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The changing classification and diagnosis of diabetes

New classification is based on pathogenesis, not insulin dependence

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At its annual meeting in June 1997 the American Diabetes Association announced the conclusions of an expert committee, which recommended changes to the way that diabetes is classified and to the choice of diagnostic method and cut off value that should be used to define the disease.[1] A provisional report from a World Health Organisation consultation group, with some overlap in members with the American committee, has recently been published.[2] These recommendations could have important epidemiological implications, but they will also affect individual patients.

The previous classification of diabetes was based on the extent to which a patient was dependent on insulin.[3] Although this was a logical distinction that separated the two main forms of diabetes, it gave rise to clumsy and sometimes confusing subcategories. Both the reports of the American Diabetes Association and the WHO recommend altering the classification to define four main subtypes of diabetes. Type 1 includes immune mediated and idiopathic forms of β cell dysfunction which lead to absolute insulin deficiency. Type 2 diabetes is disease of adult onset, which may originate from insulin resistance and relative insulin deficiency or from a secretory defect. Type 3 disease covers a wide range of specific types of diabetes including the various genetic defects of β cell function, genetic defects in insulin action, and diseases of the exocrine pancreas. Type 4 disease is gestational diabetes.

The move to a classification that allows for subgrouping by pathogenesis is an explicit recognition of the heterogeneity of processes that lead to diabetes. It is forward looking as it creates a framework that can accommodate the increasing number of specific causes for diabetes which are likely to be discovered.[4] The hope is that better subclassification will lead to more precise targeting of specific treatments and eventually to better outcomes.

The American report also considers how to define diabetes when the diagnosis is in doubt. Clinically, there is no difficulty when there are symptoms and unequivocal hyperglycaemia, but there is much greater complexity in asymptomatic patients with lesser degrees of glucose intolerance. In part, both committees were reacting to criticisms that the previous definition relied too strongly on the oral glucose tolerance test, which, although widely used in epidemiological studies, is rarely performed in clinical practice.[5] The 1985 WHO definition of diabetes,[3] based on the 75 g oral glucose tolerance test, defined diabetes either by a fasting plasma glucose concentration of ≥7.8 mmol/l or by a glucose concentration of ≥11.1 mmol/l at 2 hours after the glucose challenge. These diagnostic thresholds were selected because in certain high prevalence populations glucose concentration at 2 hours after glucose challenge has a bimodal distribution that can be separated into two distinct subgroups, and also because of the link between glucose concentration at 2 hours and future risk of the specific microvascular complications of diabetes. It is clear from longitudinal studies, however, that other tests such as fasting glucose concentration or glycated haemoglobin could equally well predict future microvascular risk, and that appropriate and equivalent thresholds could be set for any of these tests.[6] Because of its simplicity and availability, the American Diabetes Association's report recommends basing the diagnosis of diabetes on the fasting glucose concentration.

A change is also proposed to the diagnostic cut off point for fasting glucose concentration, reducing it from 7.8 mmol/l to 7.0 mmol/l. This change introduces a new intermediate category, impaired fasting glucose, defined as a fasting glucose concentration of 6.1-<7.0 mmol/l. There is evidence that these changes will have little effect on the true prevalence of diabetes, as described by Borch Johnsen et al on behalf of the DECODE group in this issue (p 371).[7] Nevertheless, there will be considerable reclassification of individuals when these new criteria are compared with the previous WHO definition, as the diagnostic emphasis is on fasting hyperglycaemia rather than the dynamic response to an oral glucose load. The DECODE group also show that this reclassification is not random but depends on age and obesity. Therefore the proposed changes will have an impact on the phenotype of people classified as having diabetes, as the new criteria are more likely to identify middle aged obese individuals. Perhaps most importantly, these changes are likely to lead to an increase in the prevalence of diagnosed diabetes as it would become practically much easier to detect the large number of people whose disease is currently undiagnosed.[8]

The most contentious part of the American Diabetes Association report, and one not considered by the WHO, is the recommendation that testing for diabetes should be considered for everyone aged 45 or over and should be repeated every three years. Testing is also recommended for younger people with a variety of risk factors such as obesity (liberally defined as a body mass index of ≥27 kg/m^2) or a family history of

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diabetes. Although the prevalence of undiagnosed disease is high[8] and many patients have evidence of complications at diagnosis,[9] the recommendations for screening are not backed by evidence that earlier detection leads to fewer adverse outcomes or that such a programme would be cost effective.

