The Genetics of Non Insulin Dependent Diabetes Mellitus (NIDDM) in Africa

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NIDDM as a genetic disorder

NIDDM is one of the commonest metabolic disorders encountered in clinical practice, affecting an estimated 3% of the population of the Western World [1]. Prevalence data from Africa have recently been reviewed [2] and it appears that NIDDM has a prevalence in South Africa comparable to that found in developed countries, with a similar rate in rural and urban populations. In the northern part of South Africa, the available data indicates a low prevalence rate in both rural and urban populations in most areas studied [3]. However, in some countries, such as Tunisia, the prevalence in urban communities is similar to that of the Western World [4].

The pathogenesis of NIDDM is not known, but it is widely believed that the disorder has a significant genetic component which acts together with environmental factors such as obesity in determining the clinical expression of the disease. The evidence for the existence of the hypothetical genotype is derived primarily from epidemiological data from three main sources; population studies, twin studies and family studies.

(a) Population Studies

The prevalence of NIDDM varies widely from <3% in some developing countries to 50% in Pima Indians [5] and there is evidence to suggest that the effect is partly accounted for by genetic factors [6]. The influence of population genetics on the prevalence of NIDDM was clearly demonstrated in a study of the Micronesian population of Nauru in 1982 [7[. HLA typing was used as a means of identifying the degree of foreign genetic admixture in this relatively isolated population, and it was shown that full-blooded Nauruans had a significantly greater prevalence of NIDDM than those with foreign genetic admixture in whom the putative diabetic genotype had presumably been diluted. Similar findings have been reported from studies in Mexican Americans [8].

Migrant Asian Indian populations have a higher prevalence of NIDDM than both the population of India and the population in the country of settlement, suggesting a founder gene effect with concentration by generations of inbreeding [9]. In South Africa, the Indian population has an age-adjusted prevalence of NIDDM of 13%, which is higher than any other population group in the country [10].

Studies of the Pima Indians have provided further evidence for a genetic component in that population, with a bimodal distribution of glucose tolerance suggesting a single major gene determining diabetes susceptibility [1].

(b) Twin Studies

Prevalence studies in monozygotic and dizygotic twins with IDDM and NIDDM have added to the thesis that the genetic influence in NIDDM is significant. Barnett et al studied 200 pairs of British monozygotic twin and found 48 of 53 pairs (90.6%) concordant for NIDDM, while only 80 of 147 pairs (54.4%) concordant for IDDM [12]. Newman et al studied American male monozygotic and dizygotic twins and found a 58% concordance rate for NIDDM in monozygotic twins, with 65% of the non-diabetic monozygotic twins demonstrating abnormal glucose tolerance [13]. Problems with follow-up precluded direct comparison with the dizygotic twins.

(c) Family Studies

It has long been noted that NIDDM tends to cluster in families [14] with a risk of 50% for the development of NIDDM in the offspring of two affected parents [15]. Furthermore, numerous studies have shown that non-diabetic first-degree relatives of NIDDM probands have abnormalities in glucose metabolism. Eriksson et al studied 26 first degree relatives of NIDDM patients, 19 patients with NIDDM and 14 healthy controls and found impaired non-oxidative glucose metabolism in normal controls, with impairment in first-phase insulin secretion additionally present in relatives with impaired glucose tolerance [16]. Similar findings have been reported by others [17, 18] and the subject has been recently reviewed in relation to the pathogenesis of NIDDM [19].

Thus, the collective evidence argues strongly for a major genetic component in the pathogenesis of NIDDM, although the nature of the defect remains unknown. Furthermore, the role of environmental factors, including diet, physical activity and obesity play an undefined role in enhancing expression of the genotype.

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Methods of searching for the diabetes genes have used traditional linkage analysis and with the advent of new biotechnology, direct molecular screening of candidate genes for mutations. Despite these techniques, the genetic defect remains undefined in majority of patients with NIDDM.

2) Studies of Candidate Genes

a) The insulin gene

The insulin gene is located on the short arm of chromosome 11[20] and is composed of 1430 base pairs with three exon and two introns. The gene is flanked by the tyrosine hydroxylase gene on the 5' end [21] and by the insulin-like growth factor gene on the 3' end [22]. Inherited defects in the coding regions of the insulin gene have been described, but these are rare and comprise a minority of the diabetic population. Studies of the insulin gene using restriction fragment length polymorphisms (RFLP's) have failed to demonstrate a significant role for the insulin gene in NIDDM using different models of inheritance [23, 24].

