Epidemiological Problems in Diabetes Mellitus

YOSHIO GOTO

*Third Department of Internal Medicine, Tohoku University
School of Medicine, Sendai, Japan*

GOTO, Y. *Epidemiological problems in diabetes mellitus*. Tohoku J. exp. Med., 1983, **141**, Suppl., 1-19 — It is generally accepted that etiology of diabetes mellitus is heterogeneous and term “diabetes mellitus” becomes too oldfashioned and vague to apply for the disease. A new term “hyperglycemosis” which involves all states of chronic blood glucose elevation irrespective of etiology, is proposed and tentative etiological classification of hyperglycemosis is shown. The prevalence of diabetes mellitus has increased remarkably in Japan as well as other countries and the factors influencing on this increase are concluded as following: 1) an increase in body mass index probably due to reduction of physical exercise and relative excess of energy intake, 2) an increase of elder population and 3) an accumulation of diabetic patients due to an improvement of prognosis of the disease. The phenomenon observed in Japan is thought to be a model in rapidly modernizing countries. Etiological classification was made in 10272 diabetic autopsy cases collected from Annual Reports of Pathological Autopsy Cases 1958-1980 and the result showed 85.9% of the cases was classified as idiopathic and 14.1% was classified as other types of WHO classification. This study showed a difficulty to discriminate idiopathic diabetes mellitus in field studies and a reasonability to use an expression of hyperglycemosis in stead of diabetes mellitus. Death of diabetic coma has decreased and death of malignant neoplasms and cardiovascular diseases, especially myocardial infarction, have increased. As frequency of the chronic complications is different according to the quality of the population and also to the examination methods, consideration for these points is important in planning of the study. The modern machine civilization has caused an increase of diabetic population and in the long history of the evolution of mankind, this increase is understood as a dysadaptation of the human body to excess food intake, less physical exercise and other diabetogenic environmental factors. The epidemiological study of diabetes will give a guide line of ideal life style of human being and contribute to sound prosperity of human society. ——— classification of diabetes, mortality rate, prevalence of diabetes body mass index, fasting blood glucose, diabetic retinopathy, epidemiology

DIABETES OR HYPERGLYCEMOSIS ?

Changes of classification of diabetes mellitus

Diabetes was first described in a medical book by Aretaeus about 2000 years ago (Reed 1954) and sweetness of the urine was found in Europe by Thomas Willis in the 17th century (Allan 1953). The cause of this sweetness was attributed to sugar by Matthew Dobson in 1776 and finally to glucose by Michel Chevreul in

1815 (Allen et al. 1919). In the middle of the last century, hyperglycemia was thought to be characteristic for diabetes mellitus and renal glycosuria, called renal diabetes or innocent diabetes, was discriminated from diabetes mellitus.

Since the middle of the last century many clinicians have felt that diabetic patients should not be categorized into one type but into at least two different types. Lanceraux (1880) pointed out the existence of lean diabetes and obese diabetes, and thereafter diabetes mellitus was classified into severe diabetes and benign diabetes; juvenile type and adult type; asthenic type and sthenic type; and so on. Recently, the National Diabetes Data Group (NDDG) of NIH (1979) and the WHO Expert Committee on Diabetes Mellitus (1980) proposed a new classification, i.e., IDDM and NIDDM. These classifications may be arranged into two categories as shown in Table 1. Of course these are all tentative ones and the final one will never be obtained because new findings, which will be obtained successively in future, will establish more and more new concepts and new classifications.

TABLE 1. *Summarization of classification of diabetes mellitus*

Author (yr)	criterion	Category A	Category B
Lanceraux (1880)	body weight	lean diabetes	obese diabetes
Naunyn (1906)	age	juvenile (true)	aged
Kylin (1928)	blood pressure	hypotensive diabetes	hypertensive diabetes
Schmidt (1930)	body type, blood pressure	asthenic-hypotensive d.	sthenic-hypertensive d.
Lyon and Lyon (1930)	complication	toxic type	degenerative type
Falta and Boller (1931)	insulin treatment	insular diabetes	insulin-resistant d.
Himsworth (1936)	insulin-glucose test	insulin-sensitive type	insulin-insensitive type
Yamakawa (1936)	treatment	insulin-requiring type	insulin-nonrequiring type
Bornstein and Lawrence (1951)	plasma insulin	no available insulin	available insulin
Wrenshall et al. (1952)	pancreatic insulin	growth-onset type	maturity-onset type
Bertram (1953)	pathogenetic	insulin-deficient d.	Gegenregulations-diabetes
Lawrence (1955)	clinical features	insulin deficient d.	lipoplethoric d.
Hugh-Jones (1955)	clinical features	type 1	type 2
Duncan (1958)	treatment, age	unstable	stable
Williams (1962)	clinical features	juvenile-onset d.	adult-onset d.
NIH (1979), WHO (1980)	treatment	IDDM	NIDDM

Heterogeneity of diabetes mellitus

The etiology of idiopathic diabetes mellitus was generally thought to be the same or similar even if the types were different and childhood diabetes was considered to be the most typical manifestation of this disease. Recent investigations disclosed that the etiology of diabetes is not one or homogeneous but multiple or heterogeneous. In some cases, the diabetic state occurs as the result of an autoimmune process (Nerup & Lernmark 1981), some are provoked by viral invasion (Yoon et al. 1979), some are associated with special HLA types (Nerup

et al. 1974), and some are produced by abnormal-insulin secretion from the pancreas (Tager et al. 1980), or by defect in the insulin biosynthetic process (Kanazawa et al. 1976). The diabetic state is also produced by defects in the insulin-insulin receptor axis, i.e. abnormalities of insulin-receptors, insulin receptor antibodies, etc. (Kahn et al. 1976). More recently, abnormalities around the insulin gene locating on short arm of the 11th chromosome are found in some of diabetic patients and this finding suggests the possibility of yet another new type.

