# Variability in the Natural History of Impaired Glucose Tolerance (IGT) : Population Differences

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## INTRODUCTION

The introduction of the category of "Impaired Glucose Tolerance" (IGT) by the National Diabetes Data Group [1] and its subsequent adoption by the World Health Organisation (WHO) Expert Committee on Diabetes [2,3], was based on the observation that there are a substantial number of individuals who have fasting plasma glucose concentrations lower than that required for the diagnosis of diabetes mellitus, but in whom the plasma glucose response during an oral glucose tolerance test ( OGTT) is intermediate between normal and diabetic levels.

Prior to this, substantial differences existed in the diagnostic criteria employed by diabetologists and there was no consensus as to the dividing line between normal and diabetic glucose levels, with respect to the fasting plasma glucose concentration or its response to an oral glucose load.

With the growth of knowledge regarding the aetiology and pathogenesis of diabetes mellitus, it was recognised that there was a need for a revision of the nomenclature, diagnostic criteria and classification of diabetes mellitus.

Owing to the lack of uniformity of standardisation in defining diabetes and other stages of glucose intolerance, problems arose in comparing data from different centres, in assessing the impact of diabetes and its complications, and in determining the epidemiology of different categories of the disease.

Interpretation of plasma glucose levels in the fasting state and during OGTT had been based on a variety of criteria. West listed at least 17 sets of criteria for interpreting the OGTT[4]; of these, the 4 commonly employed were the criteria of the US Public Health Services (USPH)[5], British Diabetic Association (1964)[6], Fajans and Conn (1959, 1965) [6,7] and the WHO (1965)[8]. However, a major problem was that tests deemed abnormal by one set of criteria could be classified normal by another, resulting in widely varying estimates of the prevalence of diabetes mellitus[9].

To this end, an international workshop was convened in 1978, by the National Diabetes Data Group[1] which proposed recommendations for the classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. This was subsequently adopted with minor modifications by the WHO Expert Committee on diabetes mellitus as the revised WHO criteria [2,3].

The decision to adopt the category of impaired glucose tolerance resulted from several long- term observations in the UK and United States on groups of adults whose initial glucose intolerance was of a degree of severity hitherto loosely termed chemical, latent, subclinical or asymptomatic diabetes, but again, not based on any uniformly defined criteria. It was therefore decided that individuals with plasma glucose levels intermediate between normal and diabetic be categorised as having impaired glucose tolerance and that the previous terminologies be abandoned, since the use of the term diabetes evoked social, psychological and economic stigma and that was unjustified in the light of the lack of severity of these categories of glucose intolerance.

This significance of IGT lies in the fact that while individuals with this condition are not considered to be diabetic, prospective studies, albeit a few, have highlighted the following risks associated with IGT.

1. Progression to non-insulin-dependent diabetes mellitus (NIDDM)[10-19].

2. Increased risk for developing macrovascular disease [20-22].

3. Paucity of microvascular complications such as retinopathy and nephropathy. [1,12,20,23,24].

As regards the natural history of diabetes mellitus, prospective studies have demonstrated that subjects with IGT may follow one of the three course.

1. Persistence of IGT.
2. Reversion to normal glucose tolerance or
3. Progression (worsening) to non-insulin-dependent diabetes mellitus (NIDDM). From the reported studies quoted above, the proportion of individuals with IGT who progress to NIDDM over a ten year period varies from 13%-52% with a rate of progression of 1% - 12.5% per year [1,19].

As regards IGT and macrovascular disease (atherosclerosis), some long-term studies have demonstrated an increased frequency of morbidity

and mortality from macrovascular disease, especially coronary heart disease (CHD). The Whitehall study demonstrated that significant predictive risk factors for CHD mortality in subjects with IGT include systolic blood pressure, resting ECG abnormalities and age. Other factors include BMI, glucose, insulin and high density lipoprotein (HDL) cholesterol levels [21]. In the Bedford survey, the risk for CHD mortality was found to be increased in subjects with IGT and was greater in females[22].

