divided by the total number of 1975 and 1976 articles published. As usual in these kinds of lists, the review journals are at the top [9–10]. The top core journals in terms of impact are *J. Mol. Biol.* (7.47), *J. Biol. Chem.* (5.84), *J. Cyclic Nucl. Res.* (5.81), and *Biochemistry* (5.12). As one would expect, these international journals perform substantially better than journals from Eastern Europe or the Third World.

As I mentioned at the beginning of this article, developing precise measurements of any part of the scientific literature is a difficult task. I have only scratched the surface of the problem. But what I have presented here represents an enormous investment of time and energy. The number of variables involved seems endless. I hope this work will interest others in conducting additional bibliometric studies of this type. ISI stands ready to assist those who take up the challenge.

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Earthworms and immunology

Edwin L. Cooper

Mentioning the word earthworm always conjures visions of fishing trips, the mass exit of worms from earthly caverns after spring rains, and the improvement of soil by their constant churning and digging, as Darwin observed. In the opinion of others, worms are ecologically sound agents for destroying wastes and, for those concerned about food shortages, worms could be rich sources of edible protein.

To the biologist, earthworms have proved to be excellent, inexpensive animals for studying regeneration, aspects of neuro-physiology, neuro-endocrinology and excretion. Now, comparative immunologists interested in the phylogenesis of immunity [1–7] have re-discovered the earthworm. The evolution of man's complex immune system [8], like his nervous system, possesses certain features which can be traced to comparatively primitive animals like the earthworm.

The most important characteristic of the immune systems of animals in the phylum Annelida (e.g. the earthworm) is that they have developed a coelom. This body cavity contains coelomic fluid, in which coelomocytes, the worm's leukocytes, are suspended. Unlike leukocytes, coelomocytes are not contained within the circulatory system but, like leukocytes, they are sensitive to perturbations such as infections and are active in defense reactions ranging from phagocytosis to the more complex mechanisms of tissue graft rejection. These responses to foreign material are mediated principally by coelomocytes which probably possess cellular recognition units or receptors. However, the nature of these receptors is unknown. The receptors for antigens in mammals are antibodies, but antibodies have not been found in earthworms. Worms must therefore have simpler, primordial receptor units and the fundamental problem in studies on the earthworm's immune system is to explain the process of recognition.

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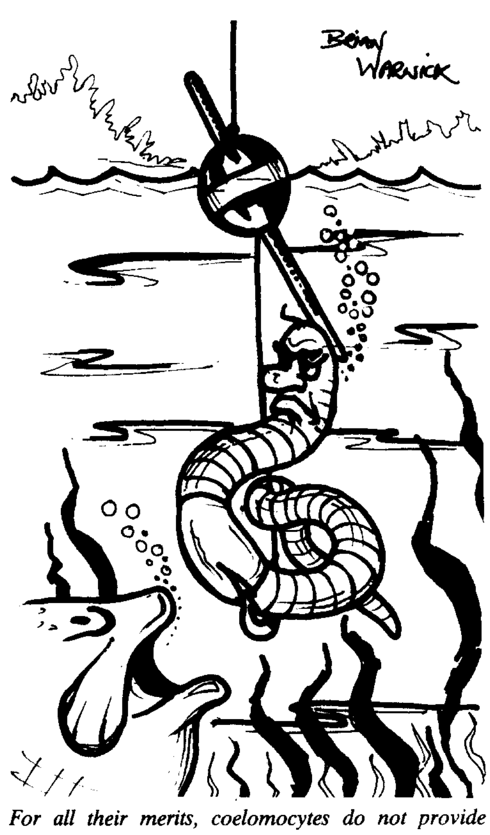
How do earthworms fit into the scheme of the history of modern immunology? It was the crucial work of Metchnikoff and other early immunologists working with the invertebrates (including earthworms) that led to a knowledge of cellular immunity. Because of Metchnikoff's contributions, immunology was then divided both conceptually and technically into its second major subdiscipline, concerned with cellular immunity, which began by emphasizing the role of phagocytosis of foreign antigens, particularly infectious microorganisms. During the early 1960s, these two chief facets of the immune response, humoral and cellular immunity were unified. Each is primarily the result of the products of a group of lymphocytes. B-cells, when stimulated, will synthesize and secrete antibody, whereas T-cells help B-cells assist in regulating the responses of B- and other cells, and mediate cellular reactions such as graft rejection and immunity against cancer.

Since it is assumed that the earthworm's graft rejection capacities are mediated by T-cell progenitors, where do they fit into the scheme of modern immunology? Phagocytosis is the defense reaction common to all animals, even the simplest, the unicellular protozoans. Earthworms contain a multitude of coelomocytes patrolling the coelomic cavity in search of foreign cells or substances. Since the end of the nineteenth century, we have known that any material introduced into the coelomic cavity will be phagocytosed and destroyed by coelomocytes. Earthworms are therefore no different from other animals in possessing an efficient, generalized but non-specific mechanism for disposing of foreign non-self material. *Non-specific* immune responses are universal and, in the earthworm, they may be even more efficient than equivalent responses in man.



For all their merits, coelomocytes do not provide immunity against fish.