The heterogeneity of diabetes mellitus is also suggested by studies on spontaneous diabetes in animals, especially in rodents. Some rats or mice mimic abrupt-onset ketosis-prone infant diabetes and others insidious-onset mild adult diabetes. Moreover, even in the case of the mild insidious-onset type, some are obese and others are non-obese as summarized elsewhere (Goto et al. 1982). Therefore, it may be reasonable to speculate that in humans there exists even a greater number of diabetes than that of spontaneous diabetes in animals.

Proposal of the term "hyperglycemosis"

Hence, we must question again what is diabetes. It is less reasonable to think of diabetes mellitus as one disease or one clinical entity and may be more reasonable to think of it as a syndrome characterized by chronic hyperglycemia with small vessel disease occurring in the long clinical course. The term "diabetes mellitus (sweet polyuria)" was coined by Cullen according to the nomenclature system of Carl Linne in the 18th century when they had no knowledge of blood glucose or carbohydrate metabolism. We feel that this term has become too old-fashioned and vague to use in this modern age of far-advanced natural sciences and knowledge of the pathophysiology of diabetic states. This can be understood by a parable that a grown-up boy can not wear infant's clothing. We use the term for at least two meanings, i.e. disorders with hyperglycemia in a broad sense and idiopathic diabetes mellitus is a narrow sense. In the future as medical science progresses and discloses other etiological mechanisms of diabetes mellitus, most of the cases now classified as idiopathic will eventually be classified as non-idiopathic.

Hence, instead of "diabetes mellitus", we would like to propose a new term "Hyperglycemosis" which involves all states of chronic blood glucose elevation, irrespective of etiology, and our tentative etiological classification of hyperglycemosis is shown in Table 2. We should use the term hyperglycemosis for cases with hyperglycemia before completion of etiological examinations such as exocrine pancreas, plasma insulin (to rule out abnormal insulin or receptor antibody), and endocrine functions, and use a term diabetes mellitus only in a narrow sense for cases in whom any etiological defect can not be found except low plasma insulin level. As mentioned above, hyperglycemic states are heterogeneous and for this reason a careful consideration should be paid in clinical investigations to select or to compare cases with homogeneous etiological background. This consi-

TABLE 2. *Etiological classification of hyperglycemosis*

A.	Decrease of insulin secretion
1.	insulinitis: a) autoimmune (ICA, ICSA), b) viral infection c) insulotropic toxin (streptozotocin, etc.)
2.	pancreatic disease: a) pancreatic carcinoma, b) chronic pancreatitis, c) hemochromatosis, d) hypoplasia, e) surgery (pancreatectomy)
3.	idiopathic diabetes mellitus
B.	Secretion of low-bioactive insulin
1.	abnormal insulin
2.	proinsulinemia
C.	Excess of anti-insulin (diabetogenic) factors
1.	diabetogenic hormones: a) acromegaly, b) Cushing disease, c) hyperthyroidism, d) glucagonoma, e) somatostatinoma, f) Cushing syndrome, g) pheochromocytoma, h) gestational diabetes
2.	anti-insulin antibody (?)
D.	Defects in insulin receptor (defects in target cells)
1.	anti insulin-receptor antibody
2.	decrease in insulin receptors
3.	qualitative abnormality of insulin receptors (including postreceptor process)
E.	Genetic syndromes
	Myotonic dystrophy, Laurence-Moon-Biedl syndrome, Turner's syndrome, etc.
F.	Miscellaneous

deration may be important in the epidemiological studies, because it is difficult to make an exact etiological differentiation or classification on hyperglycemic cases observed in field studies and in most of cases we must compromise to apply phenotypical classifications such as grade of hyperglycemia, body form, and others. Indeed, experimental results of BB rats showed that mild hyperglycemic littermates of diabetic rats also had typical findings of insulinitis in the pancreas (Nakhlooda et al. 1977). This finding indicates that there are noninsulin-dependent diabetic patients with insulinitis and teaches us that even if the etiology of a diabetic state (genotype) is the same, the clinical features of the disease (phenotype) are not always necessarily similar.

In summary, as a term "diabetes mellitus" is vague, used in various meanings and sometimes becomes a cause of confusion, we proposed a term "hyperglycemosis" for chronic hyperglycemic state of any etiology. The term of "diabetes mellitus" should be limited to idiopathic hyperglycemic cases in a strict sense. In epidemiological studies, it may be proper to use phenotypical classification rather than etiological classification.

REASON OF INCREASE IN DIABETIC POPULATION

Change of prevalence of diabetes mellitus.

