Antibody Induction and Tolerance

"Antibody viruses" may mediate the primary response and transform cells to give the secondary response.

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Discrete genetic loci, believed to have evolved by gene duplication, control the synthesis of related but not identical polypeptide chains in the hemoglobins (*1*). Partial gene duplication has been suggested as the mechanism for the evolution of the Hp^2 allele in the haptoglobin system (*2*, *3*). Intergenic crossing-over between regions of homology in such related genes has been established in both the haptoglobin (*3*, *4*) and hemoglobin (*5*) systems. I have suggested (*6*) that comparable intragenic crossing-over may occur somatically in the genes controlling antibody structure and that the resulting chromosomal rearrangements could account for variations in the structure of the polypeptides of different antibodies. At that time I made no reference to any selective (*7*) or instructive (*8*) mechanisms for the induction of antibody responses since the control of antibody structures did not appear to be necessarily coupled with either mechanism for antibody induction. I now propose a hypothesis for antibody induction and the control of tolerance which suggests that both selective and instructive stages may participate in the overall process.

In developing the hypothesis I have necessarily considered principles and ideas discussed by other writers. Particularly I draw attention to a discussion by Burnet (*9*) and a paper by Jerne *et al.* (*10*) which raise considerable doubt that a simple process of clonal selection and subsequent cell division can account for the rapidity of the primary response and the large proportion of cells responding to a given antigen. Jerne *et al.* offer several interpretations of their own data, including the ideas that "cells initially stimulated release a self-replicating RNA which infects a number of cells of the plasma cell series" or "that an episomal gene coding for antibody structure replicates in initially stimulated cells and is capable of transforming other cells." Burnet, in discussing the persistence of a committed and stabilized line of immunologically competent cells as a prerequisite of immunologic memory, briefly suggests as one interpretation "that in addition to producing stem cell descendants, the line must also give rise to cells able to transfer their genetic information to suitable nurse or mother cells which are the actual producers of antibody." Of importance in the development of my hypothesis are the experiments of Fishman and others (*11*, *12*) indicating that RNA produced by macrophages (or other cells) stimulated by antigen may initiate the production of antibody by unstimulated cells. Although the hypothesis has much in common with suggestions for the mechanism of antibody production proposed by these workers, it will be stated in full since it goes considerably further and apparently accounts for most of the general phenomena of the immune response without violation of established principles of genetics and molecular biology, and also because tests of the hypothesis will require many new types of experiments.

Outline of the Hypothesis

1) Variability in the structure of antibodies arises by rearrangements in the nucleic acids corresponding to the genes controlling the polypeptides of the immunoglobulins formed in the primary response to antigen.

2) These rearranged nucleic acids govern the synthesis of many forms of "antibody viruses" which are passed out of the cells where the rearrangements arise. An antibody virus is postulated to contain nucleic acid with information for antibody of a specific structure. At least part of the "coat protein" of a given antibody virus is made up of the polypeptides of the particular antibody corresponding to its own nucleic acid. The antigen-combining specificity of the antibody part of the viral coat is the same as when the antibody is free.

3) Tolerance is established by the elimination of those antibody viruses encountering an antigen which can combine with their coat-protein antibody in an environment in which viral replication cannot be initiated.

4) Antibody viruses escaping destruction are transferred to cells taking part in the primary immune response.

5) Primary exposure of the intracellular viruses to an antigen results in the proliferation of those viruses which react with the antigen (selective phase of the process). Excess production of the antibody component of the coat protein is initiated. The process is self-limiting in the absence of continuous administration of the antigen.

6) Transformation of the cells in which the virus is replicating can occur, mediated by virus-derived nucleic acid (instructive phase of the process).

7) The transformed cells divide and can mediate the anamnestic response after reexposure to the relevant antigen.

