LMO-2. The product of *LMO-2* is crucial for normal haemopoiesis and serves a regulatory function.[13] However, *LMO-2* is also an oncogene that is aberrantly expressed in acute lymphoblastic leukaemia of childhood. Both children are now being treated with chemotherapy and the other patients who were given gene therapy are being monitored closely. In view of these serious adverse events, all retroviral gene therapy trials are currently on hold in the USA.

Because of the above events, the treatment of genetically determined immunodeficiency disorders remains a problem, with allogeneic stem-cell transplantation seeming to be the current best option for those defects that are invariably fatal early in life. Efforts are being made to improve this therapy by giving higher numbers of affinity-purified allogeneic stem cells in preparations nearly devoid of T cells.[14] If the imperfect results seen with allogeneic stem-cell therapy in the past were due to an insufficient number of stem cells, this approach should result in better immune reconstitution. The fact that such cell suspensions are virtually devoid of T cells should also circumvent the problem of GVHD.[14] The only remaining obstacle would then be to ensure that diagnosis is early before untreatable infections develop. However, this obstacle remains formidable, since there is currently no screening for any primary immunodeficiency disease at birth or during childhood or adulthood in any country. Thus most patients are not diagnosed until they develop a serious infection, which will certainly adversely affect the ultimate outcome of definitive therapy.

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Parsing an enigma: the pharmacodynamics of aspirin resistance

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Aspirin reduces the secondary incidence of stroke, myocardial infarction, and vascular death by about a quarter,[1] an effect similar to that of statins. However, some patients on aspirin will have a second or subsequent heart attack or stroke and the phenomenon of "aspirin resistance" seems to have caught the attention of both the professional and mass media in a way that statin resistance has not. Aspirin irreversibly inhibits cyclo-oxygenase (COX) by acetylation of a serine residue at position 530.[2] COX catalyses the transformation of arachidonic acid to the unstable prostaglandin (PG) intermediate PGH_2, and thromboxane synthase (Tx) subsequently acts on PGH_2 to form TxA_2, a vasoconstrictor and platelet agonist.[3] COX has two isoforms and only COX-1 is expressed in mature human platelets. COX-2 is upregulated by inflammatory cytokines and mitogens and seems to be the dominant source of prostaglandins in inflammation and cancer.[4] A variant of COX-1, "COX-3" has been detected in canine brain.[5] However, the functional importance of this isoform remains to be determined.

The irreversible nature of COX inhibition by aspirin explains the cumulative inhibition of TxA_2 generation by platelets seen when low doses of aspirin are administered chronically.[6,7] Overview analysis[1] of indirect comparisons in clinical trials indicates that the reduction in the incidence of vascular events in high-risk patients (19% [SE 3]) with high doses of aspirin (500–1500 mg a day) does not exceed that attained (32% [6]) with lower doses (75–150 mg a day). Thus, although aspirin is anti-inflammatory due to inhibition of COX-2 at higher doses, inhibition of platelet COX-1 at low doses is sufficient to explain the cardioprotection observed in clinical trials.

Unlike aspirin, NSAIDs, such as ibuprofen and diclofenac, are reversible inhibitors of COX, competing with the lipid substrate arachdonic acid for access to the active site at the upper end of a deep hydrophobic channel in the core of the dimeric enzyme.[8] The anucleate platelet is a functional discriminant between the different modes of action of aspirin and NSAIDs. First, the capacity to regenerate COX de novo after exposure to aspirin is nonexistent (or extremely low) in platelets by contrast with other tissues, where recovery of PG formation due to resynthesis of the enzyme occurs within hours. Second, the rapid decline in COX inhibition with NSAIDs between doses has a pronounced effect on platelet function. There is a non-linear relation between inhibition of platelet TxA_2 generation and inhibition of TxA_2-dependent platelet aggregation, requiring greater than 95% inhibition of TxA_2 generation to influence function.[9] This degree of inhibition is rarely (if ever) sustained throughout the typical NSAID dosing interval. Thus, NSAIDs would not be expected to be cardioprotective like aspirin. Controlled prospective trials of adequate size that address this issue have not been reported, while epidemiological analyses have provided conflicting answers.[10–12]

