

References

1. I. W. D. Hackh, *Chemical Dictionary* (McGraw-Hill, New York, ed. 3, 1944); W. A. N. Dorland, *Illustrated Medical Dictionary* (Saunders, Philadelphia, ed. 23, 1957); *Webster's New International Dictionary of the English Language* (Merriam, Springfield, Mass., ed. 2, 1940).
2. *Webster's Third New International Dictionary of the English Language* (Merriam, Springfield, Mass., 1961).

Delayed Hypersensitivity

By their commendable effort to explain so complex a phenomenon as delayed hypersensitivity when so little is known about it, Karush and Eisen [*Science* 136, 1032 (1962)] have provided immunologists with a theoretical focal point from which enlightening discussions of various points of view can diverge. I should like to make some contributions to such potential discussions by pointing out a few aspects of delayed hypersensitivity which I believe are not adequately explained by their theory.

They make no allowance for the probability that delayed hypersensitivity exists in more than one form. The allergy which can so readily be induced in experimental animals with minute quantities of protein antigens, which can so readily be suppressed by specific desensitization, and which bears an inverse intensity relationship to immediate (anaphylactic) hypersensitivity seems distinct, phenomenologically, from classic delayed hypersensitivity of the tuberculin type. The latter is not so readily induced, does not depend for reliable elicitation on the use of small quantities of allergen, cannot be suppressed by desensitization except through heroic efforts, and bears no known relationship to anaphylactic hypersensitivity, which may or may not coexist with it. A distinction between evanescent- and tuberculin-types of delayed hypersensitivity to purified protein antigens needs to be made in any discussion of theories meant to explain this kind of allergy, so as to avoid what at first appear to be some very confusing conflicts in experimental results. Its bearing on evaluation of the theory of Karush and Eisen is illustrated by the point that although their theory may satisfactorily explain desensitization to delayed hypersensitivity of the evanescent type, it fails to explain desensitization to hypersensitivity of the tuberculin type. If high-affinity humoral antibodies were responsible for the latter type of allergy, then one would expect them to be removed preferen-

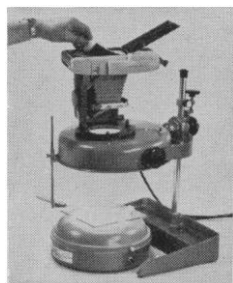
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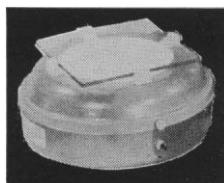
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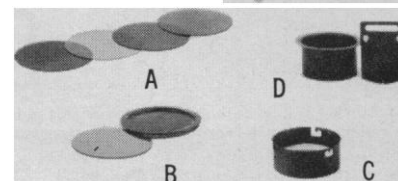
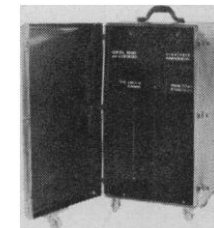


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tially with respect to the medium-affinity antibodies of anaphylactic hypersensitivity, and therefore expect also that delayed hypersensitivity would disappear before immediate hypersensitivity disappeared, whereas in fact the opposite occurs.

I doubt whether Karush and Eisen are entirely justified in assuming that the susceptibility of delayed-hypersensitivity reactions to various pharmacologic agents is irrelevant to their hypothesis, because one of the principal questions that must be raised to evaluate their theory is whether the anti-

bodies of delayed and immediate hypersensitivity are manufactured in the same way and by the same cells. Some of these pharmacologic agents and certain physical agents can be helpful in answering this question. For example, once both immediate and delayed hypersensitivities have been established, x-irradiation suppresses only the latter, presumably because the radiosensitive cells responsible for it are harmed and because there is no reservoir of radioresistant humoral antibodies available to maintain delayed hypersensitivity as there is to maintain immediate

hypersensitivity. The same objection can be made to the authors' indifference regarding cells to be found at the sites of immediate and delayed hypersensitivity skin reactions, for these may be the cause of the reactions, not necessarily their effect.

If the Karush-Eisen explanation for delayed hypersensitivity reactions in avascular or poorly vascularized areas such as the cornea is accepted, then their explanation for the invulnerability of homograft cells in Algire's Millipore filter chambers seems a very unlikely one, and vice versa. Immunodiffusion experiments performed in various laboratories have shown that humoral antibodies have no difficulty in passing through cellulose nitrate membranes capable of withholding mammalian cells.