Overall, the practical implications of these reports for clinical practice are that the diagnosis of diabetes in people with classic symptoms should be established with a random plasma glucose concentration of ⩾11.1 mmol/l, preferably repeated or confirmed by a raised fasting glucose value on a subsequent day. In less clear cases the diagnosis can be established with a fasting plasma glucose of ⩾7.0 mmol/l, again repeated on a different occasion. Although the American Diabetes Association report was published as the final findings of its expert committee, the paper from the WHO is labelled as a provisional report. Individuals or groups who want to make comments and suggest modifications should write to the cochairmen by the end of September 1998.[2]

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Extending the benefits of breast cancer screening

Still hard to know how large the benefits will really be

Ever since the implementation of the NHS breast screening programme in 1988 two important questions have been consistently raised. Should the age range of women invited be extended from the current range of 50-64 years, and should the screening interval be reduced from the current three years? If we are to believe the cost effectiveness analysis by Boer et al in this week's issue (p 376),[1] an increase in age to 69 and a two year interval would each generate substantial benefits in life years saved and deaths averted—but, needless to say, at a substantial cost. Moreover, the authors' conclusion that extending the age range is expected to prevent more deaths, whereas shortening the screening interval would save more life years leaves policymakers with a—not unfamiliar—ethical dilemma.

It is obviously desirable to improve life expectancy in those women already eligible for screening. Reducing the interval cancer rate, which is particularly high in the third year of the screening interval, may prove crucial.[2 3] Shortening the screening interval from three to two years will decrease the interval cancer rate as a proportion of the underlying incidence by 30%.[3] Extending age range to 69 years, however, exploits the fact that age is by far the most important risk factor for breast cancer.[4] Would it be equitable to deny older women the benefits of more effective routine breast screening for the sake of increasing the life expectancy of younger women (in whom breast cancer is much less common)? This is a hard choice to make. Unfortunately, the authors have not modelled the effect of the combined implementation of both strategies, which would have provided an assessment of how necessary it really is to pursue only one of these two options.

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The epidemiological model applied here depends to a large extent on the comparison of tumour stage distributions before and after the introduction of a specified screening policy.[1 5] This may have led the authors into overestimating the cost effectiveness of the suggested alternatives by modelling each policy—that is, existing policy and suggested alternative—against a baseline in which no screening has been introduced into a population and then subtracting both results from each other. The breast screening programme has in fact been running for over 10 years and the tumour stage distribution in the population has changed as a result,[6] so that using prescreening distributions may not be entirely valid when evaluating policy changes at this stage. To ascertain true marginal costs, we would need a validated modelling exercise which uses the current situation in the United Kingdom as a baseline.

The efficiency of extending the age range of breast screening will crucially depend on the acceptance rate among women aged 65 and above. Rubin et al's preliminary report shows that more than 70% of these women took up their invitation (p 388).[7] This is a much better uptake than reported from previous studies in Nijmegen[8] and London,[9] which achieved participation rates of 55% and 37% respectively. In London, however, this participation rate reflected overall attendance rates, and it was concluded that older

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women would potentially have attendance rates at routine screening similar to younger women if they were invited in the same way. If the results of Rubin et al are representative they might show how (old) peoples' attitudes have changed as interventions like breast screening have become more accepted in such communities since the Forrest recommendations.[10]

Rubin et al do, however, report much higher cancer detection rates than expected. They suggest that the particularly high cancer detection rate in women aged 68 and 69 reflects both advancing age and not having been screened for 6 years.[7] This fact cannot fully explain the result, however, since cancer detection rates were unexpectedly high in all age groups. Also, the Nijmegen study reported a detection rate of only 5.6/1000 in all women aged 65-69. This may suggest a high proportion of false positive screens, and further data on assessment and biopsies are required.

Both studies make an important contribution to the discussion about extending age range or shortening screening interval in the NHS breast screening programme, thereby departing from the recommendations of the Forrest report.[10] Nevertheless, their findings may be of only limited validity because the first study does not use the current UK situation as its baseline whereas the second study, despite its encouraging result, may have identified a quality problem. Before either of these changes are implemented, resource implications and potential opportunity costs warrant much further discussion and analysis. Breast cancer screening is by no means the best way of obtaining health benefit per billion pounds. Indeed, current programmes have yet to show any unequivocal benefit[11] in terms of either mortality or of life years. But it is still early days.