Generation of Antibody Variability

There is considerable evidence that the primary response to an antigen is the synthesis of 19*S* macroglobulin, γM-globulin (*13*, *14*). This macroglobulin consists of two types of polypeptide chain: a light chain (L_M), which may be common to antibodies of all classes, and a heavy chain (H_M), characteristic of macroglobulin antibody (*15*). Evidence has already been presented (*6*) that somatic chromosomal rearrangements, made possible by the nature of the genes controlling antibody structure, could account for the different structures of the light chains in different antibodies and Bence-Jones proteins, and that the heavy chains might vary in the same way. The recent demonstration of

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completely analogous differences in the tryptic peptides of Bence-Jones proteins obtained from individual mice of an inbred strain (*16*) suggests that this variation is indeed of somatic origin, and not the consequence of genetic variability in different animals. My hypothesis is in part based on the assumption that variations in antibody structure are the consequence of somatic rearrangements in the nucleic acids corresponding to the genes controlling the L_M- and H_M-polypeptide chains. Most probably, for the reasons given previously, this rearrangement would be by a process analogous to crossing-over. However, the rearrangements could arise in an unprecedented way in, for example, episomal DNA or RNA.

The location and type of cells participating in the rearrangements cannot be stated definitely at present. However, many observations become understandable if the nucleic acid rearrangements arise whenever there are cells dividing in the thymus, that is, to a large extent but by no means exclusively during fetal life. If, for any reason, the organism must repopulate its immune system from residual or donated thymus cells, then these rearrangements arise again. Although a molecular basis permitting the rearrangements can be suggested, I can find no evidence indicating any molecular basis for confirming their occurrence to the thymus. Nevertheless, the situation is not without parallel in other systems. Rhoades (*17*) working with maize has shown that the dominant gene *Dt* can greatly increase the rate of somatic mutation of the ordinarily very stable allele a_1 at a different locus. The effect is most marked in the aleurone and is chiefly manifested toward the end of its development. The mutation rate of the allele a^m-*1* is also increased by *Dt* (*18*) and the mutants may be any of a variety of different dominant and recessive genes. Interestingly, the a_1 and a^m-*1* alleles occur at a locus which is known from other data to take part in intrachromosomal crossing-over as a result of a duplicated region (*19*). Thus the postulation of a complex locus containing (inverted) duplications able both to undergo intrachromosomal rearrangements and to show somatic variability under the control of a different locus has a precedent in another system.

The two genes controlling the L_M and H_M chains are assumed to be linked, for reasons concerned with tolerance and the probable participation of both light and heavy chains in determining the combining sites of antibodies. The rearrangements leading to the variability of one of the two genes consequently may be related to the rearrangements in the other. These rearrangements will give rise to many different populations of cells. For descriptive purposes, a particular rearrangement will be referred to as $L_M{}^pH_M{}^q$, indicating a chromosome specifying the *p*th form of the L_M-chain gene and the *q*th form of the H_M gene. (Other chromosomes might be $L_M{}^dH_M{}^t$ and so forth.)

Transmission of Variability

"Antibody viruses" are proposed as the means whereby this variability in antibody structural genes is transmitted from the cells in which the rearrangements arise to the cells mediating the primary response. A given antibody virus is assumed (i) to contain nucleic acid corresponding to one particular rearrangement ($L_M{}^p$ and $H_M{}^q$) of the L_M and H_M genes, (ii) to be capable of initiating its own replication in a suitable environment, and (iii) to have a coat protein comprised at least in part of the polypeptides $L_M{}^p$ and $H_M{}^q$. When these polypeptides are in the virus coat protein the configuration of their variable parts is assumed to be the same as when they are in the form of free γM-globulin.

The production of antibody viruses is initially induced during development, perhaps by a process analogous to lysogeny with temperate bacteriophages. The antibody viruses may, however, contain RNA, because the primary response appears to be insensitive to inhibitors of cell division and DNA replication, including colchicine and 5-fluorodeoxyuridine (*20*). Consequently a more comparable situation may be the case of the extensively subcultured XC line of rat tumor cells, originally induced by the RNA-containing Rous sarcoma virus. The XC cells contain no detectable virus, yet even after treatment with x-rays, they induce the production of the virus when injected into chickens (*21*).