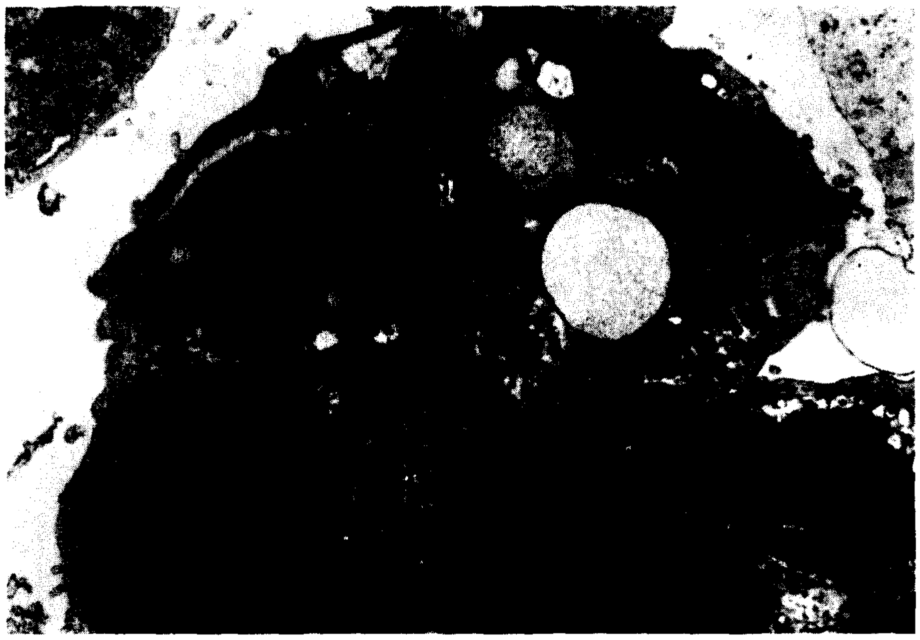


Fig. 1. Within the cytoplasm of some granulocytic coelomocytes found in xenografts 5 days post-transplantation, large fragments of muscle fibers (MF) can be seen. The cytoplasm is filled with inclusions and phagosomes (Pg). (× 12,200) Reproduced from: Linthicum, D. S., Marks, D. H., Stein, E. A. and Cooper E. L. (1977) Eur. J. Immunol. *7, 871–876.)*

The *specific* immune system of earthworms also possesses certain characteristics common to the immune systems of vertebrates, but it may be less complex [9]. There are antigen-recognizing cells as well as effector cells. Antigen-recognizing cells may be able to sense antigen via the, as yet undemonstrated, cell surface receptors. Antigen recognition, however, can be demonstrated by the fact that foreign cells such as sheep erythrocytes will bind to the surface of coelomocytes. It is assumed that they later interact with effector cells, a process which is responsible for at least one immune function, the rejection of transplants.

What is the nature of the worm's immune system? We are sure that like other invertebrates, worms possess mechanisms for ridding themselves of soluble and particulate material, chiefly by means of humoral components in the coelomic fluid, such as agglutinins, lysins and other bactericidal substances. Earthworms probably synthesize these components both in response to new antigenic challenges and to replace effete components. The chemical structure of these components is not at all clear, but assuming they are akin to those found in other invertebrates such as oysters, then they are probably specialized proteins [10]. The most unusual and interesting aspect of these components is that the agglutinins, in particular, may be synthesized by the coelomocytes and then released into the fluid. We know about the structure of worm coelomocytes, but the challenge is to identify their receptors which may turn out to be one or all humoral components of the coelomic fluid. This is how they could work. Receptors bound to the surface of coelomocytes when brought into contact with specific antigens could be stimulated to synthesize more receptor which is then shed into the coelomic fluid.

How are worms capable of distinguishing between *self* which is non-antigenic from *non-self* which is antigenic, and potentially harmful or infectious? Let us deal with how worms reject grafts as a paradigm. First, worms will always accept autografts permanently after initial healing and show no signs of rejection. However, allogeneic and xenogeneic transplants from other earthworms will first heal in, remain temporarily unaffected, rest unchallenged, but then, later, they will show gross and histological signs of graft rejection. The grafts are destroyed by coelomocytes, among which there are surely the effectors, in addition to those which first recognized the antigen. There is no direct evidence that antigen-recognizing cells are concerned with graft rejection, but antigen-recognizing coelomocytes can bind to certain antigens found on sheep erythrocytes to form rosettes. Although presumably not related to the antigens on grafts, the adherence of sheep erythrocytes to coelomocytes does indicate that receptors are present.

Graft rejection is presumed to be mediated by primed coelomocytes that infiltrate the graft matrix, and once inside, attack the graft by phagocytosis of viable muscle. Electron micrographs, which reveal the destruction of viable graft musculature, strongly support the view that the rejection process is not initiated by the death of the transplant (Fig. 1). Moreover, grafts are always vascularized, thus, they are nourished, and some often show signs of irritability due to innervation. That graft rejection is specific has been demonstrated by several experiments: 1) accelerated rejection of second grafts, 2) adoptive transfer of the response by coelomocytes, 3) specificity of local responses, 4) specificity of third-party rejection. In other words there is evidence that primed, sensitized coelomocytes are capable of remembering that they have encountered an antigen previously [11].

Earthworms are important to immunology; their specific recognition and rejection of transplants provide tangible and repeatable evidence that certain features of the immune response are common to all living creatures and that to reach its present, more complicated form in man, the immune response required a long evolutionary history [12]. In contrast, the presence of the earthworm's immune system also suggests that complicated immune responses are not essential since the earthworm's long survival against its hostile environment in soil is ensured by its apparently less complicated immune capabilities.

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