Karush and Eisen suggest that delayed hypersensitivity may be transferable with very large volumes of serum or gamma globulin containing high-avidity antibody. Indeed, such transfers seem to have been accomplished occasionally, but the factor responsible for the transfer appears to have been not a gamma globulin and typical antibody but a product of specific allergic cell injury which precedes bleeding of the donor animals, a factor which migrates electrophoretically with serum alpha globulin. If their theory is correct and delayed hypersensitivity is due to very low concentrations of high-avidity antibody (why high concentrations cannot be attained or high-avidity antibody cannot be made rapidly is not explained), then there should be no need for a priming allergic reaction in the donor animal and delayed hypersensitivity should be readily transferable with large quantities of serum or its constituents.

I do not say that high-avidity antibody may not be responsible for delayed hypersensitivity. I do suggest that making the assumption that it is a humoral antibody not unlike ordinary serum antibodies except for its high avidity and implying that it is manufactured in the same way as these serum antibodies introduces several complications in our understanding of the phenomenon with which we do not have to contend in the older theory implicating cellular antibodies in this allergic phenomenon.

Although they do not have vital bearing on evaluation of the Karush-Eisen theory, I should like to cite recent papers by Marcus and his co-

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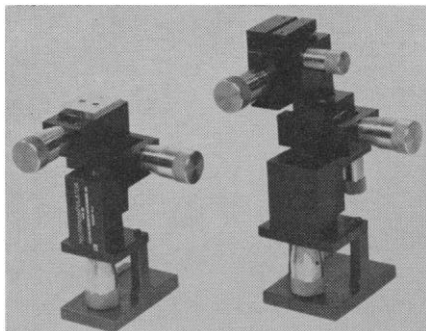
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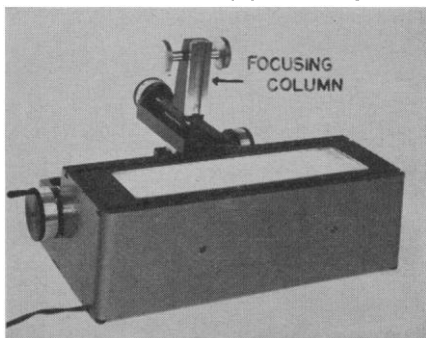


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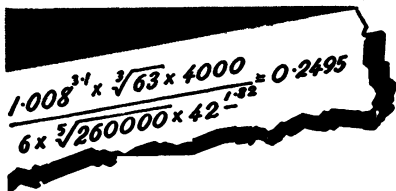
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workers (1) and by Peck *et al.* (2), which offer good evidence that delayed-hypersensitivity skin reactions to blastomycin and to histoplasmin are directed against polysaccharides, not proteins. Thus, the idea mentioned in the Karush-Eisen article to the effect that delayed hypersensitivity to carbohydrate antigens cannot be developed no longer seems tenable.

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1. P. Q. Edwards, R. A. Knight, S. Marcus, *Am. Rev. Respirat. Diseases* 83, 528 (1961); R. A. Knight, S. Coray, S. Marcus, *ibid.* 80, 264 (1959); R. A. Knight and S. Marcus, *Am. Rev. Tuberc. Pulmonary Diseases* 77, 983 (1958).
2. R. L. Peck, D. S. Martin, C. Hauser, *J. Immunol.* 38, 449 (1940).

The article by Karush and Eisen has stimulated a great deal of discussion. We are submitting the following comments in the belief that every good argument is improved by respectful disagreement. To this end we discuss two problems in the theory, which are raised by the authors but which we believe to be more serious than appears to be the case from their article.

The first problem concerns the transferability of delayed hypersensitivity with cells but not with serum. Since in the human, gamma globulin molecules have an average life expectancy of approximately 1 month, it is necessary to transfer only 100 to 200 ml of serum to give the recipient one day's output of the donor's entire lymphoid system. The number of cells one can transfer is obviously a small fraction of this, and for several days, at least, after transfer it is possible to produce a higher concentration of antibody in the recipient with a transfer of serum than of cells. It is, therefore, difficult to explain the development of delayed hypersensitivity in the recipient immediately after transfer of cells but not after transfer of serum.

To solve this problem, Karush and Eisen postulated that the antibody responsible for delayed hypersensitivity was being turned over very rapidly by complexing with circulating antigen (presumably that remaining from the immunizing injection). Thus, the amount of antibody circulating would be at any time a small fraction of that produced each day. The difficulty with this solution of the problem is that the desired effect would be produced over a relatively narrow range of anti-

gen concentration, that of moderate antigen excess. The amount of antigen required to induce delayed hypersensitivity is probably less than that required to produce this level of circulating antigen. If the appropriate antigen concentration is achieved it will remain appropriate very transiently, since the antigen as well as the antibody is cleared by the "immune elimination." If, on the other hand, a large excess of circulating antigen is established, this will suppress the concentration of circulating antibody below its effective level. The antigen would also diffuse into the tissues, making them insensitive to the test antigen.

