to socio-economic variables.

Differences between urban and rural communities in relation to the prevalence of DM seems to be diminishing in the technically advanced countries just as they are in social and economic respects. The traditional concept that worldwide DM is less common in a physically active and healthy rural community than in a sedentary, prosporous and obese poulation is not proven.

AGE DISTRIBUTION: One fact about DM which is never disputed is that it becomes more common as age advances. It has already been noted above that Zammit Maempel found that the prevailing type of diabetes was the maturity onset diabetes in the peak ages of 50-54 years, the juvenile form being uncommon (ref. Fig. 1). The following table shows the mortality figures due to diabetes for the years 1963-1972 broken down to age and sex. This gives a higher incidence for deaths recordably due to diabetes for the age group in the region of 64-79 years.

This increased incidence of DM with age reflects a general change in glucose tolerance. In early life blood glucose levels are low but rise progressively so that over the age of 70 years, approvimately 15% of a poulation show mildly abnormal GTT.

SEX VARIABLES: In most countries DM is commoner in women than in men, however, under the age of 40 years the condition appears to be slightly commoner in males. In the fifties and sixties, DM becomes nearly twice as common in women as in men. This increased ratio was demonstrated by Damato's survey on blindness, when he found a male:female ratio of 1:3. Zammit Maempel found an overall ratio of 1:1.6. The mortality figures given in Table 1 give an average ratio of 1:1.79.

This pattern of sex incidence is seen all over Europe and America but is not universal. In Japan and Malaya diabetes is 50-100% commoner in men. The reason for the female preponderance seen in Europe and America is not known but has been associated with the effects of the menopause and parity. In addition the higher incidence in females in the older age group may be a result of the early mortality of the males due to other causes.

YEAR		1963	1964	1965	1966	1967	1968	1969	1970	1971	1972
Proportional mort. rate/1000		62.0	50.0	53.0	51.0	57.0	60.4	55.6	81.5	93.2	79.6
Specific Mortality rate/10000 pop.		5.5	4.3	4.95	4.6	5.34	5.45	5.2	7.1	8.85	7.26
Both sexes:	all ages	181	139	158	146	170	174	168	251	288	232
	under 25	—	—	1	—	1	—	—	1	1	3
	25—44	3	4	4	1	3	—	2	—	4	1
	45—64	37	44	38	37	42	30	43	67	76	54
	65—74	81	50	63	55	64	76	74	101	115	85
	over 75	60	41	52	53	60	68	49	82	92	89
Males:	all ages	69	50	51	45	56	50	59	106	105	85
	under 25	—	—	—	—	—	—	—	—	—	1
	25—44	2	3	—	—	2	—	2	—	3	—
	45—64	16	15	10	16	14	6	13	34	30	25
	65—74	26	19	29	12	20	29	24	40	46	26
	over 75	25	13	12	17	20	15	20	32	26	33
Females:	all ages	112	89	107	101	114	124	109	145	183	147
	under 25	—	—	1	—	1	—	—	1	1	2
	25—44	1	1	4	1	1	—	—	—	1	1
	45—64	21	29	28	21	28	24	30	33	46	29
	65—74	55	31	34	43	44	47	50	61	69	59
	over 75	35	28	40	36	40	53	29	50	66	56

Table I

MORTALITY FIGURES WITH DIABETES GIVEN AS A CAUSE OF DEATH

FOR THE MALTESE POPULATION DURING THE PERIOD 1963-1972

(a) Effects of the menopause: It has been suggested (Oakley et al. 1973) that the menopause is responsible for the rising incidence of diabetes in women. This may be true, at least partly, although no known mechanism has so far been defined and no noticeable change in the severity of diabetes in established cases occurs at the menopause. Furthermore, change in the sex prevalence ratio occurs well before the menopause at approximately the age of 35-40 years and lasts until approximately the seventies.