Thus, whilst IGT individuals are not considered to be diabetic, they are nevertheless at a higher risk than the general population for subsequent progress to NIDDM as well as to macrovascular disease. Hence, the presence of this entity in healthy and ambulatory individuals may have prognostic implications and should therefore not be ignored.

## Rates of Progression to Diabetes Mellitus

In a prospective study in the USA, 352 non-pregnant adult females with chemical diabetes were followed up for 1-12 years [10]. Of these subjects, 25.9% were later diagnosed as having diabetes mellitus, 45% reverted to normal glucose tolerance and 30% remained in the initial impaired tolerance category. Using life-table calculations, it was found that 52.5% of these subjects would have progressed to decompensation of carbohydrate control within 10 years of diagnosis of chemical diabetes, with a rate of progression of 5% per annum.

However, these subjects could not by definition be classified IGT, since the diagnosis of chemical diabetes was based on USPHS criteria viz. 3 or more of the following parameters; fasting glucose levels > 100 mg/dl (6.1 mmol/L), 1-hour level > 170 mg/dl (9.4 mmol/L), 2-hour level 120 mg/dl (6.7 mmol/L) and 3-hour level > 110 mg/dl (6.1 mmol/L). The diagnosis of unequivocal diabetes was based on 2 or more of the following levels. Blood glucose > 300 mg/dl (16.7 mmol/L) at any time within 3-hours after 100g oral glucose load, blood glucose > 180 mg/dl ( 10 mmol/L) within 5 hours of a meal and fasting blood glucose < 120 mg/dl (6.7 mmol/L).

Not withstanding these limitations in terms of defining IGT, it is important to note that this quoted study was one of the first to highlight the increased risk of progression to unequivocal diabetes in subjects with chemical diabetes.

The second study quoted above was a 10-year follow-up study undertaken by the Birmingham Diabetes Survey Working Party (1976) in the United Kingdom[11]. In this study, 808 subjects had OGTT (using 50g glucose) performed at baseline and were classified as diabetes, normal, borderline (impaired glucose tolerance IGT) and the remainder of individuals were classed into several groups with minor degrees of glucose intolerance. Those subjects with overt diabetes were referred to their physicians, whilst those in the other categories were told that they were normal and no treatment was advised. It was the latter subjects who were followed-up at 5 and 10 years after the original test. At 10 years, 382 subjects had repeat OGTT (83% of those still alive and available for testing). At 10 years, of the 31 subjects who were originally classified as IGT 45% (14 subjects) progressed to overt diabetes, 23% (7 subjects) remained unchanged, 32% (10 subjects) reverted to normal (2 subjects) or had minor glucose abnormalities (8 subjects). Thus, the average rate of decompensation of IGT to overt diabetes in that study was 4.5% per annum. None of the subjects who had normal glucose tolerance in the original study progressed to diabetes at the follow-up.

These borderline diabetic subjects also could not, strictly speaking, be classified as IGT, because 50g oral GTT's were performed; GTT diabetes was based on fasting capillary, whole blood glucose > 7.2 mmol/L and a 2-hour level > 7.5 mmol/L with a 1-hour level > 10 mmol/L. Overt diabetes was diagnosed in those subjects whose fasting blood glucose exceeded 7.2 mmol/L. Diagnosis of normal glucose tolerance was based on fasting glucose<5.6, 1-hour <10, and 2-hour < 7.5 mmol/L.

In addition, whilst 45% of IGT subjects progressed to overt diabetes in the Birmingham study, it must be noted that the actual number studied was small i.e. only 31 of the 393 subjects who were retested at 10 years, were originally defined as IGT subjects (7.9%).

Nevertheless, the above study was important for several reasons. Firstly, it highlighted the significance of the category of IGT with regard to progression to overt diabetes; secondly higher 2-hour blood glucose levels ( 7.5 mmol/L vs 6.7 mmol/L) were adopted for follow-up study, that regardless of the original GTT category, nearly all these subjects who progressed to florid diabetes, had 2-hour blood glucose levels > 7.5 mmol/L in the first test. (Birmingham Diabetes Survey Working Party, 1970). Thirdly, the results of the study suggested that normal glucose tolerance could be redefined at a higher 2-hour blood glucose level of >7.5 mmol/L (vs 6.7 mmol/L used previously).

