How important was Murphy?

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It was interesting to read Silverstein's Commentary[1], in which he claims that the work of James Murphy ". . . appeared to prove beyond question that the lymphocyte is the active participant in the rejection of tissue allografts, in protection against infection and, by implication, in both innate and acquired immunological responses". The "active participant", however, remains undefined in both Murphy's work and Silverstein's account of it. Murphy's work was acknowledged at the time, as he summarized it in an invited Rockefeller Institute monograph[2]. However, Silverstein feels he has not received credit for his "prior discovery" and that "nobody listened".

Viewing the past armed with present knowledge may not be the ideal way to evaluate such work. The crucial question is: if we did not know what we know now, but only had Murphy's work to go on, would we be any wiser about the function of small lymphocytes? To evaluate Murphy's work critically, one should first explain what the problem was in understanding the lymphocyte at the time and then evaluate Murphy's data.

The problem related to a small cell that appeared to have a long lifespan and not to divide, which entered the blood in enormous numbers each day and circulated. It also accumulated in and around certain pathological lesions and was referred to as "a small round cell" in the pathological literature. It was also the major, although by no means the only, cell type in lymphoid tissues.

Here are Murphy's conclusions in the seven papers that make up his monograph. (i) "Small round cells" accumulate around grafts of foreign tissues, which shows the importance of the "lymphoid cell type" in "resistance" to foreign tissue grafts (in chick embryo, adult rat brain and x-irradiated rats and in grafts of normal tissues and tumors). (ii) Tumor rejection in mice is associated with a "small round cell reaction" around the tumor, lymphocytosis and "enhancement of the rate of cell division in the lymphoid centers of the spleen and lymph nodes". (iii) "The lymphoid cell is a necessary factor in the resistance mechanism" (to tumor grafts) because "destruction of these cells by x-rays or their reactibility [sic] by olive oil results in the practical annulment of resistance to transplanted tumors". (iv) Stimulation of "the lymphoid tissue" by "small doses of x-rays, dry heat, olive oil and certain unsaturated fatty acids" increases "resistance" to grafted tumors. (Actually the correlation between stimulation and resistance was poor.) (v) A "local cellular reaction" is associated with "resistance" to tumor grafts. An increased local infiltrate was induced by injecting a mixture of rat blood and tumor cells into mice previously "sensitized" with an injection of rat blood or by injecting tumor cells into a locally x-irradiated area of skin. (vi) The "lymphoid system" was stimulated by "x-ray, dry heat and fatty acid". ". . . the only possible conclusion . . . is that an increased activity of the lymphoid system is responsible for the increased resistance of the mice to the growth of spontaneous cancer". (vii) The association of "the lymphoid cell" in the local reaction to infection with tubercle bacilli and the association of lymphocytosis with favorable prognosis (in human infections and, experimentally, in mice given bovine tuberculosis and guinea pigs given a human strain) leads to the conclusion ". . . that the association of the lymphocytes with resistance is more than an associated reaction, and that these cells are at least an important if not the important resisting force of the organism, a purposeful phenomenon".

As evident from the above quotes, Murphy's experiments show only that changes in lymphoid tissue, in the local cellular infiltrate and in the level of blood lymphocytes are associated with "resistance" to tumors and to infection with tubercle bacilli. He uses the terms "lymphocyte", "lymphoid cell type" and "small round cell" interchangeably throughout these papers. He never stated that this "resistance" was immunological. His experiments are, of course, of great interest but they provide no critical evidence for the function of a defined cell type—the small lymphocyte—whose function remained a mystery until the 1960s. Gowans[3] was the first scientist to use marked purified small lymphocytes, *via* cell labeling and thoracic duct cannulation, and hence was the first to unequivocally prove their immunological competence, that is, their ability to initiate an immune response when appropriately stimulated by antigen.

1. Silverstein, A. *Nature Immunol.* **2**, 569–571 (2001).
2. Murphy, J. B. Monogr. Rockefeller Inst. Med. Res. 1–168 (1926).
3. Gowans, J. L, McGregor, D. D., Cowen, D. M. & Ford, C. E. *Nature* **196**, 651–655 (1962).

Response

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Dr. Miller makes two charges in connection with my suggestion that by 1926 Murphy had identified the lymphocyte as the active factor in graft rejection and in other immunological responses. First, he feels that I have inadmissibly interpreted Murphy's work in the context of modern knowledge of the lymphocyte, rather than in the context of the times, and second, that Murphy's terminology involved neither "a defined cell type" nor the implication of an "immune" response.

I attempted to make clear that, in the community of experimental transplantation oncologists, it was known from the work of Schöne (who coined the term "tumor immunity" in 1912[1]) and of Tyzzer (who wrote an extensive review entitled "Tumor immunity" in 1916[2]) that both tumor and normal tissue grafts are rejected by an active immune response. As a member of this small group of researchers, Murphy would have taken this for granted; I submit that it runs as a *leitmotif* through all of his work in this area. The problem for Miller is that Murphy prefers the term "resistance" when speaking of graft rejection or of protection from infection. This was a fairly common substitute among experimental pathologists of the time; even Hans Zinsser, in 1914, published a book entitled *Infection and Resistance*[3] while reviewing contemporary immunological knowledge, and that doyen of immunopathological research on tuberculosis, Arnold Rich, often spoke of resistance when he meant immunity[4]. I return to the point that, whereas the tumor people undoubtedly knew of Murphy's work, the mainstream immunologists of the time (Heidelberger, Landsteiner