Diabetes mellitus was not a common disease in the past, but now it is one of

the most common chronic diseases in Japan. The prevalence per 1,000 population from 1949 to 1980, the crude death rate from 1936 to 1980, which were reported by the Welfare Ministry of Japan, and the adjusted death rate calculated by us, are shown in Table 3. The death rate decreased during and for several years after the world war II and this pattern is very similar to our previous statistical observation on diabetic patients in our Department (Goto et al. 1958). The adjusted death rate was the lowest in 1947-48 and thereafter it turned to increase and over the rates of 1930s from 1965. The mortality rates of males are always higher than those of females as seen in the table and this preponderance of males is characteristic pattern of diabetes mellitus in Japan when compared with those in North America and European countries as described elsewhere (Goto 1978). The prevalence of diabetes increased steadily as depicted in the top of Fig. 1, with transient decreases at 1967 and 1974-75 when drastic fluctuation of economical condition occurred in this country.

Change of mean fasting blood sugar

Then, what is a reason of this increase of diabetic population? First of all, the progress of analytical methods for diabetes screening and the propagation and popularisation of diabetes detection or of health check both in communities and enterprise-workshops may attribute to this increase. However a survey of mean fasting blood sugar level in employees of small-to-medium-sized enterprises in Tokyo increase year by year as shown in Table 4 (Kitazawa et al. 1979). This fact indicates that the increase in the diabetic population is not related to the advances in the screening methods nor to the popularization of detection examinations, but to an increase in diabetogenic factors in our environment.

Influence of diet on prevalence of diabetes mellitus

What factors are diabetogenic in our environment? From an ecological viewpoint, the following factors can be assumed to influence the incidence of diabetes: food intake, physical exercise, emotional stress, and the age structure of the population. The average nutritional intake of the people living in Tokyo in 1937-38 was 63.4 g of protein, 11.6 g of fat, 414 g of carbohydrate and 2013 kcal (per capita per diem) for industrial laborers and 57.8 g of protein, 11.2 g of fat, 378 g of carbohydrate and 1,843 kcal for office workers. Since 1946, the nutrition survey has been performed on a nationwide scale and the figures have been reported by the Welfare Ministry as shown in Table 3. As depicted in the middle part of Fig. 1 and shown in the table, the total energy intake increased gradually reaching a peak during 1971-73, and then decreased. The average protein intake was relatively constant, although the percentage of animal protein has risen continuously. The average fat intake has shown a continuous increase up to the present time and on the contrary, the average carbohydrate intake which has decreased since 1950 was 424 g/day in 1951 and 313 g/day in 1980. The con-

TABLE 3. *Mortality and prevalence of diabetes mellitus, average nutrient intake, number of automobiles and average life expectancy for the year 1936-1980.*

year	Death rate (per 100,000)				Prevalence (per 1,000)	Nutrient intake (per capita per diem)				Automobiles ($\times 10^4$)	Average life expectancy	
	crude male	female	adjusted male	female		energy (kcal)	protein (g)	fat (g)	carbohy (g)		male	female
1936	4.0	3.6	4.2	3.5	—	—	—	—	—	0.19	46.9	49.6
37	4.2	3.8	4.4	3.7	—	—	—	—	—	0.21	—	—
38	4.4	4.2	4.6	4.1	—	—	—	—	—	0.22	—	—
39	4.1	3.8	4.2	3.6	—	—	—	—	—	0.22	—	—
1940	4.0	3.7	4.2	3.5	—	—	—	—	—	0.22	—	—
41	3.7	3.6	3.8	3.5	—	—	—	—	—	—	—	—
42	3.7	3.5	3.8	3.3	—	—	—	—	—	—	—	—
43	3.7	3.0	3.8	2.8	—	—	—	—	—	—	—	—
44	—	—	—	—	—	—	—	—	—	—	—	—
45	—	—	—	—	—	—	—	—	—	0.14	23.9	37.5
46	—	—	—	—	—	1903	59	15	—	0.17	42.6	51.1
47	2.6	2.0	2.8	2.0	—	2000	61	13	—	0.20	50.0	53.9
48	2.5	2.0	2.6	2.0	—	2012	63	14	—	0.25	55.6	59.4
49	2.4	2.2	2.6	2.1	0.0	2097	65	16	—	0.32	56.2	59.8
1950	2.5	2.4	2.6	2.3	0.1	2098	68	18	—	0.41	59.5	62.9
51	2.4	2.4	2.5	2.3	0.0	2125	68	18	424	0.53	60.8	64.9
52	2.2	2.4	2.3	2.3	—	2109	70	20	412	0.76	61.9	65.5
53	2.4	2.5	2.4	2.3	0.1	2068	69	20	403	1.09	61.9	65.7
54	2.2	2.4	2.2	2.2	0.1	2074	69	21	403	1.34	63.4	67.6
55	2.3	2.6	2.3	2.3	0.2	2104	70	20	411	1.50	63.6	67.7
56	2.6	3.0	2.6	2.7	0.2	2092	69	22	405	1.78	63.5	67.5
57	2.9	3.1	2.8	2.7	0.2	2089	70	22	404	2.07	63.2	67.6
58	2.7	3.1	2.6	2.7	0.2	2118	70	24	406	2.40	64.9	69.6
59	2.8	3.2	2.7	2.7	0.2	2117	69	24	406	2.90	65.2	69.8
1960	3.2	3.6	3.0	3.0	0.4	2096	70	25	399	3.40	65.3	70.1
61	3.3	4.0	3.0	3.2	0.5	2106	70	26	399	4.13	66.0	70.7
62	3.4	4.3	3.4	3.4	0.5	2080	70	28	386	4.92	66.2	71.1
63	3.8	4.4	3.4	3.5	0.5	2083	71	29	382	5.94	67.2	72.3
64	4.5	5.0	3.9	3.8	0.5	2223	74	34	398	6.98	67.6	72.8
65	5.1	5.3	4.4	4.0	0.8	2184	71	36	384	8.12	67.7	72.9
66	5.6	6.0	4.8	4.4	1.3	2193	75	40	380	9.64	68.3	73.6
67	6.1	6.2	5.0	4.5	0.8	2228	77	42	382	11.69	68.9	74.1
68	6.3	6.4	5.1	4.5	1.5	2224	77	45	375	14.02	69.0	74.3
69	6.8	7.0	5.2	4.8	1.4	2242	78	46	377	16.53	69.1	74.6
1970	7.4	7.4	5.8	5.0	1.6	2210	78	47	368	18.92	69.3	74.6
71	7.2	7.4	5.6	4.8	2.0	2287	78	49	379	21.22	70.1	75.5
72	7.4	7.5	5.6	4.8	2.4	2279	83	50	359	23.87	70.5	75.9
73	7.7	7.8	5.7	4.8	2.6	2273	84	52	351	25.96	70.7	76.0
74	8.2	8.1	6.0	4.9	2.0	2187	79	52	339	27.87	71.1	76.3
75	8.0	8.2	5.7	4.8	2.0	2188	80	52	337	29.14	71.7	76.8
76	7.9	8.5	5.5	4.8	2.4	2159	79	52	332	31.05	72.1	77.3
77	8.1	8.6	5.5	4.6	2.8	2149	79	54	326	32.97	72.6	77.9
78	8.2	8.7	5.3	5.3	2.5	2167	80	55	326	35.18	72.9	78.3
79	6.8	7.2	4.4	3.2	4.0	2113	78	55	315	37.33	73.4	78.8
1980	7.1	7.5	4.5	3.7	4.5	2084	78	52	313	38.99	73.2	78.7