The antibody-virus nucleic acid is assumed to be a single molecule corresponding to both the L_M and H_M genes and possibly also to genes specifying other proteins such as a nucleic acid replicase. There will be as many forms of the antibody viruses as there are combinations of the variable L_M- and H_M-chain genes. The nonvariable portions of the genes specify properties common to all γM-globulins.

The antibody viruses are liberated from the cells where they are formed into the extracellular spaces, and any that are not destroyed will eventually find their way to effector cells of the immune system. A macrophage intermediary could mediate the transfer. No a priori limit can be set to the number of different viruses finally transferred to any one cell, but the number is probably greater than one. It should be stressed that these antibody viruses are assumed to be the effective source of all the variations in antibody-combining site specificity eventually available to the mature animal. Their chief origin in mammals may be the thymus. However, this does not exclude the possibility that some cells leave the thymus to divide elsewhere and produce antibody viruses in new locations. Nor can the formation of antibody viruses by other types of cells be excluded. The initial formation of the antibody viruses and the generation of variability in their nucleic acids have been treated as separate events in this account, but they may be interrelated.

There is considerable experimental evidence that the thymus is responsible not only for the embryological formation of the cellular elements of the immune system (*22*) but also for the achievement of immunological competence by these cells at a subsequent stage of development (*23*). A humoral factor as mediator of the second of these functions has been proposed as a result of experiments on thymectomized animals with implanted thymus cells inside Millipore chambers. The usual pore size of these chambers (300 mμ) could permit the passage of viruses. I suggest that the humoral factor may be antibody viruses formed in thymic cells. Unfortunately, from the point of view of setting up a critical test of the hypothesis, the humoral factor may be responsible for inducing antibody-virus production by other cells. However, many experiments, such as attempts at isolation, proof of exclusion by ultrafine membranes, transfer tests, and others, could be designed to investigate the possible viral nature of the humoral factor. De Harven (*24*) has published

electronmicrographs of typical virus particles (of the membrane type) associated with thymic lymphocytes or with thymic epithelial cells from mice of several strains, including Swiss, C_3H, and AKR, which were reared either in the conventional way or under germ-free conditions. The diameter of these particles, when intracytoplasmic, averaged approximately 70 $m\mu$. They were never seen inside the nucleus or outside the cells, but one photograph shows a viral bud protruding from a thymic lymphocyte toward the extracellular space. De Harven had no evidence related to any pathological consequences of the viruses. He considered the possibility that the particles might be conventional viruses which have a long latent period and are present even in germ-free animals as a result of vertical transmission. He compared them to the leukemia viruses and also considered the possibility that they are responsible for the lymphocytosis-stimulating action of cell-free extracts of the thymus. Conceivably De Harven's viruses are thymic antibody viruses.