More recently, application of the polymerase chain reaction (PCR) and single stranded conformational polymorphism (SSCP) as a mutation screening method, identified an abnormal insulin promoter in American Blacks with NIDDM [25]. It was estimated that this abnormality contributed to diabetes in approximately 5% of this population with NIDDM.

Therefore, from the evidence to date, the conclusion is that insulin gene defects contribute to a minority of patients with NIDDM.

b) The Insulin receptor (INSR) gene

The INSR gene is composed of 22 exons and 21 introns and is located on the distal end of the short arm of chromosome 19 [26]. Metabolic studies have indicated that insulin resistance forms an integral stages of NIDDM and hence the INSR gene is a logical candidate gene to study. Mutations in the INSR gene have been found in association with states of extreme insulin resistance such as Leprechaunism and the Rabson-Mendenhall syndrome [27]. In these conditions, mutations have been described in many of the exons of the INSR gene, with consequent biochemical defects differing according to the mutation [27]. Linkage studies have implicated the INSR gene in the pathogenesis of NIDDM [28, 29] and since insulin resistance in NIDDM [28, 29] and since insulin resistance in NIDDM appears to be associated with an abnormality of signal transduction [30], molecular studies have focused on analysis of

exons 13-21 which encode information for signal transduction.

Using PCR-SSCP, however, no significant abnormalities of this part of the INSR gene have been identified in patients with NIDDM [31]. More recently, attention has been directed towards analysis of genes encoding proteins involved in the post-receptor signal transduction cascade such as insulin receptor substrate-1 [32] to further explore the mechanisms of insulin resistance in patients with NIDDM.

c) The glucokinase gene

Glucokinase (GK) is one of a family of hexokinases that is expressed in the pancreatic b -cell and the liver. In the b -cell, GK appears to act as a "glucose sensor", providing the cell with information of the prevailing blood glucose concentration and thereby regulating insulin secretion [33]. The GK gene, on chromosome 7, has been one of the most informative loci yet examined, yielding evidence of pathogenetic role in maturity-onset-diabetes of the young (MODY) sub-group of NIDDM. This disorder is inherited in an autosomal dominant fashion and has a typical clinical expression with early onset of hyperglycemia, due to a b -cell defect and slow progression [34]. The heterogeneity exists with a number of different mutations described in French and British pedigrees with MODY [35, 36]. The genetic diversity is further emphasized by the finding that mutations of the GK gene are not invariably found in pedigrees with MODY [34]. Nonetheless, this group of patients represent the largest subgroup of diabetics in whom the genetic defect is characterized.

Analysis of the GK gene in typical NIDDM has been informative [37]. The mutations described in some pedigrees have been associated with a clinical phenotype resembling MODY and thus may represent MODY diagnosed later in life [38]. It has been estimated that glucokinase gene abnormalities probably account for < 1% of cases of typical NIDDM [39].

d) Glucose transporter genes

The family of glucose transporters comprise of six facilitative glucose transport molecules with different sites of expression and physico-chemical properties [40]. Glucose transporter 2 (GLUT 2) is expressed in the liver and pancreatic islet and GLUT 4 is expressed in muscle and fat [40]. With the important roles these tissues play in glucose homeostasis, the GLUT 4 genes were considered excellent candidate genes to study in patients with NIDDM.

Evidence for GLUT 2 being important in the pathogenesis of NIDDM was provided by studies in diabetic rats which showed a significant reduction in pancreatic b -cell GLUT 2 immunostaining in diabetic rats as compared to controls which was shown to be unrelated to the effect of chronic hyperglycemia [41]. The postulates of the role of GLUT 2 dysfunction included that of chronic sub-optimal b -cell glucose transport relaying inaccurate information regarding the prevailing blood glucose concentration, consequently resulting in an inappropriately low insulin secretary response [41]. A second postulate was that GLUT 2 is lost in the development of NIDDM and is replaced by a low Km transporter (e.g. GLUT 1), thus producing the hypothetical b -cell "exhaustion" [42].

