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M E D A W A R : In opening the discussion of Burnet's characteristically fascinating paper, I shall say nothing about his avowedly speculative references to the possible role of somatic mutation in ageing or in the inception of tumours. As Burnet implies, it is antibody-formation that is likely to be the testing ground for theories of somatic mutation, so what I should like to do is simply to explain (as I see it) the train of thought which has led to the formulation of the theory of somatic mutation in this particular context. My indebtedness to Lederberg and Monod will become very clear in the course of the argument.

Consider a cell which, as a result of some stimulus impinging upon it from the outside, has come to indulge in some new synthetic activity. The relation between stimulus and response may be of several different kinds. When a cell is infected with virus (or, better, as Schramm has just explained, with virus RNA), or when a pneumococcus is "infected" with exogenous DNA, the stimulant itself provides the exact instructions in accordance with which the cell carries out its new synthetic activity. The relationship between stimulus and response may therefore, following Lederberg, be described as "instructive". That is one possible kind of relationship. But when the stimulus is an enzymic substrate and the responding cell, a bacterium, comes to manufacture a so-called "adaptive enzyme"; or when the stimulus is an embryonic inducer and, as a result of its action, a hitherto uncommitted host cell follows one pathway of differentiation rather than another; —— in such cases as these it is most unlikely that the relationship between stimulus and response is instructive. All that the stimulus seems to do is to call forth or bring out a potentiality latent in the responding cell. Lederberg describes such a stimulus as "elective"; Waddington has used the term "evocative" in essentially the same sense.

How are we to classify the relationship between stimulus and response when the stimulant is an antigen and the new synthetic activity is the manufacture of a specific antibody? Is it instructive or elective? Pauling at one time suggested that gamma globulin acquired its specific complementary pattern under the direct impress of antigen, and this would be classified as an instructive theory of antibody formation. But modern opinion is hardening

in favour of an elective theory, and if the history of the theory of adaptive enzyme formation in bacteria is anything to go by, we should be very rash to dismiss it.

But now the problem arises: can a single vertebrate lymphoid cell contain enough genetic information to underwrite the formation of any one of the almost prodigious variety of antibodies which we know a vertebrate animal can produce? My feeling still is that the answer is Yes; the zygote, after all, presumably contains within itself the far greater store of genetic information that is needed to subsidize the development of an adult organism of multitudinous complexity——not forgetting all that is entailed by the inheritance of differences of behavioural pattern. But Burnet, Lederberg and Monod (who discussed the problem at a very recent meeting organized by the Ciba Foundation in Paris) are inclined to think that the answer is No. If the true answer is No, and if antibody formation is indeed an elective process, then we must suppose that new genetic information arises within the lineage of cells that descends from the zygote. But this is equivalent to adopting a somatic mutation theory, for mutation is by definition the process by which new genetic information arises. Burnet sees no reason at present to regard these mutations as other than genic, and he suggests that the body contains genetically distinct clones of lymphoid cells each with a single and distinct immunological capability. It was this particular variant of the somatic mutation or clonal theory that led to Lederberg and Nossal's test of the "one cell:one antigen: one antibody" hypothesis. But, as Monod has pointed out, this is by no means the only possible form of the somatic mutation theory. The mutations might be "ribosomal": we are not obliged to believe in a one cell-one antibody relationship: all we are obliged to believe in is that the genetic information integrated over the lymphoid population of the body as a whole is greater than that which was originally present in the zygote. This does not logically entail a one cell-one antibody relationship

The point I am trying to make is that the key to the argument is whether or not we suppose that one lymphoid cell can contain enough information to underwrite the entire repertoire of antibody formation. If the answer is yes, the somatic mutation theory is supererogatory; if it is no, then the acceptance of a somatic mutation theory in one form or another, not necessarily Burnet's, is logically entailed.