Fig.1. Chronological changes of prevalence and death rate of diabetes, and other factors.

TABLE 4. *Change of mean fasting blood sugar levels in employees of enterprises in Tokyo*

Year	40s male	50s male
1970	85.4±0.18 (2215)	86.7±0.33 (1055)
1975	90.8±0.11 (12135)	91.4±0.15 (7020)
1977	91.2±0.21 (3171)	92.4±0.33 (1756)
M±SE (No.)		

sumption of potatoes and cereals including rice has decreased remarkably and that of animal products such as meat, fish and eggs has increased about three times during this period.

These figures seem to suggest that carbohydrate and fat intake influences the prevalence of diabetes mellitus as pointed out by Himsworth (1935, 1949). A phenomenon suggesting correlation between the prevalence of diabetes and fat intake was also reported by Schliack (1953) and Schenck and Mellinghoff (1960). We attempted to confirm their observations and analysed the relationship between average nutrient intake (per capita per diem) and mortality rate of diabetes in 23 nations (Suzuki and Goto 1983). Since data on average body weight and height in each nation were not available, percentage of the total energy was used instead of grams of nutrient. A significant positive correlation and a significant negative correlation were obtained between crude death rate, and fat, or carbohydrate intake, respectively as shown in Fig. 2a. However, no significant correlation was obtained if adjusted death rates were used instead of the crude death rates as shown in Fig. 2b. It is generally said that from the point of natural taste, human being instinctively prefer animal products such as meat and fish. For this reason, the people of more affluent countries consume more animal products higher in fat and as a result, less cereals, than people in economically poor countries. The economical condition influences not only on selection of food, but also the life-style, the medical care system and eventually the life span. Hence the truth of the matter pointed out by Himsworth was a socioeconomical phenomenon observed among developed and developing countries. Therefore, it may be incorrect to assume that a high fat and low carbohydrate diet is diabetogenic.

The explanation of the increase in diabetic population might be easy if the average energy intake showed a continuous increase. However, the real figures did not show a continuously increasing curve but rather relatively plateau curve as stated above. What changes have occurred in patterns of physical exercise and emotional stress in Japan? It is hard to find a proper indicator for emotional stress, although social conditions are definitely busier and noisier now than they were before 1950. It is also rather difficult to find a direct indicator for average physical activity of the population.

Fig. 2. Relationship between death rate and nutrient intake (percent of the total energy) in the developed and developing countries. a. crude death rate, b. adjusted death rate.

Increase in the number of automobiles.

It is our general impression that progress in technology has released us from a great deal of physical labor, and the growth in number of automobiles may be an indicator of the progress and changing lifestyle in our society. The number of registered automobiles has increased tremendously in this country as shown in Table 3; it was less than half million in 1950, but now it is more than 38 million, i.e., about an 80-fold-increase during the last 30 years. This rapid increase may indirectly reflect the reduction in physical exercise of the people.

Increase in body mass index.

If total energy intake remains constant, a decrease in physical activity would result in an increase body weight. Furthermore even if the total energy intake decreases, weight gain will occur when energy intake exceeds energy required for physical activity. In order to determine whether weight gain did actually occurred among the Japanese people or not, the body mass index was calculated from the data published by the Welfare Ministry for each decade of age. A steady increase of the index was found in both males and females in their 30s, 40s, 50s and 60s, but not in subjects in their 20s who showed a decrease as shown in

Fig. 3. Changes in body mass index 1947-80 (see text).