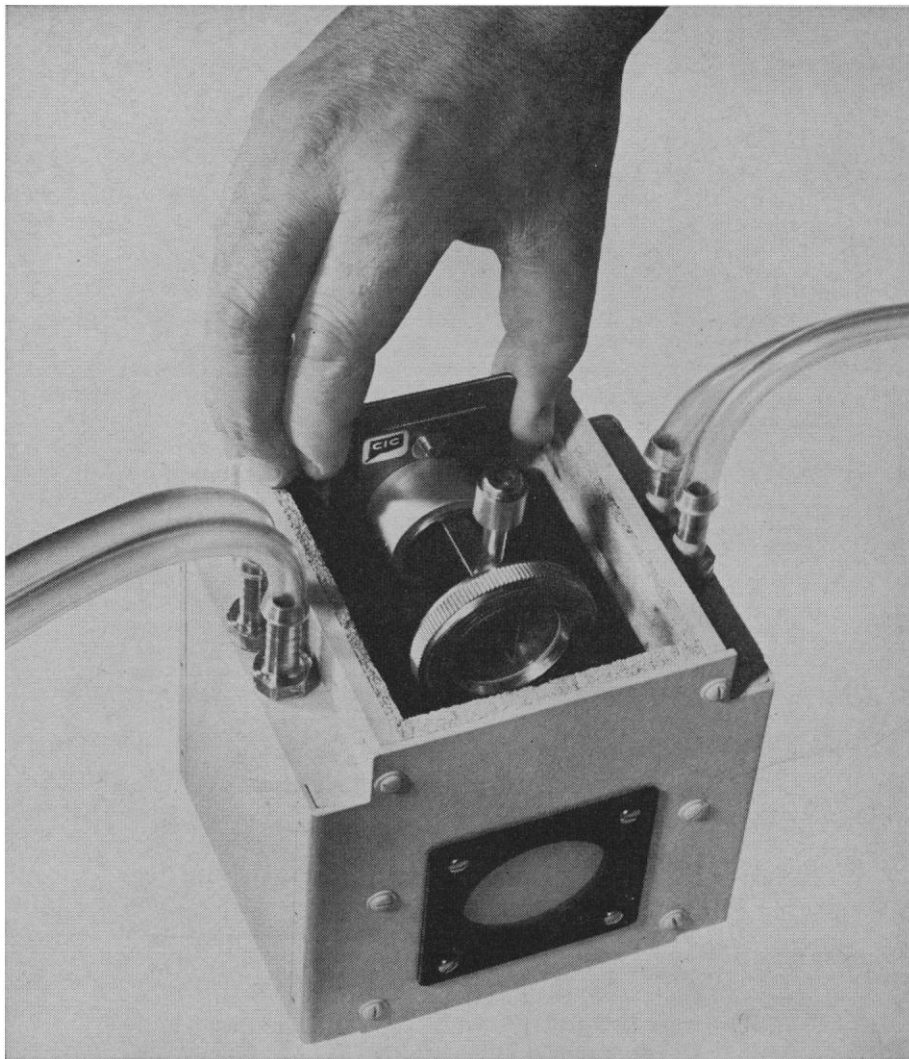
The second problem relates to the time required to accumulate the antibody from 100 ml of plasma in the tissue of the test site. If we accept the estimate that 3 to 30 ml of blood per hour pass through the capillaries of 1.0 g of skin, an additional problem remains. While small inorganic molecules in the plasma equilibrate with the extravascular fluid on one to two passages through the capillaries (in approximately 1 minute), large molecules such as those of gamma globulin take many hours or require several hundred passages through the body's capillaries. Therefore, one cannot assume that the passage of 100 ml of blood through the test site is equivalent to the removal of the antibody in it unless the capillary walls are coated with a high concentration of antigen. But the delayed reaction appears to be extravascular; in the cornea it clearly is.

We wonder if the tempo and histology of the delayed reaction could not be explained more simply by the assumption that antibody-producing cells accumulate at the test site. To use Karush's and Eisen's reasoning to explain under what circumstance a homograph might be destroyed within a Millipore chamber, "if the chamber [capillary] walls are sufficiently porous to permit host cells to enter, . . . antibody production and secretion will occur directly within the chamber [tissue] and will lead, very probably, to a concentration of free antibody sufficiently high to allow complexes with 'target'-cell antigens to form, with resultant destruction of the homograft [formation of an inflammatory reaction]."

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