The New England
Journal of Medicine

Volume 271 NOVEMBER 5, 1964 Number 19

ANNUAL DISCOURSE

THOUGHTS ON FUTURE CONTRIBUTIONS OF VIROLOGY TO MEDICINE*

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TO be chosen as its orator by this society confers upon any member a high distinction and at the same time imposes a heavy responsibility. For me, an associate member, the honor becomes overwhelming, and the task of offering a discourse that might be in general interesting to you as physicians appears highly formidable. I have therefore given much thought to the choice of subject. I first considered rather broad topics that might seem timely to anyone with a concern for the future of medicine, such as the present state of the marital relations between medicine and natural science. It occurred to me that in discussing this topic we might perhaps usefully inquire whether medicine has not lately allowed his faithful spouse, however helpful she has been in providing essential tools for his work, too much to say about what his children are to be taught during the years of their professional novitiate. Matters of yet wider scope came to mind, and I asked myself whether it would not be appropriate to touch upon problems presented by today's expanding population, problems that are becoming increasingly apparent and in the relatively near future may force profound changes in the ethics and practice of medicine as well as in many other basic features of our civilization.

Having for some time been carried aloft by visions of soaring themes like these, I was suddenly brought back to earth by the recollection of a scene from *Henry IV* that offers a potent antidote to the temptation of the elderly to be overwise. In this scene the fiery, verbose, old Glendower brags to young Hotspur of his power over his fellow men and even over the beings of the other world. Hotspur remains throughout the provocative and witty skeptic.

> I am not in the roll of common men [pompously declares Glendower and goes roaring on]
>
> Where is he living, clipped in with the sea
> That chides the banks of England, Scotland, Wales
> Which calls me pupil, or hath read to me?
> And bring him out that is but woman's son
> Can trace me in the tedious ways of Art
> And hold me pace in deep experiments.

While he stops to catch his breath Hotspur, to goad him further casually remarks:

> I think there's no man speaks better Welsh
> I'll to dinner.

Glendower thereupon puts forth his most impressive claim to superiority, his skill in magic, shouting, "I can call spirits from the vasty deep." Promptly and beautifully he is deflated as Hotspur coolly remarks:

> Why, so can I, or so can any man;
> But will they come when you do call for them?

When I remembered these words I too was deflated and decided not to attempt to call up a subject of too great breadth, lest to my Glendower you might play the Hotspur. I concluded that I should stick to my last and talk about viruses. However, because prophecy, taking off from facts, is more interesting at times than a mere exposition of the facts themselves and also because after the age of sixty the urge to foresee becomes increasingly irresistible, I shall consider my materials from the point of view of how they seem to suggest that the continuing study of viruses may contribute to a better understanding, and, so, to a more effective control not only of recognized viral diseases but possibly of other conditions in which the etiology now remains doubtful or entirely unknown.

Among several areas of animal virology that seem appropriate to a commentary of this sort, I have chosen two. The first includes the complex of phenomena that are responsible for resistance to viral infection. Of these some are well known whereas others remain for future investigation to define. Here, I shall merely offer a few remarks on how such investigation may open ways to improvement in prophylaxis.

The second area comprises the fascinating phenomena that result from the interaction of viruses

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 19, 1964.

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and cells under conditions such that the cells are not irreparably damaged but continue to survive and multiply. An association of this sort may be described for the sake of linguistic convenience as a temperate relation between cell and virus.

Temperate relations of this sort have long been known, but their intensive study has until recently been largely neglected by most investigators, although a few perspicacious souls interested in tumor-inducing viruses, such as Peyton Rous and Richard Shope in this country and Oberling in France, never lost sight of their significance. During the last decade, however, increasing numbers of workers have devoted themselves to analyses of the temperate relation, stimulated at first by the demonstrations by Gross and Stewart and Eddy that virus may cause leukemia as well as solid malignant tumors in mammals and later by the work of Vogt and Dulbecco, who showed that malignant changes appeared in isolated normal mammalian cells exposed to oncogenic viruses. Recent findings in this field that I shall later touch upon in more detail show that the temperate relation frequently results in alterations in the antigenicity of the cell. These findings appear to relate the two areas, viral resistance and the temperate relation, in what may prove to be a significant manner.