(b) Effects of Parity: The relationship between diabetes and parity is not clear cut. The fact that a family history of diabetes is less common in highly multiparous women may mean that pregnancy may provoke DM in women whose genetic tendency to the disease is not strong. This is in line with the idea that each pregnancy places a progressive demand on the maternal beta-cells and the insulin secretory system, and that pregnancy is a state of relative insulin resistance. Normal women tolerate pregnancy without significant alteration in carbohydrate tolerance. Women with a marginal pancreatic reserve develop an abnormal tolerance or gestational diabetes. As many as one pregnant woman out of 116 fall into this category. While the diabetes usually clears after delivery, 28% of such women have frank DM after 5 years and by 16 years 52% have permanent disease. The risk of impaired carbohydrate tolerance rises with successive pregnancies. A woman who has had five pregnancies has a three times chance of developing DM as the risk found in a nulliparous individual This increased risk could be result of the fact that during the course of a normal pregnancy extra insulin is needed because of:

i. maternal insulin having an abbreviated biological life due to the ability of the placenta to degenerate insulin.

ii. maternal tissue becomes resistant to insulin because of circulating placental antagonists like progesterone, oestrogens and human placental lactogen. (Fajans et al. 1976).

OBESITY AND DIET: Diabetes is more common in fat people than in lean. Diabetics are, on average, overweight and obesity is associated with insulin insensitivity. Zammit Maempel although he did not study the factor adequately elicited an increased history of overeating in diabetics when compared with controls. He also noted that 60% of diabetics in Malta were obese. These facts point towards the importance of obesity in the causation of DM.

Young diabetics are not as a rlue overweight but those over the age of 45 years at the time of diagnosis are as a rule about 15% over their expected weight. Another way of expressing the same finding is to say that half of the diabetics diagnosed over the age of 45 exceed their expected weight by 10%, compared with only a fourth of non-diabetics. As mentioned above, obesity is accompanied by insensitivity to insulin. Insensitivity of muscle and adipose tissue to insulin, hypertrophy of the pancreatic islets, higher basal insulin levels and an exagerated insulin response to glucose all characterise obesity and theoretically can be linked into a cycle which eventually results in DM. The messenger that transmits to the beta-cell that obesity is present and hence more insulin is required defies defenition at present.

In addition, it has long been known that reduction in weight of the obese diabetic leads to an amelioration of the condition. Actually this improvement appears before there is any significant loss of weight and is probably due to restriction of a carbohydrate intake. Whether the nature of dietary carbohydrate plays a role in the pathogenesis of diabetes mellitus is subject to debate.

INHERITANCE: A family tendency to diabetes undoubtedly exists, but it is not understood how these inherited factors operate. They may in fact be less important than is usually assumed. The evidence that genetic factors have some importance comes from:

(1) comparisons of family history of diabetics and normals

(2) twin studies, and

(3) remarkable pedigrees (the observation that diabetes occurs in successive generations in certain families).

The mode of inheritance of DM is still debatable, and the only theory which at present is consistent with present knowledge is that inheritance of DM depends upon several factors. Zammit Maempel elicited a positive family history of the disease in maltese diabetics as compared to control glycosurics and non-glycosuric diabetics.

OTHER AETHIOLOGICAL FACTORS:

Stress states have been associated with hyperglycaemia and glycosuria, an effect mediated by a generalized activation of the sympathetic nervous system. Even the mild stress of simple exercise has been associated with inhibition of insulin secretion, raised levels of glucagon and accelerated glucose production. It would appear that there is a continuation from the physiological response to exercise to the pathologic stress state, variously described to include trauma, surgery, burns, shock and myocardial infraction.

Though the role of infectious processes in the aetiology of permanent DM has not been fully established, infection is an important factor affecting carbohydate tolerance. Inflammatory lesions exert their effects on intermediary metabolism either by involving specific tissues such as the pancreas and liver; or indirectly by altering the body hormonal milieu. This factor may in part explain the seasonal occurence of DM, its geographical distribution and coincidence of upper respiratory tract infections in newly diagnosed cases.

Diabetics have a higher incidence of autoimmune diseases such as Idiopathic Addison's Disease, Pernicious anaemia and chronic thyroiditis. This observation suggested a possible autoimmune basis for DM. The development of a form of experimental DM in animals using the techniques of immunology and the discovery of tissue specific antibodies in acute human clinical diabetes (Malony & Coval, 1955) have provided support for the concept of a possible immune mechanism in DM.