Aspirin and NSAIDs are among the most commonly consumed drugs. The prescription market for NSAIDs in the USA is estimated at US$7·75 billion yearly, roughly three-quarters of that number accounted for by COX-2 inhibitors. The over-the-counter market for NSAIDs is

roughly US$2 billion annually, of which aspirin accounts for about 20%. It seems likely that many patients are taking both aspirin and NSAIDs chronically. However, the distinct modes of COX inhibition by NSAIDs and aspirin provide the basis for a pharmacodynamic interaction, because competitive inhibition of the active site by an NSAID may impede access of aspirin to its target, S530. This is illustrated by shuffling the order of administration of aspirin and ibuprofen, the NSAID most commonly consumed in the USA. If 81 mg of aspirin is followed 2 h later by 400 mg ibuprofen to attain steady-state effects in volunteers, maximum inhibition of platelet TxA_2 generation and consequent inhibition of platelet aggregation is sustained for 24 h after dosing. However, if the drug order is switched, the pharmacodynamic effect of aspirin is prevented, enzyme function is reversibly inhibited, and platelet aggregation declines by about 60% after 6 h. Furthermore, if ibuprofen 400 mg is administered three times a day (a typical dosing regimen), sufficient NSAID remains from the evening dose to cause the interaction even when aspirin is given before ibuprofen the next morning.[13]

What are the clinical implications of these observations? There are no data from controlled clinical trials that address this issue. Using the Tennessee Medicaid database, Ray et al[11] failed to detect a cardioprotective benefit from prescribed NSAIDs (181 441 NSAID users, 181 441 controls) and also observed that the odds ratio for serious coronary heart disease in patients taking aspirin was increased to 1·15 (95% CI 1·02–1·28) in patients prescribed ibuprofen chronically and to 1·27 (1·11–1·45) in those prescribed more than 1800 mg ibuprofen a day. These investigators did not observe a similar interaction with naproxen. More recently, Kimmel and colleagues,[12] in a case-control study (909 cases, 3030 controls) of prescribed and over-the-counter medications based on a telephone survey, found that consumption of a range of NSAIDs was associated with a reduced odds ratio of a first myocardial infarction (0·56, 0·44–0·72), but this apparent benefit disappeared in those also taking aspirin (1·01, 0·69–1·47). Thus two studies, which differed in their conclusions about the cardioprotective effects of NSAIDs, both detected evidence of an NSAID-aspirin interaction.

The study of Thomas MacDonald and Li Wei, in today's issue of *The Lancet*, involved just over 7000 patients discharged from Tayside hospitals after their first admission for cardiovascular disease. The patients had survived at least 1 month and were prescribed aspirin (less than 325 mg a day) on discharge. The adjusted hazard ratios for all-cause mortality (1·93, 1·30–2·87) and for cardiovascular mortality (1·73, 1·05–2·84) were significantly raised in patients taking ibuprofen (mean daily dose 1210 mg) as well as aspirin. Interestingly, no increase in hazard was observed in patients combining aspirin with diclofenac, the most commonly consumed NSAID in Europe.

The results of MacDonald and Wei accord with the failure to detect a pharmacodynamic interaction between aspirin and diclofenac in a study of thromboxane formation and platelet function.[13] Whilst this finding may reflect a different physical positioning of diclofenac compared with other NSAIDs in the hydrophobic channel of platelet COX-1, the lack of interaction may also reflect diclofenac's relative preference for COX-2.[4,14] The absence of COX-2 in mature human platelets explains why selective COX-2 inhibitors such as rofecoxib,[13] and perhaps also diclofenac, do not inhibit the effects of low-dose aspirin on platelet function.

Whilst the results reported by MacDonald and Wei are congruent with the understanding of the clinical pharmacology of aspirin, ibuprofen, and diclofenac, a constraint on the interpretation of their results, which they recognise, is the possibility of confounding by recognised (eg, smoking) and unrecognised variables. The relatively small sample size also limits conclusions about the interaction of aspirin with NSAIDs other than diclofenac and ibuprofen. Furthermore, the heterogeneous nature of the discharge diagnoses that comprised "cardiovascular disease", differential susceptibility of these conditions to benefit from aspirin, the potentially variable compliance with prescribed medication after hospital discharge, and the possible consumption of additional over-the-counter NSAIDs or aspirin also complicate interpretation of their findings. However, it is unlikely that a prospective controlled trial will be designed to address the clinical implications of NSAID-aspirin interactions. The report by MacDonald and Wei will prompt further epidemiological analyses to address this issue, and further studies of the clinical pharmacology of this interaction may determine whether it extends to other NSAIDs, such as naproxen.