My introduction has now already exceeded all respectable limits. Yet for the sake of clarity I shall extend it just a trifle further to recapitulate what is now known about the fundamental properties of viruses. For without a few of these facts clearly in mind, although they are probably familiar to many of you, what I shall have to say might prove to be to some confusing, or meaningless, or frankly tiresome.

A virus, whether of plant, insect or animal origin, exists in one of two states — that is, in a complete or resting form or in a vegetative state. So far as one knows, the vegetative state, during which multiplication occurs, is assumed only within the confines of a living susceptible cell. When multiplication ceases the virus particles in their complete form emerge from the cell, to encounter first the often unfavorable environment of the host's extracellular fluids and then the hostile conditions of the external world. From one or the other of these situations the virus particles must somehow again meet and enter a susceptible cell, there to pass once more into the vegetative state. All complete viruses, so far as has been determined, consist of two essential components: protein and nucleic acid. Several species of protein may be present, but in every "true" virus so far examined the nucleic acid is either DNA or RNA. In this latter respect viruses appear to be fundamentally different from other biologic entities, in which both kinds of nucleic acid are found. In some species lipid and polysaccharide are found, but in others these compounds are absent.

The role of the viral protein appears to be basically prophylactic. Thus, in all cases, with possibly a single exception, the protein surrounds the nucleic acid and so serves to protect the nucleic acid from factors in the external environment that would inactivate or destroy it — for example, the DNAses or RNAses present in body fluids. The protein envelope may also facilitate penetration of the viral particle into the susceptible cell.

As for the nucleic acid moiety, it has been abundantly demonstrated, by a variety of experimental approaches beginning with the classic work of Hershey and Chase on the DNA of colon-bacillus bacteriophage, that the viral genetic apparatus resides exclusively in this component. For example, it has been shown that the nucleic acid when freed from other contaminating substances by chemical means and brought into contact with the susceptible cell under appropriate conditions enters the cell and there with the help of the cell's enzymatic equipment is capable of directing the synthesis not only of more of itself but of viral protein as well. In the usual course of events the nucleic acid and protein thus newly manufactured combine to form many units of complete virus. This process of viral synthesis taken as a whole may be regarded as representing the vegetative state of the virus.

As a result of formation of hundreds of new virus particles in this manner, the burden of foreign matter may become so heavy that the economy of the cell is disrupted, and it disintegrates, releasing a fresh crop of complete particles. Or these may be extruded individually at the cell surface, permitting the cell to survive for variable lengths of time. When a complete virus unit infects the cell the same events follow except that the nucleic acid is first divested of its protein covering, thus permitting it to assume its remarkable biochemical functions.

Under certain conditions, not as yet clearly defined but depending in part on the type and origin of the cell, the reproduction of complete virus units may not occur after infection although replication of the nucleic acid and sometimes even of the protein takes place. The cell then remains viable and when circumstances are favorable may undergo mitotic division. In this manner the genetic component or viral genome continues to be associated with each of the descendants of the original infected cells. In some cases in which infection may not be followed by cell death, as in infection of chicken cells with Rous sarcoma virus, virus units are completed, but the rate of their manufacture is so regulated that the number present at any time is insufficient to interfere with cell growth and division.

Both these situations, then, incomplete replication of viral subunits and suppression of the rate of synthesis of complete virus, may underlie the temperate cell-virus relation. It seems probable that in the future virology will contribute to medical prac-

tice largely through the exploitation and extension of this kind of fundamental information on the nature of viruses and their interactions with host cells.

