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50 & 100 YEARS AGO

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"What mean these stones?" — The Bible is a library of books, not all of the same literary or historical importance. In some cases (especially in the Old Testament) the books themselves are composite and contain ancient fragments embedded in a more recent framework. When, therefore, Prof. Burrows suggests that archaeological researches in Palestine back up statements appearing in the writings, it must be clearly understood that in no sense can the verbal accuracy of the whole be demonstrated; all that can be said is that many topographical descriptions can be shown to be reasonably correct.

From *Nature* 7 December 1957.

100 YEARS AGO

In proposing the toast of "The Royal Society" at the anniversary dinner on Saturday last, Lord Dunedin referred to the popularisation of science as one of the functions of a society which exists for the promotion of natural knowledge. This remark provides the subject of a letter by an anonymous correspondent in Tuesday's *Times*. The writer urges that the neglect of science in this country is largely due to the indifference shown by scientific men to the intellectual interests of the average reader. Few men of science make any attempt to describe their investigations in language which can be understood by men of culture without special scientific knowledge, and it is scarcely too much to say that most investigators are so closely absorbed in their particular researches that whether the world in general knows anything of the results or not is regarded as no concern of theirs. This spirit, and the obscure and diffuse manner in which scientific investigations are often described, are to be deplored.

From *Nature* 5 December 1907.

that had been kept under immune control in the donor for all those years. In none of these previous reports, however, was the dormant state actually visualized, and the component of the immune system involved in maintaining dormancy was not identified.

Koebel *et al.*[1] take strides forward in both respects. After the initial wave of MCA-induced deadly tumours, dormant lesions in immunocompetent mice — those with a fully functional immune system — developed into progressive tumours only after treatment that resulted in the depletion of immune-system cells known as T lymphocytes (T cells), or neutralization of the cytokines interleukin-12 or interferon-γ, which are involved in adaptive immunity. Depletion of cells called natural killer cells, which are more broadly acting but less specific immune agents, had no effect. These results point to highly specific, adaptive T-cell immunity as the component of the immune system that maintains dormancy. Interestingly, in a different tumour model, immunization with tumour cells can generate antibodies that also contribute to dormancy[4].

Koebel *et al.* also found that many cells in the stable, dormant lesions showed morphological features reminiscent of those in progressively growing, MCA-induced cancers. Like the growing cancers, the stable lesions were infiltrated by immune cells, including T cells, indicating that they were immunogenic (that is, they were being recognized by the immune system). But there was a much lower percentage of proliferating cells and an increased incidence of cell death. Transient culture of cells from dormant lesions yielded atypical fibroblast-like cells that grew out as tumours when injected into immunodeficient, but not immunocompetent, mice. Even in some immunocompetent animals, however, stable lesions occasionally escaped from dormancy and became cancerous. But these lesions could do so only if they had lost their immunogenicity, as indicated by their subsequent ability to grow in immunocompetent host animals.

Thus, Koebel and colleagues' work for the first time characterizes a state of tumour dormancy. The hallmarks of this state are stable lesions of transformed immunogenic cells, which are controlled by the host's adaptive immune system in a condition dubbed 'equilibrium' because of its dynamic nature. Obviously, this is a precarious situation — loss of either immunocompetence or immunogenicity can lead to tumour outgrowth, as the authors show.

The implications of this work are far-reaching. First and foremost, the description and visualization of dormant lesions offers an opportunity to characterize their molecular signatures, as determined by their gene-expression profiles, and to compare these signatures with those of the lesions that became cancerous even in immunocompetent hosts. Indeed, such understanding may lead to the development of new treatments, including non-immune-drug interventions, to turn overt cancers into less aggressive, stable lesions. Second, as Koebel *et al.*[1] point out, cancer immunotherapy can aim not only at complete tumour eradication, but also at establishing tumour equilibrium by encouraging the production of interferon-γ-producing, tumour-specific T cells. Indeed, spontaneous T-cell infiltration into human cancers is now increasingly recognized as a favourable prognostic sign, independently of other indicators[6–8].

Third, this model of dormancy has striking parallels with the chronic infection caused by *Mycobacterium tuberculosis*, one of the world's most successful pathogens. Typically, an asymptomatic or latent infection is established, which can last for decades before the pathogen is reactivated and clinical tuberculosis ensues. Such processes often coincide with a phase of immune suppression[9,10]. Indeed, *M. tuberculosis* is thought to use special bacterial gene products to maintain latency, and it is tempting to speculate that dormant tumours use similar tricks to avoid being eradicated.

Fourth, a more intense search for dormant tumours is warranted — particularly for those tumours induced by chemicals, such as may be present in cigarette smokers, given that Koebel and colleagues' mouse system mimics that situation. Obviously, dormant tumours in smokers would pose a threat, because they can awaken and become overt cancer, at which time it is usually too late for effective therapy[11]. It may be difficult to detect truly dormant lung cancers. But perhaps patients with breast cancer offer another route for investigation: up to 22 years after undergoing a mastectomy, one-third of patients reportedly have evidence of circulating 'tumour' cells without any evidence of disease[3]. Are these cells also kept in check by immune responses, or are they controlled by other mechanisms?

A final, unwelcome, thought prompted by the new results concerns the treatment of cancer patients with immunosuppressive chemotherapy or irradiation. A downside of such treatment could be the escape of dormant tumour cells from immune control. Dormant cells themselves are likely to be less susceptible to these treatments, which primarily target rapidly dividing cells. ■

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