In addition, since in that study, the 10-year mortality was low in subjects with IGT, it was proposed that the options in management of such subjects include either treatment with oral hypoglycaemic agents ( in the hope of preventing progression to diabetes), or yearly review (so that the florid state may be recognised and treated as soon as possible). Thirteen years later and after a few more prospective studies, little has changed with respect to originally proposed recommendations for the management of IGT subjects. Finally, in the Birmingham study, it was found that no striking difference emerged as a result of 10-years of follow-up, as opposed to the 5-year follow-up. Whilst the proportion of retested subjects developing both florid and IGT diabetes had increased, it had not doubled between 5 years and 10 years. Moreover, with longer periods of follow-up, the loss of subjects for various reasons during this period may actually prevent a meaningful result.

The third long-term study, was the Bedford study in the United Kingdom [13]. In this well designed, 10 year prospective study (1962-1972) the diagnosis of IGT was based on 2-hour capillary blood glucose level 6.7 mmol/L - 11.1 mmol/L, using a 50g oral GTT. Of 241 subjects with IGT who were followed up, 15% (36 subjects) worsened to diabetes, 53% ( 128 subjects) reverted to normal glucose tolerance, 22.8% (55 subjects) persisted with IGT and 9% ( 22 subjects) remained uncategorised. The average rate of worsening to diabetes (w.t.d.) was 1.5% per annum. Of the many variables analysed, the major predictor of w.t.d., was the level of blood glucose at baseline.

BMI, whilst not a predictor for w.t.d., in the first 5 years, was an independent and significant risk factor during the second 5 years. In addition, in the Bedford survey, the subjects were randomly assigned to 4 treatment groups based on 2 x 2 designtolbutamide or placebo tablet; dietary CHO restriction or simple restriction of table sugar. However, the treatment ( tolbutamide and/or dietary CHO restriction) had no significant effect on glucose tolerance.

In another British study viz the Whitehall study [12,15],of the 204 male civil servants who were diagnosed as IGT and who were followed up for 5 years, 13.2% (27 subjects) worsened to diabetes. Of the baseline variables studied, only the blood glucose values were significantly predictive of w.t.d. As in the Bedford study, the subjects were randomly allocated to one of the 4 treatment groups : 120 g/day CHO diet + placebo; 120g/day+50 mg phenformin ; limited sucrose (table sugar) intake + 50 mg phenformin. Treatment had no significant effect on glucose tolerance in the Whitehall study.
The Whitehall study also cannot be strictly compared with other prospective studies on IGT because of different methods and criteria employed. In that study, 50 g oral GTT was performed in the afternoon and this may interfere with results due to possible diurnal variations in blood glucose levels [1,8,26]. The criteria for diagnosis of IGT was based on (I) a screening capillary blood glucose 6.1 - 11.1 mmol/L2- hours after 50g oral glucose ; and (ii) at OGTT, a peak blood glucose > 10 mmol/L and 2-hour level of 6.7 - 11.1 mmol/L and/or 2 values < 10 mmol/L and /or Mean 2- hour blood glucose levels (screening and GTT) > 6.7 mml/L. Moreover, the diagnosis of diabetes was based on arbitrary criteria viz. (1) 2 successive or 3 non-successive 2 - hour post 50g glucose capillary blood glucose level > 11.1 mmol/L (ii) 2-hour blood glucose > 11.1 mmol/L at OGTT performed on the 10th visit, irrespective of whether previous 2-hour values were also elevated; (iii) unequivocal symptoms or signs of diabetes mellitus. Of historical interest is that the authors of the Whitehall study suggested that the descriptive term of IGT be coined in order to avoid the word diabetes with all its implications.

In summary, each of the 4 studies just quoted were done in different population groups, selected in different ways, and differing in the methods used and in the criteria adopted for defining worsening to diabetes. Nevertheless, the single point that emerged was that the levels of blood glucose themselves, however defined, best predict subsequent worsening to diabetes.