Fig. 4. Chronological changes in crude and adjusted death rate of diabetes mellitus (per 100,000) in Japan.

Fig. 3. This increase in body mass index clearly demonstrate the reduction in physical activity of the people and this may be one of the reasons for the increase in the prevalence of diabetes.

Increase of elder population.

Since diabetes mellitus is more prevalent in older than in younger people, a relative increase of elder people may result in an apparent increase of the diabetic population. This phenomenon is shown in Fig. 4 in which we can see that a remarkable increase in the crude death rate after 1965 is an apparent one produced by the increase in the elderly population. The average life expectancy has been increasing continuously as shown in Table 3, and the ratio of the elderly population (65 years old or more) to the general population was 4.7% in 1940, 4.9% in 1950, 5.7% in 1960, 7.1% in 1970 and 9.0% in 1980. Therefore, the increase of diabetic population in this country can be partly explained by the change in the population pyramid and also by an accumulation of diabetic patients caused by the advances in medical care and the lengthening of the average life span.

In summary, a remarkable increase in the prevalence of diabetes did occur during last 30 years in Japan and the factors correlating or influencing to this increase are considered as follows: 1) an increase in body mass index probably due to a physical inactivity and relative excess of energy intake, 2) an increase in the elderly population and prolongation of life span, and 3) an accumulation of diabetic patients due to an improvement in the prognosis of the disease. The amount of fat consumed or the change in the fat to carbohydrate ratio may not be an accelerating factor for diabetes. These phenomena observed in Japan may be a typical model of an increase in the diabetic population seen in rapidly developing and modernizing countries.

ETIOLOGY OF DIABETES and CAUSES OF DEATH in AUTOPSY CASES

Etiological classification of the cases

The Japanese Society of Pathology has published the Annual Report of Pathological Autopsy Cases since 1958. The cases registered in the reports were collected from more than two hundred hospitals all over the country. We used these reports because based on our experience that the leading cause of death was different according to location and speciality of each hospital; for example, that in some department cancer of the stomach was first and in another clinic cerebrovascular diseases was. We feel that the results of one hospital or department does not represent the general figure because of its modest number of cases and may therefore lead to an erroneous conclusion. We collected 10,272 cases of diabetes from the Annual Reports for the years 1958-80.

According to the autopsy findings, the cases were classified as in Table 5. Of the 10,272 cases, 85.9% were classified as idiopathic or primary diabetes and 14.1% as so-called secondary or other types according to the WHO classification. In

TABLE 5. *Classification of 10,727 Diabetic Autopsy Cases*

Diabetes Mellitus (idiopathic)	8825 (85.9%)
Other Types (secondary diabetes)	1447 (14.1%)
liver cirrhosis	744 (7.3)
pancreatic carcinoma	309 (3.0)
steroid diabetes	152 (1.5)
pancreatitis	96 (0.9)
hemochromatosis	79 (0.8)
endocrine disorders	54 (0.5)
miscellaneous	13 (0.1)

TABLE 6. *Change in frequency of causes of death in diabetic autopsy cases*

Cause of death	period	I	II	III	IV
	year	1958-1965	1966-1970	1971-1975	1976-1980
	Number	811	1,943	2,515	3,536
Diabetic coma		6.3%	3.8%	2.4%	2.1%
Aggravation of diabetes		6.2	1.5	0.8	0.2
Hypoglycemia		0.4	1.0	0.8	0.4
Arteriosclerotic diseases		38.2	42.4	40.2	43.6
general		4.7	3.7	2.8	1.9
renal		17.8	19.9	14.9	15.9
cerebral		8.9	11.9	12.5	14.4
coronary		6.0	6.7	9.2	11.3
gangrene		0.9	0.2	0.8	0.1
Infection		22.6	18.6	19.6	17.3
tuberculosis		8.1	3.1	2.3	1.8
pneumonia		5.5	6.0	0.6	7.0
urinary tract		3.5	3.4	4.1	2.0
liver, biliary		1.4	0.9	1.0	0.9
peritonitis		0.6	2.1	2.0	1.5
sepsis		1.4	1.5	1.7	2.1
miscellaneous		2.1	1.2	7.9	2.0
Malignant neoplasm		15.7	16.1	19.4	20.7
stomach		3.2	4.3	4.0	4.0
lung		3.3	3.9	3.8	4.4
liver, biliary		2.1	2.4	3.5	4.7
esophagus		0.5	0.7	0.9	0.6
colon, rectum		1.2	0.8	0.7	0.9
uterus, ovary		0.9	0.8	0.5	0.4
miscellaneous		4.4	3.2	6.0	5.7
Miscellaneous		10.7	17.0	16.7	15.7

the cases classified as secondary diabetes, there were cases in which the pancreatic disease was not diagnosed until autopsy. Therefore it is extremely difficult to obtain an exact frequency of idiopathic diabetes mellitus in a mass survey and we feel that it is more reasonable to use an expression of diabetic state or hyperglycemia for such cases.