Other diseases and some rare syndromes are associated with a higher incidence of DM. Patients with gout have been observed to have a higher incidence of DM. It has been suggested that uric acid or a substance resembling it might have an alloxan-like action on the beta-cells of the pancreatic islets, so producing DM. Chronic renal disease and hypertension are associated with hyperuricaemia, however, whilst an increased prevalence of DM in persons with hypertension has been reported, chronic renal disease is not known to proceed DM in an increased prevalence.

In conclusion one can say that the aetiology of diabetes mellitus is complicated and in the great majority of cases there appears to be no single cause for the condition. A multiplicity of factors interact together to cause the disease. The prevalence of the disease in the Maltese Islands is higher than most other European countries. Though Zammit Maempel's pilot survey has helped to assess the relationship to age and sex, much more work is required to relate the disease to variables such as occupation, genetics, fertility and diet. The islands constitute a closed community which should make a local survey very feasable. Once the incidence of DM is firmly established for the total population, comparison with the incidence in special groups of this population may be indicated. This can take the form of a study of prevalence in a religious community whose dietery consumption may be accurately determined. The incidence of diabetes in descendants of first cousin marriages may also be undertaken to determine any genetic influence on the increased prevalence.

REFERENCES

Local epidemiology

Damato, F.J. (1960) "Incidence and causes of blindness in the Maltese Islands: A survey based on the examination of 638 blind persons" **Brit. J. Ophth.** 44:164-171.

Ganado, W. (1963) "Diabetes Mellitus in the Maltese Islands" **The Chest-piece** Summer Term 1963 p. 7-8.

Zammit Maempel, J.V. (1965) "Diabetes in Malta: A pilot survey" Lancet 2(7424) 1197-1200 and subsequent correspondence (1966) 1(7428)96; 1(7430) 205-206.

Central Office of Statistics (1962-1972) "Reports on the Health Conditions of the Maltese Islands and on the work of the Dept. of Health" appendix O and E Dept. of Inf.; Malta.

Anonymous (1963a) "The Incidence of diabetes" **Malta Review** 11:16.18.

Anonymous (1963b) "Population growth in Malta and Gozo" **Malta Review** 16:12:16.

General epidemiology

Butterfield, W.J.H. (1964) "Summary of results of the Bedford Diabetes survey" **Proc. R. Soc. Med.** 57: 196-202.

Fajans, S.S. editor (1976) **"Diabetes Mellitus"** Fogarty Inter. Center series on Preventive Medicine vol. 4 +361p. Dept. of Health, Edu. & Welfare. publ. no. 76-854.

Kahn, H. & Heller, M.S. (1974) "Blindness caused by diabetic retinopathy" **Amer. J. Ophth.** 78:58.

Marble, A. et al. editors (1971) **"Joslin's Diabetes** Mellitus" 11th ed. p. 10-34 Lea & Febiger; Philadelphia.

McDonald, G.W. (1964) **"Diabetes source book"** U.S. Dept. of Health, Edu. & Welfare publ. no. 1163 in Marble, A. et al (1971).

Molonet, P.J. & Coval, M. (1955) "Antigenicity of insulin — Diabetes induced by specific antibodies" **Biochem. J.** 58:179-185 in Fajans, S.S. (1976).

Oakley, W.G.; Pyke, D.A. & Taylor, K.W. (1973) **"Diabetes and its management"** p. 22-49 Blackwell Scientific Publication.

Pyke, D.A. (1969) "The geography of diabetes" **Postgrad. med. J.** (Supplement) 45:796-801.

Schliack, V.; Zegenhagen, R. & Wenthin, H. (1975) "Retrospective Investigations of borderline diabetics" p. 8-10 in Gutsch, H. & Holler, H.D. editors (1975) **"Diabetics Epidemiology in Europe"** +200p. Georg Thieme Publ.; Stuttgart.

Wilkerson, H.L.C. & Krail, L.P. (1947) "Diabetes in a New England Town. A study of 3516 persons in Oxford, Mass." **J. Am. med. Ass.** 135:209-216.