Studies based on the WHO definition of IGT with respect to methodology and criteria employed include the studies on the natural history of IGT in Pima Indians and Nauruans, two- populations with the highest prevalence of diabetes mellitus and IGT respectively [27,28,29].

In a follow up study of 384 Pima Indians with IGT over a period of 1.6 - 11.5 years, 31% (118 subjects) progressed to IGT, and 43% (166 subjects) reverted to normal glucose tolerance [18]. The cumulative incidence of NIDDM in that study was 25% and 61% at 5 years and 10 years, respectively (rate of progression 5% - 6% per annum).

Findings similar to those in Pima Indians were reported in 6-year follow-up study of 51 Nauruan subjects with IGT [17]. In that study, 26% ( 13 subjects) progressed to NIDDM, 35% (18 subjects) persisted with IGT and 39% (20 subjects) reverted to normal glucose tolerance; the crude rate of progression NIDDM was 4 % per annum.

In a 7-year follow-up of 13 Japanese subjects with IGT, 38.5% (5 subjects) progressed to NIDDM, 23.1% (3 subjects) persisted with IGT and 38.5% ( 5 subjects) reverted to normal glucose tolerance [14]. However, the obvious limitation in that study was the sample size, making comparison difficult; in addition, 50g oral GTT was performed.

In another Japanese study, 288 subjects with IGT were followed up for 5-12 years[16]. 16.7% (48 subjects) progressed to NIDDM during the study period, and significant risk factors for subsequent w.t.d., included baseline plasma glucose levels (fasting and 2-hour levels), high maximal body weight index and a diminished insulin response. However, in that study glucose tolerance was based on 100g oral GTT and the diagnosis criteria employed were those of the Japan Diabetic Society, which differs from WHO criteria; in addition the study population was clinic based. All these factors make comparison between that and the present study difficult.

A 10-year follow-up study was performed on 267 Swedish men with IGT; that study also examined the effects of tolbutamide and diet regulation on the halting progression to diabetes [30]. At follow -up, 29% of 59 subjects on no treatment (17 subjects) progressed to NIDDM ; whilst none of the 23 subjects (23 or 49 subjects) who were commenced on tolbutamide and diet regulation, progressed to NIDDM [30] . However, different diagnostic criteria employed in that study make comparison with the present one somewhat difficult.

In a 6-year longitudinal study in Malta of the 75 subjects with IGT (35 males and 40 females), 30.7% progressed to NIDDM, 36% persisted with IGT, and 33% reverted to normal glucose tolerance; the rate of progression was 5.1% per annum [31].

The highest rate of progression to diabetes was recorded in a 4-year prospective study of 128 South African Indian subjects with IGT which highlighted a progression rate of 12.5% per annum, 50.4% becoming diabetic over the study period [19]. The proportion reverting to normal glucose tolerance (24.8%) and those persisting as IGT (24.8%) were similar [23].

An interesting finding in this study was the variability of OGTT results in the same patient, at the various stages of the study. In most of the other reported longitudinal studies, each subject had 2 OGTT, - at baseline and at end-point of the study, but no GTT was performed in the interim period. In the present study, OGTT was performed at year 0, year 1, and year 4 and a subset of the subjects also had OGTT at year 2. Two subjects (IGT1) who were classified IGT at year 1 and who persisted with IGT at year 4 had in fact reverted to normal at year 2; whilst an- other 2 such subjects who reverted to normal at year 4 had persisted with IGT at year 2.

Two subjects who were classified as normal at year 1, and who progressed to IGT at year 4, had normal glucose tolerance at year 2, whilst one such subject who remained normal at year 4 had in fact progressed to IGT at year 2[19]. The significance, if any, of this finding, is unknown. Owing to the lack of reported data on the variability of OGTT in long-term studies of IGT, comparison is not possible.

## Risks factors for progression to NIDDM

With respect to examination of risk factors associated with progression to NIDDM in subjects with IGT, a multitude of clinical and biochemical factors have been studied in the literature and include plasma glucose concentration at the initial (baseline) OGTT, age, sex, BMI, family history of diabetes, blood pressure, plasma insulin during OGTT, plasma lipids and serum creatinine.