Chronological changes of cause of death

Frequency of cause of death was analysed by grouping them into four periods, i.e., 1958-65, 1966-70, 1971-75, 1976-80, as shown in Table 6. A decrease is seen in the frequency of diabetic coma and infection, whereas the frequency of malignant neoplasms and cardiovascular diseases increases, especially that of coronary and cerebrovascular diseases. Since a time difference of more than ten years exists between the first period and the last period, it may be necessary to avoid the age effect when a comparison is made, because of the differing age structures among four groups. Therefore, subjects in their 60s were selected from each group and compared as shown in Table 7. The comparison was limited to vascular disorders and the figures denote the frequencies of pathological changes found at autopsy, disregarding whether they were principal or accessory. The figures for cerebral infarction and diabetic glomerulosclerosis were relatively constant whereas those for myocardial infarction and cerebral hemorrhage showed a gradual increase. It is hard to explain the increase in cerebral hemorrhage, because of its decrease in the general population, but the increase in myocardial infarction may be related to an increase of beta-lipoprotein in the plasma and/or the weight gain in the general population. It must be emphasized that myocardial infarction was extremely rare even in diabetic patients until the 1950s. In 1962, Rudnick and Anderson reported that they had found no cases with myocardial infarction among their diabetic cases in Hiroshima. The recent increase in myocardial infarction, however, is not limited to diabetic people but also in the general population, and this increase may be closely related to the changes in lifestyle in this country.

In summary, 1,447 (14%) of the 10,272 autopsy cases were classified as so-called secondary diabetes and this figure seems to show the difficulty in discrimi-

TABLE 7. *Chronological change in frequency of cardiovascular diseases in the 60s diabetic autopsy cases (%)*

Period	I	II	III	IV
Year	1958-65	66-70	71-75	76-80
(no. of cases)	(288)	(724)	(927)	(1189)
Cerebral hemorrhage	2.1	5.4	6.9	7.7
Cerebral infarction	15.3	17.1	15.8	14.6
Myocardial infarction	13.1	15.2	18.1	22.2
Diabetic glomerulosclerosis	35.1	23.8	35.0	40.0

nating idiopathic diabetes mellitus in field study and the reasonability of using an expression of hyperglycemosis instead of diabetes mellitus. Deaths attributed to diabetic coma has decreased and deaths by malignant neoplasms and cardiovascular diseases have increased ; especially the increase in myocardial infarction is remarkable.

NOTES ON COMPARISON OF FREQUENCIES OF THE CHRONIC COMPLICATIONS

The frequency of the chronic complications is usually higher in cases with poor control and long duration of diabetes than in cases with good control and short duration, and higher in elderly cases than younger cases. Namely, the frequency is influenced by age at onset and duration of the disease, and may also be influenced by the method of treatment, grade of diabetes control and so on. The frequency of diabetic retinopathy in our patients is illustrated three-dimensionally by age at diagnosis of diabetes and duration of the disease in Fig. 5. The frequency is low at the time of diagnosis, especially in younger subjects and in contrast it is very high in any groups with a duration of over ten years. It is very important to consider these points in the planning and evaluation of epidemiological studies.

Frequency of the complications is different by examination methods for the

Fig. 5. Relationships among age of diabetes onset, duration of diabetes and frequency of diabetic retinopathy.

Fig. 6. Frequency of diabetic neuropathy and duration of diabetes.

detection. Fig. 6 shows the frequency of neurological abnormalities in our patients by the duration of diabetes. In this study, we applied electrophysiological examination methods, such as estimation of nerve conduction velocity, achilles tendon reflex duration and heart rate analysis in addition to the conventional neurological tests. Abnormal findings were obtained in all cases with a duration of more than 20 years. If the study had been made using only routine tests, the frequency would be lower, because a positive achilles tendon reflex was obtained in one-third of the cases with duration of 20 years.

In summary, it must be emphasized that in epidemiological studies, the frequency of complications varies according to the quality of the population as well as to the detection or examination methods.

DISCUSSION

Machine civilization and Diabetes mellitus

The environmental condition around us has changed rapidly in this century and the effect of this change appears as an increase in diseases incidental to civilization. The increase of diabetes mellitus is one of the phenomena associated with the modern society. We feel that one great experiment is taking place in this country, i.e., the experiment observing the effects of modernization on the health of mankind.

Since when has mankind suffered from diabetes mellitus? What has happened in the human body since beginning of the civilized era? Let us consider the length of our civilization in comparison with history of the earth. If the history of the earth is likened to one year, bacteria first appeared in April, insects appeared on the 25th of October, fishes at end of November, birds on the 7th of December, dinosaurs on the 15th and the first mammals appeared on the 20th of December. The first hominid appeared at a little past noon of the last day of the year, Australopithecus appeared at 8:12 pm, Cromagnon men at 11:56 pm, man

turned from a hunter to a farmer only 70 seconds before the end of the year, and the industrial revolution happened only two seconds before New Year Day. Although it seems like a very short time in comparison with the history of the earth, the first hominid (*Ramapithecus*) appeared six million years ago and the early South African hominid called the southern ape of Africa, small-statured and small-brained, but already adapted to walking upright, appeared two million years ago. It was about ten thousand years ago when man turned from a hunter into a farmer and only since the industrial revolution people have been released from food shortage. In the history of the evolution of mankind, it may not be unreasonable to speculate that natural selection occurred in mankind to preserve (gluconeogenesis-prone) hominids whose blood glucose was maintained within normal level even in periods of prolonged food shortage and, on the other hand, to eliminate (hypoglycemia-prone) hominids whose blood glucose fell beyond normal range in periods of mild food shortage or starvation. This may be supported by the fact that the human body has several blood glucose raising hormones (glucagon, epinephrine, growth hormone, corticotropin, glucocorticoid) and only one blood glucose lowering hormone (insulin). In the same manner as we succeeded in spontaneous-diabetes rats by repeating the selective breeding using glucose intolerance as a selection indicator (Goto and Kakizaki, 1981), the long history of mankind had enough time and sufficient generations to produce a population with diabetic (gluconeogenesis-prone) diathesis through the natural selection. The remarkable increase in the diabetic population during the last half century can be understood as a dysadaptation of the human body to excess food intake, less physical exercise, increased mental stress and other diabetogenic environmental factors.

