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Fishman M. Antibody formation in vitro. *J. Exp. Med.* **114**:837-56, 1961.
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Specific antibody against bacteriophage was initiated in cultures of lymph node fragments in response to their stimulation with a cell-free extract derived from macrophages which had been incubated with the antigen. Antibody production failed to occur if the antigen alone was added. [The *SCI*® indicates that this paper has been cited in over 545 publications since 1961.]

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"Producing antibodies *in vitro* was a major goal to be achieved in immunology during the late 1950s and early 1960s. Culturing immunocompetent organ tissues or cells with a variety of antigens had been generally unsuccessful. While working at the Public Health Research Institute of the City of New York in 1957, I entered this research arena after my interest was piqued by several investigators' observations on the anatomical intimacy between macrophages and lymphocytes.[1,2] The scavenger property of macrophages, which would result in degradation of antigens, provided the basis for the then current thinking that if macrophages had a role in antibody production, it was a passive one. The concept of a positive involvement of these cells in antibody formation was considered heresy. Yet it remained intriguing, despite the phagocytic characteristic of macrophages, that they might fill a helper role for lymphocytes in antibody production. This was put to the test and the results were published in the *Journal of Experimental Medicine*.

"From our experiments, we found that macrophage-antigen interaction was required to initiate a primary immune response in lymph node fragment cultures or in immunocompetent chick embryos. The product of this interaction was then reported to be sensitive in RNase digestion, thus introducing the phenomenon of immune RNAs.

"On a lighter note—in a separate experiment—some of the chick embryos were allowed to hatch with the eventual reward of a continuous supply of fresh eggs for everyone in the lab. The results of that experiment need not be discussed here.

"The results of the work with macrophages led to the positive personal recognition of my receiving the Waksman award for *in vitro* antibody production. It also began the stormy controversy over immune RNAs that today remains unresolved, even though mRNAs responsible for rabbit immunoglobulin synthesis are currently being used to obtain the cDNAs used for Southern and Northern blot analysis. The immune RNA story—thrust perhaps before its time on the immunological community in the early 1960s—may soon be buried under the more newsworthy and more rapidly arriving reports of progress in monoclonal antibody research and immunotherapy for a variety of diseases.[3-7]

"The work described in this paper was intended to test the role of the macrophage in the immune response, an unbelievable concept at that time. I did not intend to give birth to immune RNA, although I do not have any regrets about the appearance of the phenomenon.

"I feel that the most likely reason for the paper being cited so often is that it describes one of the first successful attempts to produce antibodies *in vitro*.

"Reports of recent studies of the macrophage-antigen relationship have come from the laboratories of Jakway and Shevach at the National Institutes of Health and Lu and Unanue at Harvard Medical School."[8,9]

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3. **Miller R A, Maloney D G, Warnke R & Levy R.** Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. *N. Engl. J. Med.* **306**:517-22, 1982.
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