Establishment of Tolerance

The first known step in the process of infection by a simple RNA virus (such as poliovirus) is the irreversible attachment of the virus to trypsin-sensitive receptor sites on the cell surface (*25*). Failure to attach irreversibly leads to lack of infection. The attachment causes configurational changes in the virus coat protein and renders it susceptible to proteases against which it was previously extremely resistant; the viral RNA becomes ribonuclease-sensitive after proteolytic digestion of the coat protein. The more complex membrane viruses may exhibit similar phenomena (*26*). By analogy, I suggest that any antibody virus encountering an "antigen" with which its coat protein can combine will be rendered protease-sensitive as a result of configurational changes brought about by the combination. This in turn will render the nucleic acid sensitive to nucleases. Thus when an antibody virus encounters an antigen with which it can combine, in an environment in which protein synthesis and viral replication cannot occur, then the virus and its information will be destroyed. These events could lead to the removal of those viruses which specify (autoimmune) antibodies against self-antigens and ensure tolerance. However, tolerance will be established only for accessible antigens, such as intracellular antigens of the cells in which the viruses are formed, circulating antigens, tissue-bound antigens in contact with the circulation, and so forth. The establishment of tolerance must be (in the theory) a process continuing for as long as the variable forms of antibody virus are being produced by the organism. If this production is neither initiated nor terminated abruptly, many puzzling observations become understandable. For example, cow red cells, given in large amounts within hours of birth and at intervals thereafter, in mice and rats do not lead to tolerance (*27*) as judged by antibody-producing cells in the spleen (although circulating antibody may be virtually undetectable because of antigen excess). Also antibodies have been detected in adult humans against the Gm factors (hereditary antigenic differences) of the γG-globulin of their mothers, even though the persons with antibodies received the γG-globulin only *in utero* by placental transfer from their mothers' serum (*28*). The observations on rats and mice are understandable if some antibody viruses are already incorporated into effector cells *before* birth. The observation in humans is accounted for if new antibody viruses are still being formed at the time the circulating maternal γG-globulin has fallen below the amount necessary to destroy all the corresponding viruses. Those antibody viruses escaping destruction could then initiate an immune response against the residual traces of maternal γG-globulin.

The experimental production of "runts" requires special comment. In mice, for example, runts frequently occur as a consequence of neonatal thymectomy, but not when the animals are raised in a germ-free environment (*29*). This type of runt disease thus appears to be due to some failure of antibody production against ubiquitous microbial agents. However, although the production of runts by neonatal thymectomy can be prevented by thymus cells from the same or a different strain of the same species, and by spleen cells from the same strain, it is not prevented by the thymus of a different species (*30*) or spleen cells from a different strain. Furthermore, runt disease was originally obtained (*31*) in the absence of thymectomy by injecting newborn mice with immunologically competent cells of some other strains of mice (the graft-versus-host reaction). These observations all appear explicable in terms of my hypothesis in that most, if not all, of the antibody viruses of a given animal species are likely to be destroyed by any antibodies directed against antigenic determinants in the unvarying species-specific parts of the antibody-virus protein coat. Even a small number of immunologically competent cells present in either the donor or the host could be effective in making antibodies against all the viruses of a second species, or a sufficiently divergent strain of the first.

If the establishment of tolerance occurs in the way suggested here, then there must be time and opportunity (between the liberation of the antibody viruses and their incorporation into effector cells) to permit any autoimmune viruses to be destroyed.

Mode of Antibody-Virus Transfer

Transfer of antibody viruses to cells mediating the primary response could occur directly, or indirectly by way of an intermediate cell. No experiments permitting a decision between these alternatives appear to have been made. However, there is considerable evidence (*32*) that macrophages and histiocytes form cytoplasmic connections with other cells of the immune system, so that mechanisms exist for intercellular transfer.

Nature of Primary Response

The primary response is assumed to be the consequence of interactions between intracellular antibody viruses and antigens which cause sufficient configurational changes in the virus coat protein to permit the nucleic acid to be released in a suitable environment for protein synthesis to be initiated. Whether all stages of the process resulting in the formation of primary-response antibody occur in the antibody-producing cell directly or whether the released virus nucleic acid has to be passed from, for example, a macrophage to the cell in which it can direct antibody synthesis cannot be decided on a priori grounds. The experiments of Fishman (*11*) suggest that RNA from macrophages exposed to anti-

gens can induce antibody formation, but the experiments do not exclude the presence in other cells of nucleic acid with information for antibody structure. Nor can the possibility be excluded that the antigen may require degradation at some stage during the stimulation of antibody production; rather, it appears frequently necessary to assume the reverse (*33*). Haptens may fail to induce antibody formation because their combination with corresponding antibody viruses does not cause sufficient configurational change in the virus coat protein to permit the release of the virus nucleic acid. However, once the virus nucleic acid is present in a protein-synthesizing cell and released from its protecting coat or coats, the sequence of events for virus replication should be initiated. It has been shown that virus nucleic acid, once inside a cell, can mediate replication of viruses normally unable to infect the same cells (*34*). Failure of simple viruses to infect appears frequently to be a function of the nature of the virus coat, or lack of receptors which can interact with the virus coat, or both, rather than a property of the nucleic acid (*25*).

