Does cyclosporin A cause cancer?

To the editor—Hojo *et al*. described a tumor growth-promoting effect of the immunosuppressive drug cyclosporin A (CsA) in immunodeficient mice[1]. The effect was attributed to the upregulation of the cytokine transforming growth factor beta by CsA. CsA is used not only in transplant medicine to prevent rejection but also in autoimmune diseases. An unwarranted effect of CsA in the induction, growth or behavior of malignant tumors would be of the utmost importance for clinicians and patients.

In the medical field of rheumatology, we also have feared an increased frequency of malignancies in CsA-treated patients and in particular in patients with rheumatoid arthritis (RA), an autoimmune disease with an intrinsically increased risk of malignant lymphomas. To address this concern, we undertook a retrospective controlled cohort study of all RA patients who participated in CsA clinical trials in the Netherlands between 1984 and 1992 (ref. 2). Every index patient was matched (for age, sex and duration of disease) with two control patients who had never been exposed to CsA. Neither index patients (n = 208) nor control patients (n = 415) had a history of malignancies (according to the Pathological Anatomical National Automated Archives, a database of all histological examinations in the Netherlands since 1974). No increased risk of malignancies was found, either in general or for site-specific cancers. In fact, the relative risk of developing cancer for the CsA-treated patients (relative risk, 0.41; 95% confidence interval, 0.19–0.89) suggested a protective rather than a tumor-promoting effect. This effect did not disappear after correction for many potential confounders.

Challenged by the findings of Hojo *et al*., we assessed whether the observed effect of CsA was dependent on CsA dose or CsA treatment duration, and how the observed incidence of cancer in our study cohort compared with the expected incidence in the general population. The protective effect by CsA was dependent on the duration of treatment—patients who had used CsA for more than 1 year had approximately 400% less chance of developing a malignancy than patients who had used CsA for 1 year or less. The standardized incidence ratio (compared with the normal population) for malignancies was 0.82 (0.36–1.62) in the subgroup of RA patients that were treated with CsA for more than 1 year, compared with 1.98 (1.37–2.69) in the control group. This suggests that RA patients who are on long-term treatment with CsA have a risk of developing malignancies that is equal to the risk in the general population, and lower than the risk in other RA patients.

These epidemiological results suggest that in the absence of further evidence, the tumor-promoting effects of CsA seen in the laboratory setting should not be extrapolated to the clinical situation.

Table Cases of cancer per 1,000 follow-up years with respect to treatment duration with cyclosporine A

	Treatment duration	Relative risk[a]	Treatment duration	Relative risk[a]
	< 1 year	(95% CI)	> 1 year	(95% CI)
CsA group	9.1		3.1	
		0.64 (0.20–2.11)		0.16 (0.03–0.76)
Control group	15.2		17.2	

[a]Adjusted for age and sex. CI, confidence interval

ROBERT B.M. LANDEWÉ[1], BEN E.E.M. VAN DEN BORNE[2], FERDINAND C. BREEDVELD[3] & BEN A.C. DIJKMANS[4]

[1]*Dept. of Rheumatology, Atrium Medical Center Heerlen, The Netherlands*

[2]*Dept. of Lung Diseases, Catharina Hospital, Einedhoven, The Netherlands*

[3]*Dept. of Rheumatology, University Hospital Leiden, The Netherlands*

[4]*Dept. of Rheumatology, Free University Hospital Amsterdam, The Netherlands*

Email: ReumatologenAtrium@compuserve.com

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Clinical research, or classical clinical research?

To the editor—In the May issue, Bell emphasized the enormous potential of molecular medicine[1]. Iterating the view that classical, clinical investigations have had their day, the author were enthusiastic that the new molecular medicine will unravel "the nature of disease." However, knowledge of disease based on physiology, pharmacology and histopathology can still be gravely inadequate. Even with the most common and severe chronic diseases, such as bronchial asthma, central aspects remain undetermined. Asthma can be described as an eosinophilic, exudative airway disease with epithelial shedding, airway remodeling and hyperresponsiveness to many inhaled factors. But what about the cellular and organismal physiology/pathology beyond these general terms?

Bell's idea that the classical observation-based techniques that characterize classical clinical research have nothing more to offer the medical investigator, does not stand up to scrutiny. For example, many classical issues remain unstudied, conjectural or, at best, controversial: the shapes of eosinophil degranulation and disappearance *in vivo* in the blood-perfused bronchial mucosa; the appearance of pluripotent plasma-derived proteins/peptides in the diseased tissue milieu; the epithelial shedding–restitution processes *in vivo* and their inflammatory/remodeling sequelae; the particular tissue remodeling that contributes to the non-specific bronchial hyperresponsiveness; and so on. Admittedly, this is a subjective effort at making a list, but rather than being parried easily, I think it can be expanded into a substantial enumeration of disease aspects that require innovative but classical medical research.

Of course, given these unresolved matters, molecularly defined disease phenotypes would be more than welcome, as would the associated unraveling of molecular events that are causative and that determine progress and chronicity of the disease(s). It is promised that molecular medicine will disentangle the heterogeneity of common diseases and provide a new taxonomy for illness based on molecular abnormalities[1,2]. With a *de novo* sub-grouping of asthmatic individuals into molecularly based phenotypes, we can probably stop struggling with the complex pathophysiology/histopathology of the elusive and capricious asthma that is now showing an alarming increase in prevalence. Considering the difficulties involved in obtaining truly relevant *in vivo* data in this disease, even in animal models[3], this