The improvement of socioeconomical and environmental conditions has undoubtedly resulted in the decrease of bacterial epidemic diseases and the prolongation of our life span. On the other hand, this improvement, however, has caused an increase of other diseases such as diabetes, obesity, atherosclerosis, malignant neoplastic diseases, and so on. As the discovery of more efficient food production using DNA technology is expected, sufficient amount of food will be supplied continuously and we, human beings, shall continue to pursue convenience and comfort in the future. In such circumstances, we shall have less occasion and less time for physical exercise and perhaps, the consequences will be a languid flabby-potbelly man with muscles so feeble that it is impossible for him to carry a gallon bottle. Hence we must establish a good lifestyle to maintain our health and avoid so-called modern diseases such as diabetes, obesity or ischemic heart disease in an affluent society.

Standardization, regulation and problems in the epidemiology of diabetes mellitus

A proposal for the standardization of glucose tolerance test and new diagnostic criteria was made by the NDDG and WHO Expert Committee. This is a

great progress and will produce many fruitful results in this field, although the method and the criteria are tentative and will have to be revised. We should continue to investigate better methods and criteria which can be applied universally.

The standardization of examination methods and of diagnostic criteria is essential especially in the studies on the diabetic chronic complications as mentioned in this dissertation and above all, guidelines should also be established for diabetic neuropathy and nephropathy in the very near future. We feel that every effort should be made to compile the data on population pyramids of each country, the standard or average body height and weight, and average nutrient intake etc, in order to facilitate the world-wide surveys on diabetes mellitus, because lack of data from the developing countries makes impossible at the present time. Kelly West, who had designed the world-wide scale study, described that the aims of epidemiological studies on diabetes were to clarify or solve the following problems: 1) the definition and classification of diabetes mellitus, 2) the analysis of the distribution of diabetes in relation to time, place, individual and natural history of the disease, 3) the clarification of the risk factors for diabetes (analytic epidemiology), and 4) prevention and treatment, and experiments to test specific hypotheses (experimental epidemiology and clinical trials). We feel that there are many problems to be solved in this field, for example: 1) whether there really are any diabetes resistant ethnic groups? 2) whether there are any microangiopathy-prone or-resistant populations? 3) whether there is any universal genetic marker for idiopathic diabetes, especially NIDDM, such as HLA? 4) which is the better for world-wide comparison of the prevalence of hyperglycemia — the glucose tolerance test or fasting plasma glucose? 5) what is the best diet for human health? We believe that the epidemiological study of diabetes will give a guideline of ideal lifestyle of human beings and finally contribute to the prosperity of our society.

References

- 1) Allan, F.N. (1953) The writings of Thomas Willis, M.D. Diabetes three hundred years ago. *Diabetes* **2**, 74-78.
- 2) Allen, F.M., Stillman, E. & Fitz, R. (1919) Total dietary regulation in the treatment of diabetes. Monograph No. 11, pp. 1-78, *Rockefeller Institute for Medical Research, New York*.
- 3) Bornstein, J. & Lawrence, R.D. (1951) Two types of diabetes mellitus with and without available plasma insulin. *Brit. med. J.* **1**, 732.
- 4) Chabanier (1953) cited from Falta, W. and Höglér, F., Die Zuckerkrankheit. *VEB Carl Marhold, Hall*, pp. 306-317.
- 5) Duncan, G.G. (1958) The modern aspects of the diabetic problem. *Bull. New York Acad. Med.* **34**, 73-84.
- 6) Falta, W. & Boller, R. (1931) Insulär und insulinresistenter Diabetes. *Klin. Wschr.* **10**, 438-443.
- 7) Goto, Y. (1978) Vascular complications in diabetes in Japan. *Adv. Metabol. Disord.* **9**, 167-200.