Whether DNA or RNA, single- or double-stranded, is the nucleic acid in the antibody viruses must await direct experiments. The insensitivity of the primary response to inhibitors of DNA synthesis (*20*) suggests that RNA is more likely. On the other hand, actinomycin D, an inhibitor of DNA-instructed RNA synthesis, may abolish the primary response, although reports on this are conflicting (*10*, *35*). Unfortunately, such experiments are inconclusive when inhibition is observed; thus, if the primary response requires as a prerequisite the continued RNA-synthesizing functions of any part of the DNA of the cell (such as the genes for ribosomal RNA), the primary response would be sensitive to the antibiotic even if the antibody virus contained RNA.

Once the antibody-virus nucleic acid becomes functional it is presumed to serve directly or indirectly as a source of messenger RNA both for initiating the replication of the virus and for the synthesis of its specific coat-protein antibody. Many viruses induce production of their coat proteins in excess of that required to encapsulate their nucleic acid (*36*). Such an excess of the antibody component of coat protein (in the form of γM-globulin) is assumed to be the primary response antibody. Whether the replication of the antibody virus and the production of the primary-response antibody always occur in the same cell cannot be stated on the basis of available evidence. The specificity of the antibody-combining site, which is probably a function of both the L- and the H-chains, must however be the same whether the chains are in the form of viral coat protein or circulating antibody, as stated above. The production of the γM-globulin is likely to be self-limiting in the absence of continued antigen administration. Antibody-producing cells may eventually be killed or functionally exhausted by excessive virus-directed activities, or the nucleic acid of the virus may eventually all be trapped in the form of complete virus, or both. Since effector cells mediating the primary response may contain viruses specifying more than one antibody or be capable of responding to any type of virus nucleic acid transferred to them from other cells, they could be multipotent in their ability to respond to antigens.

The increase in number of antibody-producing cells during a primary response might be due to the transfer of newly replicated viruses to effector cells previously lacking viruses of the relevant specificity or to division of cells in which the viruses are replicating, or both. The hypothesis does not exclude either possibility, although it clearly requires that the information for the structure of primary-response antibodies be in the virus nucleic acid rather than in the genome of the effector cells. Once the cycle of events involved in the primary response is completed, the debris of any killed cells, or self-limited cells which eventually die, will be taken up by macrophages (*37*). Any viruses contained in these cells would thus be available for later responses. These several processes could ensure the return to the immune system of at least as many specific antibody viruses as were present initially. As a result immunological competence, once established by the antibody viruses, would be perpetuated by recirculation of the viruses without their continued production by the cells in which they initially arose.

The number of antibody viruses replicated after a primary administration of antigen is likely to be dose-dependent. A very low dose might leave the *status quo* unchanged so that repetition of the dose would give an essentially invariant response. A higher dose might restore more than were initially present.

Acquisition of Immunological Memory

Many experiments require a distinction between the primary response, which may be transient, and the anamnestic secondary response, which may persist for many years and frequently involves a different class of antibody (including γG-globulin, γA-globulin, tissue-bound antibody, and others). The clonal hypothesis provides an explanation of immunological memory, namely, that multiplication of cells with a suitable and fixed genetic endowment can lead to the development of an anamnestic response, but it fails to account for the many qualitative differences between the two responses. Multiplication of antibody viruses could account for some immunological memory as being a consequence of an increase in the number of antibody viruses after a primary stimulus; however, an anamnestic response of this type would consist of antibody of the same class as that of the primary response (γM-globulin). Therefore the mechanism of an anamnestic response which leads to the production of other classes of antibody must be different.