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The genetics of Alzheimer's disease

The number of genetic risk factors associated with this disorder is increasing steadily

The genetics of Alzheimer's disease is proving to be complex and controversial. *Nature Genetics* this month contains a paper from Tanzi's group in Boston suggesting that a common polymorphism of α_2 macroglobulin is associated with a major increase in the risk of developing late onset Alzheimer's disease.[1] The data generated heated debate at the sixth international conference on Alzheimer's disease held in Amsterdam at the end of July. At least 70 other reports on the genetics of Alzheimer's disease were presented, implicating over a dozen other genes or genetic loci.[2] So what is our current state of knowledge?

Missense mutations in three genes are known to cause autosomal dominant forms of early onset Alzheimer's disease: these are the amyloid precursor protein gene located on chromosome 21[3] and genes for presenilin 1 and presenilin 2 located on chromosomes 14 and 1, respectively.[4 5] Studies on these missense mutations have given strong support to the "amyloid cascade hypothesis" of Alzheimer's disease.[6] The amyloid precursor protein mutations code for amino acids at or near points where the precursor is cleaved enzymically and result in slightly longer forms of β amyloid being secreted. These aggregate readily into highly insoluble amyloid fibrils which form the major component of senile plaques. Similar changes in β amyloid production are observed with the mutations linked to Alzheimer's disease in presenilin 1 and 2. The presenilin proteins show marked homology, with multiple membrane-spanning domains, and may act as chaperone molecules in the processing of amyloid precursor protein, exposing sites in the molecule to enzymatic cleavage.[7] While mutations associated with amyloid precursor protein are extremely rare, the 50 or so mutations associated with presenilin 1 may explain up to half of all cases of early onset Alzheimer's disease.

In contrast to early onset Alzheimer's disease, there is to date only one genetic factor indisputably linked with late onset forms of this disorder, and that is the e4 allele of apolipoprotein E.[8] Three common allelic variants of apolipoprotein E exist—e2, e3, and e4—encoded at a single gene locus on chromosome 19; several large, neuropathologically verified cohort studies have shown that apolipoprotein E e4 predicts risk of Alzheimer's disease. However, apolipoprotein E e4 is neither necessary or sufficient to cause Alzheimer's disease, and a population based study of

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almost 5000 elderly people by Meyer et al,[9] also reported in this month's *Nature Genetics*, indicates that the apolipoprotein E genotype predicts when—not whether—individuals are predisposed to develop Alzheimer's disease. A "plateau" appeared in the survival curve for all groups surviving to old age, so that even with the homozygous e4/e4 condition the last onset of dementia occurred at 84 years, with a significant number of individuals surviving disease free for longer periods. At most only half of individuals with late onset Alzheimer's disease carry an apolipoprotein E e4 allele, and the study by Meyer et al indicates that even in the presence of this susceptibility factor other genes are likely to be involved.

A whole string of genetic associations with late onset Alzheimer's disease have been reported by various groups, including polymorphisms in angiotensin converting enzyme, α_1 antichymotrypsin, bleomycin hydrolase, butyrylcholinesterase, HLA, low density lipoprotein receptor related protein, various mitochondrial enzymes, and a presenilin 1 intronic mutation.[2] So far none of these findings has been consistently replicated, and it remains to be seen whether the recent report on α_2 macroglobulin[1] will stand this test. The mutation reported by the Boston group is a common variant of the α_2 macroglobulin gene that causes a deletion in the nucleotide sequence for the "bait" region of the molecule, which binds proteases, and which in Tanzi's view may be implicated in the clearance of β amyloid from the synaptic cleft. It is present in 20% of the population, and the level of risk conferred for Alzheimer's disease appears to be similar to that associated with apolipoprotein E e4. However, the statistical analysis of this work used an as yet unpublished family based association method which, though it measures relative risk for the actual families studied, does not indicate the general population risk. In discussion at Amsterdam several groups claimed that they had been unable to confirm the association with α_2 macroglobulin in population samples, so it may be relevant to only a small proportion of familial cases of Alzheimer's disease.

The mutations in amyloid precursor protein, presenilin 1, and presenilin 2 allow for genetic screening in suspected cases of familial Alzheimer's disease with early onset and for appropriate genetic counselling and support. Studies on the underlying pathophysiological mechanisms support the rationale for therapeutic strategies aimed at preventing the formation of amyloid fibrils in vivo or promoting their dissolution. Tanzi's work, if confirmed, will extend the hunt for rational therapies based on the biological functions of α_2 macroglobulin and its role in Alzheimer's disease. Until disease slowing treatments become available there is little justification for predictive testing based on apolipoprotein E, α_2 macroglobulin, or any of the other genes so far linked with late onset Alzheimer's disease.

