accompanies immunizations[12]. But clonal cell division might permit somatic mutation, the raw material of affinity maturation, assuming that there is self-antigen present to perform the selection process of the activated anti-self clonal precursors.

Finally, polyclonal activation with proliferation carries with it a potential benefit. Such a process should produce antibodies reflecting the entire immunological history of the host (and perhaps a modest sample of its future potential as well). As Ahmed and Oldstone pointed out 20 years ago[2], the stimulation of bystander B cells by any polyclonal activator may be a significant contributor to the maintenance of long-term immunological memory in the absence of specific antigenic stimulation.

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Hunziker *et al.* reply:

It is certainly interesting to consider polyclonal B cell activation in a broader context than the virally induced hypergammaglobulinemia that we analyzed in our paper[1]. As Silverstein and Rose point out, some polyclonality of the antibody response is widely seen after immunization or infection. This is almost certainly beneficial in generating inflammatory and antibacterial responses through chemotaxis and complement fixation; however, it is detrimental in autoimmunity. It is more difficult to be sure about the relevance of the polyclonal responses to B cell memory[13] or the generation of new specificities, because this requires longitudinal studies of a complex repertoire in which somatic mutation, receptor editing and class-switch recombination will all be operative. For new specificities to be generated during proliferative expansion with improved affinities, there would have to be effective selection according to the B cell receptor (BCR); this might be possible in some circumstances, but we found that virally induced hypergammaglobulinemia is BCR independent.

The physiological relevance of polyclonal B cell activation differs according to the infectious agent. It is well known that patients with agammaglobulinemia are protected against extracellular bacterial infections by pooled gammaglobulin preparations, and some natural antibodies are also experimentally protective in rodents[14], so amplification of the natural repertoire will be beneficial. The repetitive nature of the capsular polysaccharides of extracellular bacteria means that even low-affinity antibodies can bind well enough to fix complement and opsonize. An experimental polyclonal response to *Escherichia coli* can be protective against *Hemophilus influenza* infection[15]. These are functional protective polyclonal B cell responses, but without the need for mechanisms to selectively improve affinity. For cytopathic viruses such as vesicular stomatitis virus or vaccinia, the antibody response is also partly polyclonal, but only high-affinity specific antibodies will neutralize the virus and are important in clearance.

Lymphocytic choriomeningitis virus (LCMV) is noncytopathic and is normally controlled by perforin-dependent T cell cytotoxicity[16]. Antiviral antibodies are not required (as B cell–deficient animals can clear the virus). Here there is clear hypergammaglobulinemia (mainly caused by increased IgG), and virus-specific T helper cells trigger the response regardless of B cell specificity. The evidence for direct interaction of LCMV-specific T cells on nonspecific B cells comes not only from cytokine-deficient mice but also from the ablation of the response in mice that lack B cell expression of surface MHC class II molecules. To be effective, antiviral antibodies must neutralize viral infectivity. This requires high affinity, but the LCMV hypergammaglobulinemic response produces neither substantial neutralizing activity nor cross-neutralization against vesicular stomatitis virus or poliovirus. It seems that the inability of the immune system to discriminate accurately between infections means that immunopathological polyclonal B cell activation is a consequence of high-level, relatively focused T cell activation required for control of viruses that tend to persist.

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1. Hunziker, L. *et al. Nat. Immunol.* **4**, 343–349 (2003).
2. Ahmed, R. & Oldstone, M.B.A. in *Concepts in Viral Pathogenesis* (eds. Notkins, A.L. & Oldstone, M.B.A.) 231–238 (Springer, New York, 1984).
3. Coutelier, J.P., Johnston, S.J., El Idrissi, M.E. & Pfau, C.J. *J. Autoimmunity* **7**, 589–599 (1994).
4. Hirsch, R.S. and Proffitt, M.R. in *Viral Immunology and Immunopathology* (eds. Notkins, A.L. & Oldstone, M.B.A.) 419–434 (Academic Press, New York, 1975).
5. Boyd, W.C. & Bernard, H. *J. Immunol.* **33**, 111–122 (1937).
6. Shimada, K. & Silverstein, A.M. *Cell. Immunol.* **18**, 484–488 (1975).
7. Silverstein, A.M., Thorbecke, G.J., Kraner, K.L. & Lukes, R.J. *J. Immunol.* **91**, 384–395 (1963).
8. Snapper, C.M. & Finkelman, F.D. in *Fundamental Immunology* 4th edn. (ed. Paul, W.E.) 831–861 (Lippincott-Raven, Philadelphia, 1999).
9. Silverstein, A.M. & Rose, N.R. *Semin. Immunol.* **12**, 173–178 (2000).
10. Ramseier, H. *J. Exp. Med.* **130**, 1279–1294 (1969).
11. Bloom, B.R. *Adv. Immunol.* **13**, 101–208 (1971).
12. Rich, A.R. *Proc. Soc. Exp. Biol. Med.* **32**, 1349–1351 (1935).
13. Bernasconi, N.L., Traggiai, E. & Lanzavecchia, A. *Science* **298**, 2199–2202 (2002).
14. Benedict, C.L. & Kearney, J.F. *Immunity* **10**, 60–617 (1999).
15. Moxon, E.R. & Anderson, P. *J. Infect. Dis.* **140**, 471–478 (1979).
16. Kagi, D. *et al. Nature* **369**, 31–37 (1994).