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## Why is apoptosis important to clinicians?

*Because its mechanisms are being used to develop drugs*

See *Clinical review*  
pp 1525-31  
*Education and debate*  
pp 1536-40

Apoptosis—programmed cell death—was discovered in 1972,<sup>1</sup> and now that it approaches its 30th birthday its clinical importance is becoming clear. The excitement of apoptosis for doctors lies in the clinical implications of perturbed-restored control of cell number and function through a balance between cell death and cell survival.

Apoptosis may become disrupted in two major ways, and, as predicted over 20 years ago,<sup>2</sup> each seems to be associated with different types of disease. Inappropriate activation of the apoptotic process leads to disorders associated with pathological loss of cells—such as the immune defect in AIDS and possibly neurodegenerative diseases. In contrast, inadequate apoptosis, leading to inappropriate cell survival, leads to diseases associated with excessive accumulations of cells—such as cancer, chronic inflammatory conditions, and autoimmune diseases.

The defect in immunity associated with AIDS is the result of a profound reduction in the population size of CD4+ T helper cells caused by excessive apoptosis; this occurs even at comparatively low levels of HIV infectivity, so that many non-infected T cells must also be lost. The exact mechanisms are uncertain but may include transfer of regulatory viral gene products (such as HIV-1 Tat) from HIV infected cells to bystander T cells, rendering them susceptible to T cell receptor-induced, CD95-mediated apoptosis.<sup>3</sup> Neurodegenerative disorders have also attracted attention,<sup>4</sup> but the relative contribution of apoptosis to neurone cell loss in Alzheimer's disease is uncertain because not all degenerating neurons show clear features of apoptosis (which are extraordinarily difficult to quantify in situ, especially in chronic disease processes).

Nevertheless, an increasing body of indirect evidence suggests that neuronal cell apoptosis may be triggered by amyloid  $\beta$  and other neurotoxic abnormal protein structures or aggregates in Alzheimer's and other adult neurodegenerative diseases (including Huntington's chorea, Parkinson's disease, and amyotrophic lateral sclerosis).<sup>4</sup> A central role for amyloid  $\beta$  protein is supported by the effects of genetic mutations that cause Alzheimer's disease, all of which predispose to amyloid deposition. It is also supported by the observation that amyloid  $\beta$  can exert neurotoxic effects in vitro and in vivo, and by mechanisms which may involve the generation of intracellular oxidative stress and increases in calcium ions, both of which can trigger apoptosis in susceptible cell types.<sup>4</sup> These effects may be induced by amyloid  $\beta$  cross linking receptors for

advanced glycosylation end products (RAGE), amyloid precursor protein (APP), or a receptor called P75, all of which can trigger neuronal apoptosis. In situ, however, the situation is much more complex, and other resident cells may play important roles. For example, microglial activation, which occurs in response to local amyloid plaque formation, is known to stimulate secretion of the tumour necrosis factor  $\alpha$  and other factors that can induce apoptosis in vitro.

Many therapeutic approaches to counter inappropriate apoptosis have been mooted. Since proteolytic enzymes called caspases are critical to the control of apoptosis (they reorganise the dying cell from within and make it ready for safe clearance by phagocytes), several pharmaceutical companies are developing potent and specific caspase inhibitors. None is yet suitable for use in humans. Nevertheless, non-specific caspase inhibitors have shown great promise in in vitro and murine models of inappropriate neuronal apoptosis.<sup>5</sup>

Cancer, on the other hand, occurs when mutations affect the control mechanisms of apoptosis and cell survival. Indeed, the *bcl-2* gene was identified as blocking apoptosis because of its abnormal overexpression in follicular lymphoma. Furthermore, mutations in p53 (a protein believed to be the "guardian of the genome") prevent the deletion, by apoptosis, of cells with damaged DNA, so that tumours develop. Inflammatory disorders such as rheumatoid arthritis may also reflect prolonged survival of leucocytes that are normally programmed to die by apoptosis.

In both cases the therapeutic objective is to remove unwanted cells. The treatment of certain lymphomas by antisense oligonucleotides (which block gene transcription) to *bcl-2* is a realistic prospect. Furthermore, death-inducing cytokines of the tumour necrosis factor family, such as TRAIL, are showing promise in colon cancer. Recent evidence has shown that normal and cancerous cells show major differential susceptibility to apoptosis stimulated by TRAIL.<sup>6</sup> Moreover, death receptor-mediated apoptosis may be particularly valuable in cancer treatment since it is likely to be independent of p53 status (which is corrupted in 50% of all primary cancer tumours) and it is also largely independent of Bcl-2.<sup>7</sup> Nevertheless, caution is necessary, since excessive generalised activation of cell death pathways can trigger a fatal form of haemorrhagic liver necrosis.