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Minimisation: the platinum standard for trials?

Randomisation doesn't guarantee similarity of groups; minimisation does

When we have to decide which of two drugs, interventions, or management strategies is the better, the most secure evidence is generally obtained from a randomised controlled trial. The primary objective of randomisation is to ensure that all other factors that might influence the outcome will be equally represented in the two groups, leaving the treatment under test as the only dissimilarity. Any difference in outcome can then be attributed to the treatment effect. But how realistic is this assumption in practice?

When published a randomised trial typically includes a table listing all the prior factors known actually or possibly to influence outcome. The average age and its distribution in each group and the proportion of men and women usually head the list, followed by other likely determinants of outcome. In the case of heart disease these will probably include details of left ventricular function; the proportions in each group with diabetes, hypertension, hyperlipidaemia, or a smoking history; the relative incidence of arrhythmia, obesity, symptoms of heart failure; and any others factors that may have been collected. If these are similar in the two groups (which is not the same as showing that they are not statistically different) then we can go on to attribute any difference in outcome to the benefit of treatment over placebo, or of one treatment over another. But what if there are differences?

Indeed, if there are many possible prognostic factors there will almost certainly be differences

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between the groups despite the use of random allocation. In a small clinical trial a large treatment effect is being sought, but a large difference in one or more of the prognostic factors can occur purely by chance. In a large clinical trial a small treatment effect is being sought, but small but important differences between the groups in one or more of the prognostic factors can occur by chance.

Supposing one group has more elderly women with diabetes and symptoms of heart failure. It would then be impossible to attribute a better outcome in the other group to the beneficial effects of treatment since poor left ventricular function and age at outset are major determinants of survival in any longitudinal study of heart disease, and women with diabetes, as a group, are likely to do worse. At this point the primary objective of randomisation—exclusion of confounding factors—has failed.

Attempts are then made to retrieve the situation by multivariate analysis, allocating part of the difference in outcome to the known, unwanted difference in the groups, but there is always an air of uncertainty about the validity of the conclusion. This may seem to be less of a risk in a very big trial, because we can expect things to even out, but big trials are done to seek small differences, and even a small difference in other determinants of outcome may be important. If a very big trial fails, because, for example, the play of chance put more hypertensive smokers in one group than the other, the tragedy for the trialists, and all involved, is even greater.

The way to avoid this is by minimisation—not a well known technique—first described by Taves in 1974[1] and shortly after by Pocock and Simon[2] and Freedman and White.[3] With this method the group allocation does not rely solely on chance but is designed to reduce any difference in the distribution of known or suspected determinants of outcome, so that any effect can be attributed to the treatment under test. The trialists determine at the outset which factors they would like to see equally represented in the two groups. In our study of aspirin versus placebo in the two weeks before elective coronary artery surgery we chose age, sex, operating surgeon, number of coronary arteries affected, and left ventricular function.[4] But in trials in other diseases those chosen might be tumour type, disease stage, joint mobility, pain score, or social class.

At the point when it is decided that a patient is definitely to enter a trial, these factors are listed. The treatment allocation is then made, not purely by chance, but by determining in which group inclusion of the patient would minimise any differences in these factors. Thus, if group A has a higher average age and a disproportionate number of smokers, other things being equal, the next elderly smoker is likely to be allocated to group B. The allocation may rely on minimisation alone, or still involve chance but "with the dice loaded" in favour of the allocation which minimises the differences.

This process must be handled out of sight of any individual who might introduce bias, but this is equally true of randomisation—which we know can be subverted by the (often unconscious) vested interests of the trialists. The individual trialist does not know how the risk factors are accruing and cannot influence the allocation. If the trial is double blind the trialists do not know which groups the present patients are in so subsequent decisions to include a patient in the trial cannot be influenced by any knowledge of which group they are more or less likely to enter. Exclusion of bias is as readily achieved as it is with properly performed randomisation, but with the advantage that similarity of the two groups is ensured, rather than hoped for.

The theoretical validity of the method of minimisation was shown by Smith,[5] and White and Freedman have reviewed alternative methods of patient allocation.[6] A recent example of the use of minimisation is found in Kallis et al.[4] If randomisation is the gold standard, minimisation may be the platinum standard.

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Staring into the abyss: walking the nuclear tightrope in south Asia

Sanctions can only make things worse for the people of India and Pakistan

Pokaran and Chagai, two remote wastelands in India and Pakistan, convulsed painfully under the impact of 11 nuclear explosions in May this year, as both countries overtly crossed the nuclear threshold. In the weeks that followed the widespread euphoria and irresponsible jingoism witnessed in the streets of Delhi and Islamabad has given way to introspection and the beginnings of a real debate on the implications of a nuclear arms race in the subcontinent.