Let us now venture to envision in a general way how such data may be applied in the solution of important problems that remain in the area of vaccination. The two types of vaccines now in general use — that is, inactivated vaccines of the Salk type and living, attenuated-virus vaccines — consist essentially of complete virus particles suspended in a complex and largely unknown mixture of cellular derivatives. The latter, of course, are derived from the tissue of the living animal or the cell cultures employed for the propagation of the virus. Although the incidence of known harmful effects, such as reactions of hypersensitivity, induced by cellular products is not a cause of great concern in many vaccines (though in some such as rabies vaccine prepared in nervous tissue they are of great significance), the possibility cannot be disregarded that in rare cases these cellular products will cause in quite unrecognized ways pathologic changes in the recipient. For instance, one can speculate that DNA of extraneous origin might penetrate cells of the recipient and combine with a segment of the genome. A combination of this sort might lead to suppression or modification of normal cellular metabolism. On any ground, however, the presence of all contaminants is a priori undesirable, and efforts have already been made, such as those of Hilleman and his coworkers with poliovaccines, to reduce such extraneous substances while increasing the concentration of the viral component to enhance antigenic potency.

In addition to the elimination of all tissue constituents, and of probably far greater importance, is the exclusion of viruses that may by chance contaminate the materials used in the production of the vaccine. An impressive example of such contamination is afforded by the history of the manufacture of poliovaccines. In 1960 — that is, five years after the beginning of mass vaccination in this country — a simian virus, which turned out to be exceedingly widespread in the kidney tissue of Indian monkeys then used for vaccine production, was detected in many lots of both inactivated and attenuated vaccines. This agent was not recognized as a contaminant because the technics then available for the detection of extraneous viruses did not reveal its presence. Another illustration of troublesome contamination is afforded by the widespread occurrence of the agents of the fowl-lymphomatosis group in many chick embryos that are extensively employed in the preparation of prophylactics against measles, yellow fever and influenza. A very recent case of the accidental inclusion in smallpox vaccine of the virus causing milkers' nodules has been described in France by Vieuchange and his co-workers.

Increasing knowledge of the finer details of the morphologic, biochemical and biophysical properties of the complete virus particles to be used in a vaccine should provide the means whereby they may be separated with greater efficiency from cellular derivatives than is now possible in the mass production of vaccine. Accumulation of information of this sort about each of the known viruses should also do much to provide means whereby unwanted agents may be eliminated with greater assurance from vaccines as well as other biologic products, although the most sensitive tests for the presence of viral contaminants will probably continue, as at present, to consist in the demonstration of characteristic lesions in susceptible animals or cultured cells.

Another major question in the field of artificial immunization still awaits a final answer even after years of investigative effort: Is the resistance induced by inactivated vaccines qualitatively the same as that evoked by live, attenuated virus? So much has been written and spoken on this subject since the beginning of the development of inactivated poliovaccines that some apology is in order for daring to add even one more comment. I excuse myself for so doing because there seem to be good reasons to believe that through the solution of this problem new mechanisms of resistance to viral infections may be brought to light. If the event should so prove, less empirical ways of immunization might suggest themselves, and from the practical standpoint we should all be able to agree upon which of the presently available methods is preferable.

To visualize lines of investigation that may eventually lead to a better understanding of viral resistance, I shall briefly recapitulate the essentials of what is now known about similarities and differences in the effects of the two kinds of vaccine, although many here are no doubt familiar with them. Both vaccines stimulate the formation of a specific antibody that when mixed with a suspension of the virus will neutralize or block its capacity to infect susceptible animals or cells growing in culture. In addition blood serums of vaccinated persons may contain antibodies that fix complement in the presence of the virus and inhibit agglutination of red blood cells by the agent. The viral-protein components alone or, occasionally, when associated with lipid or polysaccharides are the antigens that stimulate the development of these antibodies. When inactivated virus is introduced into the body it cannot multiply in the host cells, and consequently its antigenic effect appears to be determined solely by the amount of viral protein present in the inoculum. So far as is known, the induction of antibody is usually the only antiviral response that inactivated virus can elicit. It follows, therefore, that resistance to subsequent infection is directly related, within limits, to the concentration of antibody induced and absolutely to its persistence in the body fluids. The initial concentration of antibody attained tends to decline with time, eventually

to reach an ineffective level. It can be restored, however, to its original, or an even higher, level, and the rate of antibody decay retarded by repeated administration of antigen after an appropriate interval or by natural exposure to the specific virus. Antibodies are similarly induced after administration of attenuated-virus vaccine, but the initial antigenic mass is usually not sufficient to stimulate antibody production. This deficiency is soon repaired, however, by extensive multiplication of the virus. In general the antibody concentrations achieved with a single dose of attenuated virus are equal to or surpass those induced by inactivated virus when several doses are given. Moreover, effective antibody levels are ordinarily held for much longer periods after vaccination with attenuated virus.