Linkage studies with GLUT 2 gene polymorphisms have not shown a significant association with NIDDM [43, 44] and direct molecular scanning has identified a missense mutation in exon 3 of the gene in Pima Indians, but is of uncertain significance [45].

Similarly, analysis of the GLUT 4 gene by linkage studies and direct molecular approaches have failed to demonstrate a significant role for this locus in the pathogenesis of NIDDM [46, 47] and it appears unlikely that mutations of glucose transporter genes will account for more than a minority of cases of NIDDM.

(e) The mitochondrial genome

The mitochondrial genome is a small double-stranded circular structure composed of 16,569 base pairs with no intron sequences [48]. The genome contains 37 genes which encode 13 proteins involved in the respiratory chain as well as molecules involved in protein synthesis [48]. The mitochondrial genome is entirely maternally derived and evidence has been presented that the inheritance of NIDDM has a maternal predominance [47, 49, 50]. This observation, coupled with the fact that oxidative metabolism in the b -cell is important in the regulation of insulin production [51] has led to analysis of the mitochondrial genome in NIDDM.

Mitochondrial cytopathies are recognized causes of disease and abnormalities in mitochondrial DNA have been described in association with the Kearns-Sayre syndrome, Pearson syndrome, Leber hereditary optic neuropathy, myoclonic epilepsy with ragged red fibres (MERRF), mitochondrial myopathy, lactic acidosis and stroke-like episodes (MELAS) and others [48].

Recently, Reardon et al [52] described a family with diabetes, sensorineural deafness and cardiomyopathy associated with the same mutation in mitochondrial DNA previously described by Goto et al in the MELAS syndrome [53]. This mutation was a point mutation at position 3243 of the t-RNA (leu) mitochondrial gene and has subsequently been found in other pedigrees in whom diabetes forms part of a variable syndrome including deafness and other neurological disorders (54, 55).

A second mitochondrial genetic abnormality associated with diabetes and deafness has been described in a family without evidence of neurological disease. This abnormality was 10.4 kb deletion of mitochondrial DNA [56].

Studies of the mitochondrial genome in diabetes are ongoing and additional defects may well be found. These will account for a subgroup of diabetics in defined as that of maternally inherited late onset insulinopaenic diabetes variably associated with deafness and other neurological disorders [57].

(f) Other candidate loci

Other genetic loci examined in relation to NIDDM include, amongst others, the glycogen synthase gene [58], insulin receptor substrate-1 gene [32], the hexokinase II gene [59] and HLA loci [60].

Taken together, the results of analysis of candidate genetic loci provide evidence of specific genetic susceptibility only for and estimated 5% of the cases of NIDDM. Thus, the nature of the putative loci conferring disease susceptibility in majority of the cases of NIDDM remain unknown, albeit the subject of earnest research.

The genetics of NIDDM in Africa

The contribution of genetic factors to NIDDM susceptibility in Africa is unknown and, indeed, the question as to whether diabetes in Africa is the same disease as that found in the developed world is unanswered.

A limited role for genetic factors in NIDDM in Africa was suggested by McLarty et al in a review of diabetes in Africa, with the finding that a positive family history of diabetes was reported in most published studies, although in the majority, was less than 10% [3]. Apart from the information provided by these studies, there is little further detail regarding inheritance patterns of NIDDM in the various countries of Africa.

Malnutrition is common in Africa and other developing countries, yet malnutrition-related diabetes (MRD) is uncommon as a recognized disease entity [61]. Apartment MRD, there may be a role for

malnutrition in the intrauterine and early post-natal life in the genesis of typical adult NIDDM. It is possible that the "inheritance" of NIDDM in Africa is related to pre and post-natal malnutrition with consequent impairment of normal pancreatic islet development. This would manifest as NIDDM in adults as the development of obesity or other factors induce insulin resistance, in a manner analogous to the thrifty phenotype hypothesis proposed by Hales and Barker [62].

These mechanisms have been suggested by Joffe et al in South African Blacks living in the Johannesburg region [63] with support provided by earlier studies showing that insulin secretary capacity is reduced in obese non-diabetic Blacks as compared to obese non-diabetic Whites [64].

