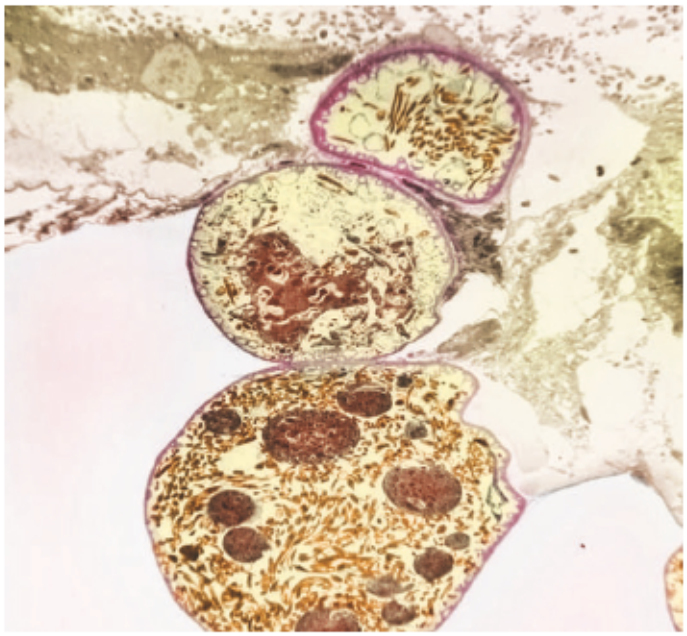

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Figure 1 | Malaria parasites. If a mosquito feeds on malaria-infected blood, the parasite attaches itself to the insect's gut wall and forms 'oocysts'. These spherical structures support the development of sporozoites (small, brown shapes), which can be transferred back to humans through the mosquito's saliva.

encoding PyCSP into mouse oocytes (eggs). The resulting transgenic mice produced PyCSP as though it were a normal mouse protein. This meant that PyCSP should not be recognized as potentially harmful foreign material, so the mice would not raise a T-cell immune response to the protein. The transgenic mice were then bred with mice that were unable to produce any antibodies and thus had no antibody-based immunity against the PyCSP protein either. The final mice were therefore expected to be immunologically tolerant to PyCSP. Scientists have been attempting to engineer such mice for more than 15 years, so these animals are a considerable technological achievement by Kumar and colleagues.

The authors immunized the PyCSP-tolerant mice with attenuated *P. yoelii* sporozoites to determine whether animals that could not respond to PyCSP could still produce protective immunity against the malaria parasite. When the mice were immunized with two doses of attenuated *P. yoelii* sporozoites and then infected with untreated sporozoites, they produced only minimal protection — there was only a 10% reduction in the number of copies of parasite ribosomal RNA in the animals' livers compared with non-immunized controls. In contrast, normal mice that had been immunized had a 10,000-fold reduction in copy number compared with controls. So, lack of an immune response to PyCSP led to a dramatic reduction in protection as measured by parasite burden in the liver.

However, immunization with two doses of attenuated *P. yoelii* sporozoites often does not fully protect mice, whereas immunization with three doses is almost always associated with 100% protection against development of blood-stage infection — the gold standard of protection against malaria. When Kumar *et al.* immunized their PyCSP-tolerant mice with three doses of attenuated *P. yoelii* sporozoites, and then infected them with normal *P. yoelii* sporozoites, there was 100% protection against blood-stage infection.

Therefore, PyCSP can elicit an early, if incomplete, protective immune response. In fact, the authors conclude that PyCSP is responsible for 90% of the protection, and is thus immunodominant — that is, the majority of the protective cellular and antibody responses are directed against this protein rather than against other proteins. However, the experiment with three doses of attenuated sporozoites demonstrates that an immune response against PyCSP is not required for protective immunity.

Although these results strongly suggest that PyCSP is involved in the protection elicited by radiation-attenuated *P. yoelii* sporozoites, they do not definitively establish this because several possible alternative interpretations exist. The most obvious explanation for the difference in protection in the transgenic mice after two and three doses of *P. yoelii* sporozoites is that it took the full three doses to elicit a protective immune response against one or many proteins other than PyCSP, and that these other proteins — not PyCSP — elicited the whole protective immune response. In normal mice, these proteins could be the immunodominant ones, or at least equal partners in the full protection that is produced by three doses.

Another explanation concerns the fact that there are two types of T cell: effector T cells that actually do the job of eliminating invading pathogen-infected cells, and helper T cells that facilitate the work of the effector T cells. So it may be that responses against proteins other than PyCSP were responsible for effector-T-cell-induced protective immunity after two or three doses of the vaccine, but that helper-T-cell responses against PyCSP were required to facilitate protective T-cell responses against other proteins after two doses, but not after three.

A third possibility is that PyCSP truly is the immunodominant protective antigen in

50 & 100 YEARS AGO

50 YEARS AGO

The U.S. National Academy of Sciences at its autumn meeting in Washington adopted the following resolution respecting recent events in Hungary: "[We]... unite in expressing [our] profound admiration and sympathy to fellow scientists in Hungary and to all the men and women of that nation who have demonstrated their love of liberty with sacrificial devotion during the tragic events of the past few weeks. American scientists look forward with hope to a time when their Hungarian colleagues, freed from external oppression, will be able to join fully in the international exchange of information, discussion and encouragement which is essential to the progress of science".
From *Nature* 15 December 1956.

100 YEARS AGO

There is much knowledge enshrined in Parliamentary Blue-books, and doubtless some wisdom. Very often it remains enshrined in them. A better fate, however, has awaited the report of the Departmental Committee appointed by the President of the Local Government Board in 1899 "to inquire into the use of preservatives and colouring-matters in foodstuffs."... The policy of our laws has been to allow food-producers a free hand, subject to the restriction that any preservative added shall not render the food injurious to health. But has this *laissez faire* attitude been a wise one? True, it leaves the food manufacturer free to experiment—which is, so far, so good. But it gives him the consumer's living body as *corpus vile*—which is not so good... Let a responsible body be appointed, competent to examine the newer substances; let it hear what is to be said on either side, and let it make whatever experiments are necessary and practicable to test the evidence. And let no preservative or colouring-matter whatever be added to foodstuffs until it has been at least provisionally approved by this responsible authority.
From *Nature* 13 December 1906.