If, then, it were clear that circulating antibody was the sole factor in resistance to viral infection, there would be little to choose between the two types of vaccine, except for the practical considerations of ease of administration and maintenance of protection. In these respects attenuated vaccine would obviously be preferred, since a single dose may confer immunity of indefinite duration. These advantages, however, are considered by some to be overborne by the greater reactogenicity of certain live-virus vaccines. Moreover, on theoretical grounds the cell proliferative effect of viruses to which I shall later refer can perhaps be regarded a priori as representing a further disadvantage of attenuated vaccines.

But there is evidence that points away from the simple assumption that the sole effect of both vaccines lies in the stimulation of circulating antibodies. I can here do hardly more than mention a few of the observations and experimental data that strongly suggest, if they do not prove, that actual infection whether with attenuated or fully virulent virus evokes defensive mechanisms that appear to be quite independent of circulating antibodies.

These data fall naturally into two groups: the first includes findings indicating that a state of resistance may be established and persist in the absence of demonstrable antibody; and the second includes data indicating that infection may occur or persist in the presence of antibody.

The findings of the first group have been mainly derived from the study of factors in the recovery from primary viral infections of man and laboratory animals. From such studies it has become increasingly apparent that circulating antibodies are relatively unimportant in checking vifal multiplication and limiting its spread within the tissues. I shall mention only two of many observations that support this conclusion. In the first place, it is well known that agammaglobulinemic or hypogammaglobulinemic children usually recover from measles, vaccinia and other viral infections in a normal manner, although their capacity to produce antibodies is so reduced that they can be detected during convalescence only by special technics if at all. Similarly, in animals pretreated with x-rays or chemicals to suppress antibody formation, recovery from vaccinia and influenza-virus infections has been found to proceed normally to completion.

A number of factors that appear to contribute to the establishment of resistance in the absence of antibody have been defined. Most of these are physiologic and nonspecific in character such as increased body temperature, increased local acidity and decreased oxygen tension. The stimulation of interferon, a nonspecific protein that retards viral synthesis resulting from cellular infection by the viruses, is also considered by many workers to play an important part in this complex of antiviral forces.

Even when regarded as acting in combination, these factors do not seem to account for the highly efficient suppression of virus and complete histologic and clinical recovery that is observed. Accordingly, one may postulate that other mechanisms are involved. These might be pictured as consisting of changes induced by the virus in a proportion of the target cells while these were partially protected by interferon or certain of the physiologic factors that I have just mentioned.

It is possible to think of such changes as comparable to those occurring in cells when they become hypersensitive to tuberculin or other substances that elicit reactions of delayed hypersensitivity, since many viral infections are accompanied by manifestations of this sort of sensitization, which does not appear after inoculation of inactivated virus. In fact evidence now available indicates that cells of the monocytic series do indeed become sensitized to viral antigens so that when removed from the animal and exposed to the antigen in vitro they exhibit signs of gross injury. Possibly, cells altered in this way in turn react against the virus in a manner analogous to that in which immunologically competent cells of the lymphoid series are held to react against foreign tissue grafts. Beveridge, who considers that an allergic factor may be of significance in viral immunity, has recently summarized the facts that offer support to this hypothesis. However, as he makes clear, there is as yet no conclusive experimental demonstration that sensitized cells have the capacity to inhibit or destroy virus. Furthermore, there is a certain amount of direct evidence to the contrary, since Friedman and his co-workers have shown that animals rendered incapable of developing delayed hypersensitivity as well as antibody recover in a normal manner from vaccinia-virus infection. And so other kinds of cellular alterations that condition resistance should be sought although I believe the allergic hypothesis should continue to be vigorously investigated, since at the moment it is by no means disproved.