Conclusion

The genetic contribution to NIDDM in the developed world is widely accepted with much supportive evidence, but the situation in Africa is at present unclear with insufficient data on which to base such an assumption. Clearly, there is a need for well-planned epidemiological surveys complemented by research into the pathogenetic mechanisms of NIDDM specific to Africa.

REFERENCES

1. Harris MI, Hadden WC, Knowler MC, Bennett PH. Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in US populations aged 20-74 yr. Diabetes 1987; 36 : 523-34.
2. Motala AA, Omar MAK, NIDDM in Africans – is it increasing? IDF Bulletin 1992; 40 : 23-6.
3. McLarty DG, Pollitt C, Swai ABM. Diabetes in Africa. Diabetic Med 1990; 7 : 670-84.
4. Papoz L, Ben Khalifa F, Eschwege E, Ben Ayed H. Diabetes mellitus in Tunisia : descriptions in urban and rural populations. Int J Epidemiol 1988; 17 : 419-22.
5. King H, Rewers M. WHO ad Hoc Diabetes Reporting Group: Global estimates for prevalence of diabetes mellitus and impaired glucose tolerance in adults. Diabetes Care 1993; 16 : 157-77.
6. Wendorf M, Goldfin ID. Archaecology of NIDDM : excavation of the "thrifty" genotype. Diabetes 1991; 40 : 161-5.
7. Serjeantson SW, Owerbach D, Zimmet P, Nerup J, Thoma K. Genetics of diabetes in Nauru : effects of foreign admixture, HLA antingens and the insulin-gene-linked polymorphism. Diabetologia 1983; 25 : 13-7.
8. Gardner LI, Stern MP, Haffner SM et al. Prevalence of diabetes in Mexican American Sources. Diabetes 1984; 33 : 86-92.
9. Dowse GK, Gareeboo H, Zimmet PZ et al. Mauritius non-communicable disease study group : high prevalence of NIDDM and impaired glucose tolerance in Indian, Creole and Chinese Mauritians. Diabetes 1990; 39 : 390-6.
10. Omar MAK, Motala AA, Seedat MA et al. South African Indians show a high prevalence of NIDDM and bimodality in plasma glucose distribution patterns. Diabetes care 1994; 17 : 70-3.
11. Bennett P, Rushforth N, Miller M, Le Compte P. Epidemiologic studies of diabetes mellitus in the Pima Indians. Recent progress in hormone research 1976; 32 : 333-75.
12. Barnett AH, Eff C, Leslie RDE, Pyke DA. Diabetes in identical twins : a study of 200 pairs. Diabetologia 1981; 20 : 87-93.
13. Newman B, Selby JV, King MC et al. Concordance for Type 2 diabetes mellitus in male twins. Diabetologia 1987; 30 : 763-8.
14. Harris H. The familial distribution of diabetes mellitus : a study of the relatives of 1241 diabetic propositi. Ann Eugen 1950; 15 : 95-110.
15. Viswanathan M, Mohan V, Snehalatha C, Ramachandran A. High prevalence of Type 2 diabetes among the offspring of conjugal Type 2 diabetic parents. Diabetologia 1985; 28 : 907-10.
16. Eriksson J, Franscila Kallunki A, Ekstarnd A et al. Early metabolic defects in persons at increased risk for non-insulin-dependent diabetes mellitus. N Engl J Med 1989; 321 : 337-43.
17. Gulli G, Ferrannini E, Stern M et al. The metabolic profile of NIDDM is fully established in glucose tolerant offspring of two Mexican American NIDDM parents. Diabetes 1992; 41 : 1575-86.
18. Vaag A, Henriksen JE, Beck Nielsen H. Decreased insulin activation of glycogen synthase in skeletal muscles in young non-obese Caucasian first-degree relatives of patients with non-insulin-dependent diabetes mellitus. J Clin Invest 1992; 89 : 782-8.
19. Beck Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states. J Clin Invest 1994; 94 : 1714-21.
20. Werbach D, Bell GI, Rutter WJ, Shows TB.The Insulin gene is located on chromosome 11 in humans. Nature 1980; 286 : 82-4.
21. O'Malley KI, Rotwein P.Human tyrosine hydroxylase and insulin gene are contiguous on chromosome 11. Nucleic Acids Res 1986; 14 : 9927-32.
22. Bell GI, Gerhard DS, Fang NM et al. Isolation of the human insulin-like growth factor gene : insulin-like growth factor II and insulin genes are contiguous. Proc. Natl Acad Scie USA 1985; 82 : 6550-4.
23. Shoelson S, Haneda M, Bllix P et al. Three mutant insulin's in man. Nature 1983; 258 : 2357-63.
24. Permutt MA, Elbein SC. Insulin gene in diabetes : analysis through RFLP. Diabetes 1990; 13 : 364-74.
25. Olansky L, Welling C, Giddings S et al. A variant insulin promoter in non-insulin-dependent diabetes mellitus. J Clin Invest 1992; 89 : 1596-1602.
26. Seino S, Seino M, Nishi S, Bell GI. Structure of the human insulin receptor gene and characterization of its promoter Proc Natl Acad Scie USA 1989; 86 : 114-8.
27. Seino S, Seino M, Bell GI. Human insulin receptor gene. Diabetes 1990; 39 : 129-33.
28. Morgan R, Bishop A, Owens DR et al. Allelic variants at insulin receptor and insulin gene loci and susceptibility to NIDDM in Welsh population. Diabetes 1990; 39 : 1479-84.
29. Raboudi SH, Mitchell BD, Stern MP et al. Type 2 diabetes mellitus and polymorphism of the insulin receptor gene in Mexican Americans. Diabetes 1989; 38 : 975-80.

