for at least a week. If discrimination thresholds for each nerve remained constant throughout, the animals were again anesthetized and recordings were taken from the exposed peripheral nerve bundles conveying the sensory volleys. This control procedure allowed evaluation of the types of fibers activated with the various stimulus intensities used during the bar-pressing trials. Compound action potentials were recorded from the cut posterior division of the brachial plexus (for superficial and deep radial nerve volleys) with stimulus intensities identical to those utilized during testing procedures. Afferent volleys from the hamstring nerve were obtained from cut dorsal root bundles at the level of L_7. The threshold of nerve activation was taken as the stimulus intensity needed to produce a just noticeable deflection in the oscilloscope tracings. Stimulus intensities were then also plotted as multiples of the threshold intensity for the conducted action potentials. Figure 1*A* illustrates increase in amplitude, expressed as the percentage of maximum, of the low threshold afferent groups in superficial radial, deep radial, and hamstring nerve compound action potentials with graded stimulus intensities relative to the nerve threshold. Irrespective of nerve type, all attained maximum between 2.3*T* and 2.7*T* (where *T* is the multiple of the nerve threshold).

Figure 1*B* illustrates the number of correct responses expressed as a percentage of the total number of trials at different stimulus intensities. Except for cat 3, which made errors 31 percent of the time, all animals pressed the bar with essentially no errors. The animals commenced bar-pressing with cutaneous volleys at stimulus intensities slightly below 1.00*T*. A few nerve fibers were activated below observable nerve thresholds but because of the noise inherent in the recording system they could not be detected. Between 1.00*T* and 1.20*T*, cutaneous volleys induced correct responses in 100 percent of the trials. In contrast to this no significant responses occurred with deep radial volleys until stimulus intensities exceeded 1.8*T*. Above a critical intensity muscle afferent stimuli evoked correct responses in all trials, as with cutaneous stimuli, but the slope of the response curves for muscular volleys was less steep than that observed for cutaneous effects; this presumably is related to gradual inclusion of joint afferents in the deep radial sensory volleys which are known to reach thalamic levels (*6*).

An even greater divergence from the cutaneous response patterns was observed with hamstring volleys. The response curve for cutaneous volleys for cat 6 (not shown) was almost identical to that of cat 1, but, with hamstring volleys, essentially devoid of joint afferent discharges, and with a full complement of groups I and II stretch receptor afferents, the same cat failed to make any discrimination below 3.81*T*. Considering the exquisite sensitivity of cutaneous volleys in promoting active discrimination in all animals studied, it is all the more remarkable that comparatively strong muscular nerve stimulation always failed to produce a response in the same animals unless a sharply defined limit was passed.

Figure 2 illustrates monophasic recordings of a graded series of compound action potentials from cats 3 and 6. All conducted volleys placed above the horizontal line failed to evoke discrimination whereas all examples below the line initiated bar-pressing within 15 seconds.

It may be concluded from Figs. 1 and 2 that activation of only a very small number of cutaneous fibers is sufficient to elicit nonpainful sensations. Essentially the same findings have been recorded in humans (*7*). Group I volleys in the deep radial nerve, however, may attain 75 to 95 percent of maximum before any discrimination of the volley is evident. Results from the hamstring nerve in Fig. 2 show that 100 percent activation of group I components and extensive activation of group II occurred before discrimination thresholds were attained. This allows a more definitive interpretation concerning the central projections of the stretch receptor sensory fibers. Since secondary sensory fibers from muscle spindles become activated between 1.7*T* and 1.8*T* and are extensively activated at or above 3.5*T* (*3*, *5*), it seems likely that all myelinated sensory fibers originating from muscle stretch receptors in the mammal, whether in group I or II fiber spectrums, do not influence those rostral elements of the brain involved in conscious perception. It furthermore substantiates the hypothesis that afferent nerves from muscle stretch receptors play no direct role in kinesthesis.

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Immunocompetent Cells: Committedness

The ability of peritoneal exudate cells from previously immunized mice to give a logarithmic antibody response in x-irradiated isogenic recipients without further antigenic stimulus (*1*) is remarkable for several reasons. This kind of nonspecific anamnestic response has been looked for by several investigators without success, and in general no important qualitative difference has been found between peritoneal exudate cells and lymph node or spleen cells. Several years ago I was attempting to induce a nonspecific anamnestic response in rabbits previously immunized with bovine serum albumin (BSA). When the animals were "nonspecifically" stimulated with aggregated rabbit γ-globulin (RGG), their level of serum antibody rose threefold within a few days. I was on the point of reporting a brilliant success when in a moment of caution it occurred to me that a truly nonspecific stimulus should give a proportionate rise in all types of γ-globulin. A test of serum γ-globulins showed no detectable rise during this period, and subsequently the RGG preparation was found to be contaminated with BSA (*2*).