Of all the factors studied to date, the single most important predictor (risk factor ) for the subsequent progression to NIDDM in IGT subjects has been the plasma glucose concentration at the initial OGTT [10, 12, 13,14, 16 -19, 31]; other less consistent factors include BMI [13, 14, 31,32] and plasma insulin levels [14, 18, 33].

In the study on South African Indians, when baseline variables at year 0 were examined, the significant independent predictive risk factors for subsequent progression to diabetes in IGT subjects included both, fasting and 2-hr plasma glucose levels; sex and BMI which were significant in the univariate analysis, failed to achieve significance in the multivariate analysis [19,23].

In three reported studies, only the 2-hr plasma glucose levels were found to be a significant predictor [13,32,34]. In the Bedford survey and Whitehall survey only 2 -hr plasma glucose values were include in the analysis, whilst in pima Indians and South African Indians both fasting and 2-hr plasma glucose values were examined. The finding of baseline fasting plasma glucose level as a predictor was reported in a study which examined the effect of diet and chlorpropamide on IGT subjects over a six year period [35].

Therefore, each of the studies quoted, including the present study have observed different population

groups, some selected in different ways and differing in the methods and criteria adopted for defining progression to diabetes - nevertheless, the single point that emerges is that the baseline levels of blood glucose themselves, however, defined, best predict subsequent progression to diabetes mellitus in IGT subjects.

The role of BMI (and obesity) as a predictive risk factor for progression to diabetes in IGT subjects is less consistent. Obesity has sometimes [10,13,16,31] not invariably [12,13,14,17,18,19] been a significant predictor for subsequent development of diabetes.

In the South African Indians with IGT, the mean BMI (P=0.0019) and the prevalence of obesity (51.8% vs 28.6%, p=0.012) was significantly higher in subjects who progressed to NIDDM compared to those who did not [19]. However, BMI which was significant in the univariate analysis failed to achieve significance in the multivariate analysis. This finding is consistent with reported studies on other populations viz. Pima Indians [18], Nauruans [17], Japanese [14].
In the Bedford survey BMI was not a significant predictive marker in the first five years, but achieved significance in the second five years of the study period [13]. In the Whitehall study BMI was not significant even in the univariate analysis [12].

However, the role of BMI (and obesity) should not be completely dismissed, since it is possible that if the subjects were followed up for longer periods its significance may assume greater importance.
In the South African Indians, univariate analysis showed that of the females 59.6% progressed to diabetes whilst 40.4% did not progress; the reverse was true for males in whom 41% progress to NIDDM whilst 59% did not. This appeared to indicate that the risk for subsequent development of NIDDM was higher in IGT females than males[19]. However, sex, which was significant in the univariate analysis, failed to achieve significance in the multivariate analysis. Whether this was due to the confounding effect of obesity which was more prevalent in females, is not clear; but perhaps a close relationship between obesity and female sex could explain this finding.

Therefore, it would appear that in South African Indians subjects with IGT, the risk of progression to diabetes is total, if baseline 2-hr plasma glucose is ≥ 10.2 mmol/L or if baseline plasma glucose ≥ 7.3 mmol/L [19].

In the 4-year prospective study in this population group, a separate analysis of data with year 1 baseline was also undertaken, since more detailed clinical and biochemical parameters were examined.

When year 1 was used as the baseline, the single independent predictive risk factor for subsequent progression to diabetes was the 90 min plasma glucose level (mid-test level). Systolic blood pressure, 30 min plasma glucose and 60 min plasma glucose and a positive history of paternal diabetes, which were significant in the univariate analysis failed to achieve significance in the multivariate analysis. None of the remaining numerous variables analysed were found to be significant viz. Plasma insulin response during OGTT, insulin ratios, lipid levels, glycated haemoglobin, serum uric acid as well as fasting and 2-hr-plasma glucose.

An interesting finding in that study was that in the univariate analysis, systolic blood pressure was significantly higher in subjects who progressed to NIDDM although it lost significance in the multivariate analysis[19]. Blood pressure has been analysed in four other reported studies [12, 13, 17, 18, 32].