30. Truglia JA, Livingston JN, Lockwood DH. Insulin resistance : receptor and post-receptor binding defects in human obesity and non-insulin-dependent diabetes mellitus. Am J Med 1985; 879. (Suppl. 26) : 13-21.

31. O'Rahilly S, Choi WH, Patel P et al. Detection of mutations in insulin receptor gene in NIDDM patients by analysis of single-stranded conformation polymorphisms. Diabetes 1991; 40 : 777-82.

32. Almind K, Bjoerback C, Verstergaard H et al. Aminoacid polymorphism of insulin receptor substrate-1 in non-insulin-dependent diabetes mellitus. Lancet 1993; 342 : 828-32.

33. Matschinsky FM. Glucokinase as glucose sensor and metabolic signal generator in pancreatic b -cells and hepatocytes. Diabetes 1990; 39 : 647-52.

34. Hattersley AT, Turner RC. Mutations of the glucokinase gene and Type 2 diabetes. QJM 1993; 86 : 227-32.

35. Froguel P, Zouali H, Vionnet N et al. Familial hyperglycemia due to mutations in glucokinase : definition of a subtype of diabetes mellitus. N Engl J Med 1993; 328 : 697-702.

36. Hattersley AT, Turner RC, Permutt MA et al. Type 2 diabetes is linked to the glucokinase gene in a large pedigree Lancet 1992; 339 : 1307-10.

37. Elbein SC, Hoffman M, Qin H et al. Molecular screening of the glucokinase gene in familial Type 2 diabetes mellitus. Diabetologia 1994; 37 : 182-7.

38. Katagiri H, Asano T, Ishihara H et al. Nonsense mutation of glucokinase gene in late-onset non-insulin-dependent diabetes mellitus. Lancet 1992; 340 : 1316-7.

39. Permutt MA, Chiu KC, Tanizawa Y. Glucokinase and NIDDM : a candidate gene that paid off. Diabetes 1992; 41 : 1367-72.

40. Bell GI, Kayana T, Buse JB et al. Molecular biology of mammalian glucose transporters. Diabetes care 1990; 13 : 198-208.

41. Orci L, Ravazzola M, Baetens D et al. Evidence that down-regulation of b -cell glucose transporters in non-insulin-dependent diabetes may be the cause of diabetic hyperglycemia. Proc Natl Acade Scie USA. 1990; 87 : 9953-7.

42. Unger RH. Diabetic hyperglycemia : link to impaired glucose transport in pancreatic b -cells. Science 1991; 251 : 1200-5.

43. Matsutani A, Koranyi L, Cox N, and Permutt MA. Polymorphisms of GLUT 4 genes: use in evaluation of genetic susceptibility to NIDDM in Blacks. Diabetes 1990; 39 : 1534-43.