Although the genie of nuclear capability in both countries has been well and truly let out, it is imperative that India and Pakistan refrain from embarking on a nuclear weapons build up. It may already be too late to

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prevent such a build up, but there are several compelling reasons why such a programme in the subcontinent may not serve as a real deterrent to war but greatly enhance its risks and costs.

The analogy with the nuclear stalemate between the United States and the Soviet Union is misguided, as neither India nor Pakistan possesses the technology or resources for the requisite safeguards and early warning systems that the United States and Soviet Union eventually established. Even if such fail safe systems were available, contiguous borders and missile delivery times of under 10 minutes, coupled with fragile democracies and volatile political systems, make the effectiveness of such systems highly questionable.

Despite sophisticated systems of command and control, the cold war was fraught with numerous instances of near miss accidents, and a recent analysis suggests that the risk of accidental nuclear conflict may have actually increased since the breakup of the Soviet Union.[1] Despite claims of safety, significant radiation leakage has resulted from accidents involving nuclear weapons and production facilities in the West[2 3] and it is debatable if the fragile economies of India and Pakistan could sustain better weapons manufacturing, control, and monitoring systems. In the aftermath of the chemical disasters in Bhopal (India) and Seveso (Brazil) some have asserted that the sociopolitical turmoil and unstable economic structures make developing countries considerably more vulnerable to industrial accidents.[4]

More importantly, the enormous costs of nuclear weapons must be weighed against the abysmal state of human development and health in south Asia. Both India and Pakistan have some of the highest rates for maternal and infant mortality in the world.[5] Of every 1000 children born in these countries, at least 80 will not live to see their first birthday.[6] Between 20% and 33% of all newborn infants are of low birth weight,[7] and the region boasts over half of all the malnourished children in the world.[8] These horrifying health indicators, coupled with lack of basic facilities for health and education, make the diversion of scarce economic resources to weapons of mass destruction even more incongruous. Since the nuclear explosions India's defence budget has already been increased by 10% and Pakistan has imposed a 10% tax surcharge to meet increasing defence needs. These allocations have led to an unfortunate but predictable reduction in the existing meagre allocations to health and education.[9]

Few among the unruly mobs celebrating in the streets of Delhi and Islamabad truly appreciate the horrors of nuclear war and the futility of available measures aimed at reducing the costs of nuclear conflict. The shocking calculations of the human costs of such an exchange, highlighted over 36 years ago,[10] not only still hold true, but are amplified severalfold by the growing sophistication of weapons design and burgeoning urban populations. In a hypothetical calculation of the impact of a 20 megaton ground burst nuclear device in Boston, USA, Ervin et al estimated that 2.1 million residents would perish and a further 0.5 million would be at risk of dying subsequently from major injuries.[10] With large urban populations living in highly inflammable and flimsy shanty towns, the casualty rates in comparable cities of India and Pakistan would inevitably be much higher. It is estimated that an exchange of much smaller (20 kilotons) nuclear devices between India and Pakistan would cause at least 1.2 million immediate deaths, with many more succumbing later from the effects of fall out and lack of medical facilities.[11]

Neither side would be immune to the effects of even a limited nuclear exchange: a truly mutually assured destruction. The only way to ensure that such a conflict never occurs is by educating the populace and opinion leaders to the true horrors of nuclear conflict and the human costs of embarking on an expensive and futile programme of weapons building.

In a subcontinent teetering on the brink of a nuclear abyss, a rapprochement between India and Pakistan can be achieved only by pragmatic confidence building measures[12] and by publicising the views of the many proponents of peace on both sides of the border.[13 14] It should dawn on politicians in both countries, asserting their right to rub shoulders with global nuclear superpowers, that true nuclear capability only comes with the necessary "nuclear responsibility," a responsibility to their impoverished, destitute, and sick populations and to a world already made unsafe by stockpiles of nuclear, chemical, and biological weapons.

Nor do the old nuclear powers hold any sort of moral high ground—with their continued nuclear weapons programmes and a pitifully slow disarmament process. Surely some of the blame for recent events in south Asia lies at their doorstep. Given this failure of the leading nuclear powers to set an example by getting rid of their own nuclear arsenals, it is imperative that international sanctions against India and Pakistan do not add to the misery of millions of children and poor people in the subcontinent, who will undoubtedly bear the brunt of such measures.

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