The phenomena of bacterial virus transduction and virus-induced cell transformations demonstrate that many viruses can alter the genome of a host cell permanently so that the cell can transmit the change to its progeny. Particularly relevant in the present instance is the recent work with Rous sarcoma virus which indicates that an RNA virus can induce a cell transformation which appears to be DNA mediated (*38*). I postulate, accordingly, that the acquisition of immunological memory leading to the production of a different class of antibody from the primary-response antibody is due to the insertion of some of the nucleic acid of a replicating antibody virus into the genome of the cell in which the antibody virus is being replicated. The net result of the process is the viral transduction (carrying across) of information from the genome of the cell in which the virus was first formed to the genome of the second-

ary-response cell. For this to occur, sufficient antigen must have been administered to ensure enough free nucleic acid to mediate the transduction. If the replicating form of the nucleic acid is DNA, this process has enough parallels from bacterial genetics; if the nucleic acid is RNA, it becomes necessary to suppose that this RNA, or its double-stranded replicating form, can act as a transducing or transforming agent. Observations (*39*) that double-stranded RNA can be copied into DNA by DNA-polymerase suggest that this is not unreasonable.

In many bacterial virus systems transduction is not random, but directs the insertion of the transduced nucleic acid into specific regions of the genome. This appears to be the consequence of homologies between the nucleic acids of the receptor region and the transducing bacteriophage (*40*). Examples of multiple loci in mammals that have a large degree of homology are well known in the case of the hemoglobin loci (*1*). It is thus reasonable to suggest that the receptor sites for the antibody-virus transduction are regions (duplications) of nucleic acid where there is homology between part of the viral nucleic acid and the receptor nucleic acid. In this way the transducing nucleic acid could insert genes carrying already selected antibody specificity into genetically determined regions of the receptor cell genome. This represents the instructive phase of the immune response. The observation of Nossal *et al.* (*14*) that single lymph-node cells may produce 19*S*, 19*S* and 7*S*, and 7*S* antibodies alone, at different stages of the response, are compatible with this mechanism. A continuing source of untransduced (uncommitted) cells may be necessary for the transduction to be possible, since, for comparison, many bacteria show resistance to a second temperate phage when already lysogenic for one of a closely related type (*41*).

Any discussion of the details of the transduction must be speculative at this time. However, in order to account for the retention of tolerance during the secondary response and for the concurrent divergence of classes of antibody, it is necessary to postulate that: (i) The transduction involves sufficient portions of both the L_M and H_M genes to ensure preservation of the specificity of the antibody-combining site. (ii) The receptor genes are incomplete before transduction and carry no information for the antigen-combining site, although they carry information for the nonvariable properties of their own class of antibody. For example, the *Gm* locus would be such a receptor locus, but could not instruct for the synthesis of γG-globulin until transduced by an antibody virus with information for a particular antibody specificity. Thus the $L_M{}^pH_M{}^q$ virus could transduce the *Gm* locus to give an antibody with the formal structure $L_G{}^pH_G{}^q$, where $L_G{}^p$ and $H_G{}^q$ represent γG-globulin light and heavy chains carrying variable portions corresponding to the $L_M{}^p$ and $H_M{}^q$ chains. (It should be noted that $L_G{}^p$ and $L_M{}^p$ may be identical, but that $H_G{}^q$ and $H_M{}^q$ differ.) This postulated process whereby two initially discrete genes (*A* and *B*) can give rise to a single hybrid gene (*A–B*) specifying a new type of polypeptide with sequences corresponding to parts of both the *A* and *B* genes has been discussed (*3*). (iii) There are several different receptor loci specifying the nonvariable parts of each class of anamnestic antibody (γG-globulin, γA-globulin, tissue-sensitizing antibodies, and others). The relative proportions of cells transduced at the different receptor loci might be controlled by the relative lengths of the nucleic acid at each receptor locus which is homologous with the nucleic acid of the transducing antibody virus (*42*).