- 8) Goto, Y. & Kakizaki, M. (1981) The spontaneous-diabetes rat : a model of noninsulin dependent diabetes mellitus. *Proc. Japan Acad.* **57**, Ser. B, 381-384.
- 9) Goto, Y., Kakizaki, M. & Yagihashi, S. (1982) Neurological findings in spontaneously diabetic rat. *Excerpta Medica Internat. Congr. Ser.* No. 581, 26-38.
- 10) Goto, Y., Nakayama, Y. & Yagi, T. (1958) Influence of the world war II food shortage on the incidence of diabetes mellitus in Japan. *Diabetes* **7**, 133-135.
- 11) Goto, Y., Sato, S. & Masuda, M. (1974) Causes of death in 3151 diabetic autopsy cases. *Tohoku J. exp. Med.* **112**, 339-353.
- 12) Himsworth, H.P. (1935) Diet and the incidence of diabetes mellitus. *Clin. Sci.* **2**, 117-148.
- 13) Himsworth, H.P. (1936) Diabetes mellitus : its differentiation into insulin-sensitive and insulin-insensitive types. *Lancet* **1**, 127-130.
- 14) Himsworth, H.P. (1949) Diet in the aetiology of human diabetes. *Proc. Roy. Soc. Med.* **42**, 323-326.
- 15) Hugh-Jones, P. (1955) Diabetes in Jamaica. *Lancet* **2**, 891-897.
- 16) Kahn, C.R., Flier, J.S., Bar, R.S., Archer, J.A., Gorden, P., Martin, M.M. & Roth, J. (1976) The syndromes of insulin resistance and acanthosis nigricans : insulin receptor disorders in man. *New Engl. J. Med.* **294**, 739-745.
- 17) Kanazawa, Y., Hayashi, M., Ikeuchi, M., Kasuga, M., Oka, Y., Sato, H., Hiramatsu, K. & Kosaka, K. (1979) Familial proinsulinemia : a rare disorder insulin biosynthesis. *Excerpta Medica Internat. Congr. Ser.* No. 468, 262-269.
- 18) Kitazawa, Y., Uchida, T. & Goto, Y. (1979) Chronological changes in fasting blood sugar in the Japanese. *J. Japan Diab. Soc.* **22**, 527-533.
- 19) Kylin, E. (1928) Erfahrungen mit der Funktionsprobe des Inselapparates nach Depisch-Hasenöhr. *Dtsch. Arch. inn. Med.* **160**, 348-360.
- 20) Lancereaux, E. (1880) Le diabète maigre : ses symptômes, son évolution, son pronostic et son traitement : ses rapports avec les altérations du pancréas ; étude comparative du diabète maigre et du diabète gras ; coup d'oeil rétrospectif sur les diabètes. *Union méd., Paris* **29**, 161-167, 205-211.
- 21) Lawrence, R.D. (1955) Three types of human diabetes. *Ann. Int. Med.* **43**, 1199-1208.
- 22) Lyon, D.M. & Lyon, M.M. (1930) The cause of death amongst diabetes. *Lancet* **2**, 293-295.
- 23) Nakhooda, A.F., Like, A.A., Chappel, C.I., Wei, C.-N. & Marliss, E.B. (1978) The spontaneously diabetic Wistar rat (the "BB" rat). *Diabetologia* **14**, 199-207.
- 24) National Diabetes Data Group (1979) Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* **28**, 1039-1057.
- 25) Naunyn, B. (1906) *Der Diabetes mellitus*. p. 161, Hölder, Wien.
- 26) Nerup, J. & Lernmark, A. (1981) Autoimmunity in insulin-dependent diabetes mellitus. Skyler, J.S. & Cahill, G.F. Jr. eds. *Diabetes mellitus* pp. 31-37, Yorke Medicam Books.
- 27) Nerup, J., Platz, P., Anderson, O.O., Christy, M., Lyngsøe, J., Poulsen, J.E., Ryder, L. P., Nielsen, L.S., Thomsen, M. & Svejgaard, A. (1974) *Lancet* **2**, 864-866.
- 28) Owerbach, D., Poulsen, S., Billesbolle, P., Nerup, J. (1982) DNA insertion sequences near the insulin gene affect glucose regulation. *Lancet* **1**, 880-883.
- 29) Reed, J.A. (1954) Aretaeus, the Cappadocian. *Diabetes* **3**, 419-421.
- 30) Rudnick, P.A. & Anderson, P.S. (1962) Diabetes mellitus in Hiroshima, Japan. A detection program and clinical survey. *Diabetes* **11**, 533-543.
- 31) Schenck, E.G. & Mellinshoff, C.H. (1960) *Der Diabetes Mellitus als Volkskrankheit und seine Beziehung zur Ernährung*. pp. 133-198, Steinkopff Verlag, Darmstadt.
- 32) Schliack, V. (1954) Mangelernährung und Diabetesmorbidity. Untersuchungen an 11,294 Diabetikern. *Z. Klin. Med.* **151**, 382-396.
- 33) Schmidt, R. (1930) Klinik des "sthenischen" Überdruckdiabetes. *Klin. Wschr.* **9**,

1969-1974.

- 34) Suzuki, H. & Goto, Y. (1983) High fat diet and death rate of diabetes. *Tohoku J. exp. Med.* this issue, p. 309.
 - 35) Tager, H., Given, B., Baldwin, D., Mako, M., Markese, J., Rubenstein, A., Olefsky, J., Kobayashi, M., Kolterman, O. & Poucher, R. (1979) A structurally abnormal insulin causing human diabetes. *Nature* **281**, 122-125.
 - 36) WHO Expert Committee on Diabetes Mellitus (1980) *Second Report. Techn. Rep. Ser.*, No. 646, pp. 7-14, WHO, Geneva.
 - 37) Williams, R.H. ed. (1962) *Textbook of Endocrinology* p. 612, Saunders, Philadelphia.
 - 38) West, K.M. (1978) Epidemiology of diabetes and its vascular lesions. *Elsevier*. p. 3-4, p. 156, New York.
 - 39) Yamakawa, S. & Yamauchi, R. (1936) Treatment of diabetes mellitus with high carbohydrate-low fat diet. *Shindan To Chiryō* **23**, 619-641.
 - 40) Yoon, J.-W., Austin, M., Onodera, T. & Notkins, A.L. (1979) Virus induced diabetes mellitus: isolation of a virus from the pancreas of a child with diabetic ketoacidosis. *New Engl. J. Med.* **300**, 1173-1179.
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