Thus apoptosis is no longer an arcane pathological phenomenon. Instead, the molecular basis of pro-

grammed death and cell survival is one of the most vibrant areas of laboratory research. Clinical trials are imminent, so we predict that this promising youngster will show many achievements by its 50th birthday.

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## Depression, suicide, and the national service framework

*Suicide is rare and the only worthwhile strategy is to target people at high risk*

The National Service Framework for Mental Health<sup>1</sup> seeks to cut the suicide rate by a further fifth from Health of the Nation targets. Standard 7, preventing suicide, advises about health promotion and improved services, including assessment and treatment of depression in primary care and assessing risk among individuals at greatest risk. Will these improvements deliver results? Are there other more promising strategies?

It is widely assumed that early and accurate identification of depressive episodes will reduce suicides. This follows from a belief that suicide is a common adverse outcome in depressive disorders: a 15% lifetime risk is often cited. However, clinical experience and population based studies challenge this view. Every week 10% of the UK population aged 16-65 report significant depressive symptoms, and one in 10 of these admits to suicidal thinking.<sup>2</sup> But fewer than two people in a million will kill themselves. A typical primary care group of 100 000 expects 10 suicides a year.<sup>1</sup> Depressive disorders are therefore common, while suicide remains rare.

The estimate of 15% lifetime risk of suicide emerged from a review of 17 studies of depressed patients, mainly in secondary care, all before 1970.<sup>3</sup> A recent meta-analysis revises the figure to 6%,<sup>4</sup> but this may still be biased towards recurrent inpatients at tertiary centres.<sup>5</sup> A study from the United States sharpens the focus, describing 62 159 person years' follow up for 35 546 insured patients treated for depression.<sup>5</sup> Risk of suicide declined from 224 per 100 000 patient years for inpatients to 64 for outpatients, 43 for those receiving antidepressants in primary care, and 0 for those without drug or secondary treatment. These estimates are much lower and relate to treatment history.

What does this mean for the national service framework strategy? Better quality primary mental health care for all depressed patients can reduce disability and improve functioning, but the result is unlikely to be a visible and cost effective reduction in the rare phenomenon of suicide.

The second approach in the framework of improving risk assessment must be linked to intervention, but

only in genuinely high risk groups to avoid prohibitive expense and patient inconvenience. The US findings offer little encouragement. Even with an entirely effective programme, 400 inpatients would require intervention to prevent one suicide a year. In general practice the number needed to treat would be almost 5000. The national confidential inquiry into suicide<sup>6</sup> found that 15% of those who did kill themselves had already been identified as being at moderate or high risk. A 100% improvement in risk assessment would identify only 30% of future suicides, and effective interventions would still be needed. Geddes argued in the *BMJ* that suicide is unlikely ever to be a realistic outcome measure for randomised trials and for high risk groups more common outcomes such as self harm should be considered.<sup>7</sup> The national service framework strategy to "ensure that staff are competent to assess the risk of suicide among individuals at greatest risk" begins to look threadbare at the clinical level.

Clinicians and researchers are challenged to identify a group with genuinely high suicide risks and to study intermediate outcomes common enough to be influenced by individual and team interventions. The performance indicators in the national service framework do include a promising intermediate candidate, readmission of those with severe mental illness. We can predict groups of depressed inpatients with a 50% risk of readmission within two years. These include those with: four previous admissions,<sup>8</sup> a family history of suicide or admission for depression, and treatment with electroconvulsive therapy.<sup>9</sup> Recurrence of severe depressive disorders multiplies the cumulative risk of suicide, as admission and discharge are periods of higher risk. The long term risk of suicide in this group is likely to exceed 15%—for example, the confidential inquiry showed that 22% of patients who committed suicide had had five or more admissions.<sup>6</sup>

We can therefore specify a common adverse outcome—readmission—in a group who may be at a relatively high risk of suicide. Proved interventions to prevent recurrence of depression exist—for example cognitive behavioural therapy and interpersonal psychotherapy,<sup>10</sup> but these are not routinely available in

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