In the Bedford survey and the 5-year report on the Whitehall study (1979), blood pressure was not found to be significantly different in the group which progressed to NIDDM compared to the group which did not. In both the Nauruan and the 10 year report on the Whitehall study systolic blood pressure, which was not significant in univariate analysis was found to be negatively associated with subsequent diabetes in the multivariate analysis; in the Nauruan study this finding was explained by the confounding effect ; of age but in the Whitehall study the finding was difficult to explain[17,32].

A further interesting observation in the South African study was that in the univariate analysis, a positive history of paternal diabetes was significantly higher in subjects who progressed to NIDDM, although it lost significance in the multivariate analysis. Family history of diabetes has not been found to be a predictive risk factor for w.t.d. in most of the studies in which it has been examined, even in populations in which the prevalence of diabetes is high viz. pima Indians and Nauruans [13,16,18,32]. Family history as a risk factor was not analysed in some of the prospective studies [11,14,30]. In the Maltese study, parental history of diabetes was only a significant predictor of future diabetes in older normoglycaemic men, not in subjects who were IGT at baseline[31].

Most studies have shown that IGT is characterised by hyperinsulinaemia (fasting and 2 hr levels) and

insulin resistance. However, their role in predicting progression to diabetics is not clear.

In Pima Indians, those IGT subjects who progressed to NIDDM were characterised by higher baseline fasting insulin, lower post load (2-hr) insulin, lower post load insulin: glucose ratio and lower post-load ratio of increment of insulin to increment to glucose [18]. The finding of decreased post-load insulin as a predictor for subsequent diabetes has been reported in two other studies [16,33]. In the Japanese study, decreased 30 min insulin level was significant whilst in Nauruans, a decreased 2-hr insulin level was found to be a significant predictor. Of note, though, was that in the Nauruan study, a diminished 2-hr insulin response just failed to achieve significance with the use of the glucose-insulin interaction term.

Saad's finding that decreased insulin response served as a predictor for diabetes in Pima Indians was confirmed in another study [18,36]; however in a third and earlier study on Pima Indians, no evidence was found that subjects destined to have diabetes has either excessive or diminished insulin response[37]. In the Bedford study, 2-hr plasma insulin was analysed but was not found to be a predictor[13].

Whilst South African Indians with IGT do show hyperinsulinaemia and insulin resistance, this parameter appears to play little role as a risk factor for progression to NIDDM[19].

The finding in the South African Indian study that when year 1 was used as baseline, the significant predictor was 90 min plasma glucose (mid test level) deserves comment [19]. As discussed earlier, some of the prospective studies on IGT were undertaken prior to the introduction of the currently employed WHO criteria for glucose tolerance [10,11,14,16,32].

Not withstanding their value with respect to the understanding of the category of IGT, they differed from later studies in that different criteria for glucose tolerance were employed [10,11-13] or that different glucose loads were employed (all the studies quoted above), or that OGTT's were performed in the afternoon [12,32] or that subjects were clinic based [16].

Prospective studies employing WHO criteria (75 g OGTT after overnight fast) includes those on Nauruans [17,18,31,34], Pima Indians, and Maltese. In all these studies which were large scale epidemiological studies, only fasting and 2-hr plasma glucose levels were estimated ( as recommended by WHO ), as was the case in the baseline examination (year 0) of the present study; mid-test glucose levels were not estimated.

Currently, the most widely employed criteria for glucose tolerance include those of the WHO [2,3] and the NDDG[1]. Whilst the recommendations of the two groups are similar in many ways, two major differences between them include; (a) cut off levels for fasting plasma glucose and (b) the requirement for mid-test samples in the NDDG recommendation as opposed to only fasting and 2-hr samples recommended by WHO.