Three epidemiological studies provide evidence consistent with a clinically important, pharmacologically plausible interaction between aspirin and ibuprofen. This interaction may contribute to the spectrum of aspirin resistance. However, resistance as defined by treatment failure, applies to all drugs. Rather than promote such a universal descriptor, the molecular, behavioural, and technical elements of this phenomenon might more usefully be parsed separately. The place of aspirin in the secondary prevention of myocardial infarction and stroke is well established.[1] When patients taking aspirin for cardioprotection require chronic treatment of inflammation with an NSAID, the addition of diclofenac or a conventional selective COX-2 inhibitor[13] would seem preferable to ibuprofen.

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Diabetes: prevention needed

There are and will be more people with diabetes,[1–3] requiring ongoing, preventive, and corrective management, even if existing health-care systems are improved and made maximally efficient and effective.[4] For example, David Dunston and colleagues[2] recently report more than a doubling in the prevalence of diabetes in Australia within two decades. In adults, the overall prevalence of diabetes was 7·4%, and the prevalence of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) was 16·4%. In those aged 75 or over, the prevalence of diabetes was 23%. In addition, only half of all individuals with diabetes had been diagnosed.[2] With the outlook for further population ageing and continued increases in obesity, Dunston and colleagues rightly conclude that their findings "should ring alarm bells for governments and public health planners". Thus there is concern that no matter how effective clinical diabetes-care could become, health-care systems will soon become overwhelmed with providing appropriate care for an ever-increasing number of people with diabetes. There is now compelling evidence for the effectiveness of primary prevention of type 2 diabetes through behavioural or pharmacological approaches.[5–7] However, all studies to date have targeted only individuals at very high risk for subsequent type 2 diabetes—ie, those with extant IGT.

IGT has been recognised for many years, and is a "condition", or "risk factor", associated with a high likelihood of subsequent type 2 diabetes,[8] and risk for, and a higher than normal incidence of, cardiovascular disease (although not as great as in established type 2 diabetes).[8,9] More recently, a category of IFG has been designated[10] with an increased risk of subsequent diabetes mellitus similar to that with IGT.[11] Underlying pathophysiological mechanisms may differ between IFG and IGT, and to date, no study indicates that correction of isolated IFG will reduce the subsequent incidence of type 2 diabetes.[8] Whilst observational studies suggest that IGT and probably IFG are associated with subsequent cardiovascular disease, whether treating either IGT or IFG will reduce the actual incidence of cardiovascular disease is unknown. IFG and IGT have been called "prediabetes".[12] This term may not be new or even perfect, but it parallels nomenclature in other related fields (eg, precancer), and it can effectively inform the general public and health professionals about a modifiable risk factor which, if reversed, could reduce the likelihood of type 2 diabetes.[5–7]

How should the prediabetes states of IFG and IGT be viewed? These risk factors for subsequent type 2 diabetes exist in all populations investigated,[8] are typically prevalent at levels at least equal to, if not greater than, that of diabetes itself (with IGT usually more common than IFG),[2,8] are increasing in prevalence in parallel with type 2 diabetes,[2,8] and are correlated with increasing population obesity or inactivity.[3] These observations suggests that the "epidemic" of type 2 diabetes will likely continue into the future—the burden of diabetes is going to get worse before it gets better.

But should persons with IFG and IGT be identified? In screening, the availability of convincing science that interventions can make a difference in outcomes shifts the balance between specificity and sensitivity of testing in favour of sensitivity. Thus efficient screening procedures for prediabetes that are sensitive and as specific as possible are needed. Further, translation of diabetes primary prevention from basic science poses special challenges for health-care professionals,[13] traditional health-care systems,[4] and community settings in which behavioural interventions will occur and be sustained.[14] But the critical step will be active engagement of policy makers and the reimbursement systems, which share responsibility for putting into place the necessary incentives for identification and treatment of "prediabetes", particularly the behavioural interventions that will likely need to last a life time.

These are no small challenges, particularly given finite resources. There is still much to do to improve the preventive care and management of people with diabetes. But by ignoring the power of primary prevention, as well as the accelerating increase in demand for health services that will surely occur with the epidemic of type 2 diabetes, society will fail to obtain return on its substantial investment in clinical research. As the profound results of the Diabetes Control and Complications Trial[15] and the United Kingdom Prospective Diabetes Study[16] mandated improved diabetes management, so the various primary prevention trials require that steps be taken—perhaps small and hesitant ones at first—to stop the development of type 2 diabetes.

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