Tests of the transduction stages of the hypothesis are apparent. For example, all secondary response antibodies of a given class should have amino acid sequences that are class-specific and nonvariable as part of their heavy chains. The variable portions of the light and heavy chains of anamnestic antibodies should be equivalent to the variable portions of the corresponding γM-globulin, since antibodies are assumed to have been already selected during the primary antibody response.

Secondary Response

What stimulates the transduced cells to divide, and the details of the process whereby the genomically determined secondary response is mediated, cannot be stated at this time. A "conventional" DNA to messenger-RNA process may be involved. On the other hand, the possibility should be considered that there is a secondary-response antibody virus which can be formed by instructions contained in the DNA of the transduced region of the cell genome. If such a secondary-response virus also contained information for an enzyme necessary for cell division (for example, thymidylate kinase), its activation by the antigen could initiate antibody production, virus multiplication, and cell division. This phase of the process should also be considered in relation to the observations that virus-transformed cells frequently divide rapidly (*43*) and incorporate into their cell surfaces protein coded by the nucleic acid of the virus (*44*).

Conclusion

In order to avoid stating my hypothesis in terms of experimentally untestable or poorly defined generalities, each phase of the process has been discussed in detail. Consequently the detailed statement is likely to be overly specific and subject to modification in the face of new evidence. However, the main points in the outline of the hypothesis are regarded as critical in the sense that evidence completely disproving any of them would require serious modification to the overall hypothesis, but would not necessarily discount all parts of it. Finally, if the controlled transfer of portions or the whole of genes from one locus to another can be proved to play a part in the differentiation of the immune system, then similar transfer should be considered in relation to other differentiation processes and the control of gene expression (*42*).

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Scientific Policy in Britain

The central issue is that of determining priorities in the light of available money and manpower.

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Before I attempt to discuss scientific policy in Britain, perhaps it would be helpful to consider first why countries need concern themselves at all with scientific policy. Why is it necessary to introduce this new kind of policy at all? To answer this question in full detail would require a treatment too elaborate for inclusion here, but the essentials of an answer can be given fairly easily. The past hundred years have certainly brought about a greater change in the material aspects of civilization than occurred in the whole previous history of mankind. Not only has the speed of change been staggering, viewed over this period as a whole, but the rate has been continuously accelerating, and at present there is no sign of a slackening. And all the changes that have occurred can be attributed to science and to the modern form of technology which is the application of the scientific method and the results of scientific research to the problems of industry, agriculture, medicine, defense, and administration. As a result, science and technology now permeate almost every aspect of public and private life and they have had a profound effect on our social systems, which have been slowly evolving over many centuries. The trouble is that, although science and technology advance very rapidly, social attitudes and social patterns are slow to change, and it is the disparity between the rate of change in science and that in social behavior in its broadest sense that lies at the root of most of the stresses and strains in the world today. It is this that has been responsible for devastating wars in this century and which has caused the appearance of all sorts of political systems—communism, capitalism, socialism, fascism, and all the rest. All these political and politico-social experiments can be regarded as attempts to come to grips with this disparity in rate of change.

If my thesis be correct, as I believe it to be, then it follows that a country's policy on both the national and international levels must be affected at almost every level by scientific and technical considerations. It is therefore necessary that the country should seek to develop a coherent scientific policy through which it can seek to ensure that its scientific and technological knowledge and potential are deployed to maximum advantage. This fact now seems to be slowly gaining general recognition, and in recent years the number of countries seeking to establish a basis for scientific policy has been rapidly increasing, although the methods which are employed vary somewhat according to political and ad-

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