In Weiler's experiments the number of cells transferred (10 to 40 $\times$ 10^6) is equivalent to at least 1 percent of

the total lymphoid tissue of a 20-g mouse. A 10,000-fold rise in specific antibody if nonspecifically induced should have been accompanied by a considerable increase in total γ-globulins. I have two questions concerning his experiments: (i) Was a rise in the recipient's total γ-globulin observed? (ii) Has the same kind of nonspecific anamnestic response been obtained with peritoneal exudate cells obtained from mice which have been immunized without placing antigen in Freund's adjuvant within the peritoneum? If the answer to both questions is negative, then isn't it possible that the logarithmic antibody response was induced specifically by small quantities of antigen released from adjuvant depots in the peritoneum during the process of washing the peritoneum?

With respect to Weiler's interpretation, few immunologists today would quarrel with the concept of a determined or committed cell, the latter term having been used by Good (*3*). Szilard (*4*) postulated a "locked" cell; and a precommitted cell is a basic assumption of the clonal selection theory. An important question, which Weiler does not discuss, is whether there is any evidence for an uncommitted immunocompetent cell. Such a cell, if it exists, probably arises in the thymus, and thymectomy should cut off the supply of new cells. If the competent cells already present in extra thymic tissue can become committed by contact with any antigen, then response of the thymectomized adult to a new antigen should gradually fall off. This has not been observed, and for this reason I doubt the existence of an uncommitted immunocompetent cell.

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Talmage has classified the delayed antibody formation after transfer of immune peritoneal fluid cells together with the anamnestic response. But the two phenomena differ from each other in certain basic aspects. In my experiments the peritoneal fluid cells are harvested from an animal that has previously received intensive, repeated stimulation by antigen and adjuvant. At the time of harvest it is in a state of near-maximum antibody production, and its lymph nodes and the granulomatous tissue lining the peritoneal cavity are full of plasma cells. Such an animal contains in a certain anatomically defined location the ascitic fluid, a population of cells not engaged in antibody synthesis; an unknown number of cells in this population have the capacity to commence antibody production without further exposure to antigen, after they have been transferred to a host animal, and after a lag of a few days (*1*). The relation between this phenomenon and the anamnestic response as it is commonly understood (that is, the rate increase of antibody production after administration of a secondary antigen to an animal) remains to be investigated. To apply the same notions and criteria to such different phenomena is therefore not justified at the present time.

Cell transfer in the peritoneal fluid cell system obviously may be understood as a stimulus. But whether the stimulus is specific or nonspecific is an open question. It may be specific, yet not involve renewed exposure to antigen: antibody formation in the host could conceivably be due to the release of determined cells from an immunologically specific repression by the large amounts of antibody present in the donor. The suppressive effect of passively administered antibody on antibody synthesis (*2*) indicates that such a mechanism might very well exist. But by specific stimulus Talmage means with antigen, and by nonspecific stimulus, without antigen. He proposes, as a criterion to distinguish between the two possibilities, that a nonspecific stimulus for antibody synthesis would also have to lead to a proportionate increase in total γ-globulins. This view is based on two unproven assumptions: (i) That the peritoneal fluid cell population is a representative sample of the whole lymphoid system. On the contrary, it is an anatomically defined compartment within the mouse, developed under the influence of a locally administered antigen. (ii) That a nonspecific stimulus which accelerates antibody production after previous administration of antigen must necessarily also stimulate all globulin production in a given cell population. This would be predicted by the hypothesis (*3*) that all γ-globulin consists of antibodies of varying specificities, produced by cells which may never have met an antigen, and that the only function of an antigen is to stimulate the proliferation of cells with the corresponding specificity, without changing their character. But as yet this is pure speculation. While the question of total γ-globulin synthesis in this system is an interesting one, it is not illuminating for the results under discussion.

The point of the experiments I reported is that an immunologically nonspecific agent, actinomycin D, affects the cellular capacity to produce antibody differently, depending on whether in the experiment the encounter with antigen happens before or after the actinomycin treatment. Thus it distinguishes between the antigen-initiated ("determined") and the noninitiated ("competent") state in a cell population. With this in mind, it is really irrelevant whether or not a trace of the earlier antigen in a hidden form is carried along with the cells. The presence of antigen cannot be excluded directly, but it is made unlikely by the washing procedure for cells, consisting of three centrifugations into a sucrose layer, and by the finding that antigen in a quantity sufficient to immunize a competent mouse is just not found. The peritoneal cavity was, however, not washed, as Talmage infers.

I used the term "competent cells" at its face value: cells able to respond, by antibody production, to the encounter with a new antigen, without prejudice as to whether such cells are already specifically committed before they meet the antigen in the experiment or not. The experiment simply declares that the cellular state called "competent" differs from that called "determined" with respect to actinomycin sensitivity. One may still postulate that competent cells are always precommitted, but then the differential actinomycin effect would mean that there exist two different states of cellular committedness: competence and determination. The fact that the word "committed" is currently used in varying experimental or speculative contexts led me to adopt the term "determined," in its embryological sense, to describe the particular phenomenon observed in these experiments.

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