Subsequent to its original recommendation (1979), the NDDG reviewed the international criteria for the diagnosis of diabetes and IGT [38]. From the review it was concluded that the WHO system represented a simpler, inclusive classification scheme and that there was insufficient evidence from longitudinal studies of any prognostic difference that would justify the more complicated NDDG diagnostic criteria (which included mid- test samples). Another reason why mid-test values were not considered essential was that whilst there were studies which confirmed fasting and 2-hr plasma glucose values as predicted risk factors for the development of diabetes in IGT subjects, there was no data to support such findings for any particular mid-test value.

One of the reasons for the appeal from the WHO for population based studies on IGT1 is that such studies might provide evidence concerning the present diagnostic criteria for glucose tolerance [2,3].

In the South African study, at year 0, fasting and 2 hr plasma glucose levels were estimated (in accordance with WHO recommendations). Those subjects examined at year 1,2 and 4 had OGTT with mid-test plasma glucose estimations as well (0,15,30,60,90 and 120 min). At year 1, 47 subjects were diagnosed as IGT (IGT1). In order to assess the significance of the numerous biochemical parameters examined, year 1 was used as baseline for the follow-up of IGT1 subjects. An interesting finding was that with year 1 as baseline, the most significant predictive risk factor for subsequent progression to diabetes was the 90 min plasma glucose (mid test level); a surprising finding was that neither fasting nor 2-hr plasma glucose were significant [19].

Comparison with other studies is not possible since none of the quoted prospective studies has examined mid-test glucose levels, and therefore there is no existing data to indicate whether a particular mid-

test glucose value is a better predictor than fasting and 2-hr glucose values.

In the more recent evaluation of WHO and NDDG criteria for IGT [39], it has been suggested that, in prospective studies of IGT, at least 3 plasma glucose samples during OGTT viz. fasting + 2-hr + mid-test (30, 60, or 90 min) be used. The finding of the present study would support this view; however, whether subjects should have 3 mid test values (30, 60, and 0 min) or only a single mid test values (and if so, which mid-test value) is not clear, especially in view of the finding in the present study that the 90 min and not 60 min value was a significant predictor; moreover there still exists the practical problem of multiple venepunctures in large scale epidemiological studies. Certainly, the South African study emphasises the need for further studies to assess the significance of mid-test glucose values in subjects with IGT.

## Intervention Studies on IGT

The arguments for detection of IGT would appear to rest on the ability to institute prophylactic measures against progression to NIDDM or to detect diabetes mellitus early after its development and so possibly prevent diabetic vascular complications by therapy.

However, evidence from the few prospective studies done to date show conflicting results in terms of any beneficial effect that therapy in such patients may have in the subsequent progression to NIDDM [ 16, 17, 25, 30 ].

As regards the effect that treatment has on IGT worsening to diabetes, only three studies, using oral hypoglycaemic agents, have thus far been reported [ 16, 17, 30]. However, all these studies have shortcomings in terms of sample size. Moreover there was a significant cohort drop out rate in the Swedish study [30]. Not withstanding the shortcomings, the last study showed that while none of the twenty three subjects who continued on a regimen of dietary restriction and tolbutamide progressed to diabetes mellitus over a ten year period, 29 % of those on no treatment progressed to diabetes mellitus. In contrast, the two British studies, the Whitehall survey and the Bedford survey demonstrated that worsening to diabetes was not significantly influenced by treatment, which included carbohydrate restriction combined with phenformin (Whitehall survey) or tolbutaminde (Bedford survey), or carbohydrate restriction alone [16,17].

On the basis of these studies, a number of possible strategies may be implemented regarding the approach to management of subjects with IGT[40]: these include 1) observation without treatment but with follow-up OGTT. 2) Weight reduction by caloric restriction and exercise . 3) management of risk factors for CHD viz. Hypertension, and 4) drug therapy.

The lack of uniformity in decisions on management is largely due to the fact that there have been surprisingly few studies done to determine the effects of intervention on IGT. As Bennet has highlighted, there is a need for further population-based studies, since if intervention could successfully alter the natural history of IGT, it would be a major public health achievement, which could lead to a reduction in the incidence of diabetes mellitus and perhaps also CHD[40].

However, before interventional studies are undertaken, it is vital that more prospective population based studies be performed to determine the significance of IGT with respect to its mechanisms and prognostic implications in different populations.

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