44. Patel P, Bell GI, Cook JTE, Turner RC, Wainscoat JS. Multiple restriction fragment length polymorphisms at the GLUT 2 locus : GULT 2 heptotypes for genetic analysis of Type 2 diabetes mellitus. Diabetologia 1991; 34 : 817-21.

45. Janssen RC, Bogardus C, Takeda J et al. Linkage analysis of acute insulin secretion with GLUT 2 and glucokinase in Pima Indians and the identification of a missense mutation in GULT 2. Diabetes 1994; 43 : 558-63.

46. Kusari J, Verma US, Buse JB et al. Analysis of the gene sequences of the insulin receptor and the insulin sensitive glucose transporter (GULT-4) in patients with common type of non-insulin-dependent diabetes mellitus. J Clin Invest 1991; 88 : 1323-30.

47. Chai WH, O'Rahilly S, Buse JB et al. Molecular scanning of Insulin responsive glucose transporter (GULT 4) gene in NIDDM subjects. Diabetes 1991; 40 : 1712-8.

48. De Vivo DC. The expanding clinical spectrum of mitochondrial diseases. Brain and Development 1993; 15 : 1-22.

49. Alcolado JC, Alcolado R. Importance of maternal history of non-insulin-dependent diabetic patients. BMJ 1991; 302 : 1178-80.

50. Thomas F, Balkan B, Vanzele-Kervroedan F, Papoz L. The Codiab Inserm-Zeneca Study Group. Maternal effect and familial aggregation in NIDDM. Diabetes 1994; 43 : 63-7.

51. Sener A, Malaisse WJ. Stimulation by D-glucose of mitochondrial events in islet cells. Biochem J 1978; 246 : 89-95.

52. Reardon W, Ross RJM, Sweeney MG et al. Diabetes mellitus associated with a pathogenic point mutation in mitochondrial DNA Lancet 1992; 340 : 1376-9.

53. Goto Y, Nonaka l, Horai S. A mutation in the t-RNA Leu (UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature 1990; 348 : 651-3.

54. Sue CM, Holmes-Walker DJ, Morris JGL et al. Mitochondrial gene mutations and diabetes mellitus. Lancet 1993; 341 : 437-8 (Letter).

55. Van de Ouweland JMW, Lemkes HHPJ, Ruitenbeek W et al. Mutation in mitochondrial t-RNA Leu (UUR) gene in a large pedigree with maternally transmitted Type 2 diabetes mellitus and deafness. Nature Genetics 1992; 1 : 368-71.

56. Ballinger SW, Shaffner JM, Hedaya EV et al. Maternally transmitted diabetes and deafness associated with a 10.4 kb mitochondrial DNA deletion. Nature Genetics 1992; 1 : 11-5.

57. Alcolado JC, Majid A, Brockington M et al. Mitochondrial gene defects in patients with NIDDM. Diabetologia 1994; 37 : 372-6.

58. Groop LC, Kantauri M, Schalin-Jantti C et al. Association between polymorphism of the glycogene synthase gene and non-insulin-dependent diabetes mellitus. N Engl J Med 1993; 328 : 10-4.

59. Lehto M, Xiang K, Stoffel M et al. Human hexokinase II : localization of the polymorphic gene to chromosome 2. Diabetologia 1994; 36 : 1299-1302.

60. Tuomilehto-Wolf E, Tuomilehto J, Hitman GA et al. Genetic susceptibility to non-insulin-dependent diabetes mellitus and glucose intolerance are located in HLA region. BMJ 1993; 307 : 155-9.

61. Abu-Bakare A, Gill GV, Taylor R et al. Tropical or malnutritional-related diabetes : a real syndrome? Lancet 1986; 1 : 1136-7.

62. Hales CN, Barker DJP. Type 2 diabetes mellitus : the thrifty phenotype hypothesis. Diabetologia 1992; 35 : 595-601.

63. Joffe Bl, Panz VR, Wing JR et al. Pathogenesis of non-insulin-dependent diabetes mellitus in the Black population of Southern Africa. Lancet 1992; 340 : 460-2.

64. Shires R, Joffe BI, Seftel HC. Maximal pancreatic beta-cell stimulation and the counter-regulatory hormonal responses in South African Black and White obese subjects. S Afr Med J 1985; 67 : 845-7.