Another approach lies in exploring the possibil-

ity that modifications of normal cellular metabolic processes induced by contact with infectious virus result in interruption at some point of the intricate process of viral reproduction. Experimental straws in the wind suggest that a mechanism of this sort may be involved in establishing at least a temporary resistance to unrestricted viral proliferation.

The data indicating that the presence of antibody in the blood does not always prevent infection of local anatomic sites also testify against the unique role of antibody in resistance. A striking illustration of the failure of antibody to block viral multiplication has been revealed through comparative studies of the effects of attenuated and inactivated measles vaccines. It has been repeatedly demonstrated that in susceptible children who have received the inactivated vaccine and as a result have developed virus-neutralizing antibodies, administration of attenuated vaccine is followed by a marked increase in the antibody titer. Since there is good evidence that the quantity of attenuated virus introduced is too small to act as a booster antigen, this rise in antibody level appears to result from the multiplication of the virus in the cells of the recipient. This conclusion is reinforced by the experiments of Warren, who recovered measles virus from the blood of monkeys that had developed antibodies after vaccination with inactivated virus and were later exposed to the active agent.

Another instance of the failure of pre-existing antibody induced by inactivated vaccine to prevent infection is found in a report of Brown. Monkeys were given inactivated Type I poliovaccine and as a result developed significant levels of neutralizing antibodies. After receiving the virulent homologous virus a number of the animals came down with paralytic disease. The consistent failure of inactivated poliovaccine to prevent subsequent intestinal infection as demonstrated by Sabin is another relevant finding that is known to all.

In contrast to this partial resistance conferred by antibody alone is the efficient protection established by infection with attenuated or virulent agents. Reinoculation with virulent virus of animals that have experienced such infections is not usually followed by viremia or other signs of viral multiplication. For instance, my associates and I were unable to demonstrate virus in the blood of monkeys that had been given attenuated measles vaccine and thereafter inoculated parenterally with virulent measles virus. And as Sabin has shown, in human subjects the cells of the intestinal tract become refractory to infection after administration of attenuated vaccine.

In view of the differences that I have reviewed and many others that I have not time to consider, it must, I think, be concluded that mechanisms other than those dependent upon circulating antibodies are evoked by infection and that these tend to persist indefinitely. It remains for further investigations to define them in precise terms. If this is accomplished ways may be found to bring them into play without the necessity of subjecting the recipient to infection with the complete virus particle.

In concluding this fragmentary discussion of factors in active immunization I would make it clear that I do not have any doubts about the major defensive role of specific antibody present before infection, for the evidence on this point is conclusive. I intend only to emphasize the fact that other factors may account for the greater efficiency of the protection conferred by infection as compared with inactivated virus and that a clearer understanding of these might contribute substantially to the better control of viral infections and perhaps even to their treatment.

I shall now offer for consideration a few thoughts on how researches on the temperate relation between virus and susceptible cell that are now being actively pursued by many workers promise to give new insight into a number of perplexing problems of immunity and pathogenesis. So far as I am aware this phenomenon was first observed with an oncogenic virus, and it is to the association between agents of this sort and the cells that they inhabit and in which they induce malignant transformation that the attention of workers of the present day is for the most part being directed. But I believe that the results that have been reported in this field during the last few years, however valuable they promise to be for the study of the neoplastic process, may have even broader implications, as I shall point out at the end of this paper.

To illustrate the phenomenon itself, I shall briefly describe a few of the principal observations that Dr. Harvey Shein and I have made on the effects of the simian agent SV40 in hamster-kidney cell cultures. Comparable experiments by several other investigators have yielded results that agree with ours in all essential respects. SV40 virus belongs to a rapidly expanding group of agents that are capable of inducing tumors when introduced parenterally into rodents. In cell cultures many of these viruses tend to form temperate relations that are accompanied by malignant transformation of the cells. I would emphasize, however, the fact that SV40, along with other agents of known oncogenic capacity, has not been found to differ in its basic properties from similar viruses that as yet, at least, have shown no neoplastogenic capacity. The ability, therefore, of SV40 and other oncogenic viruses to enter into nondestructive relations with cells need not be regarded as an attribute peculiar to this class of agents, although clearly the establishment of such a relation is a condition necessary for the expression of their oncogenic activity.

When SV40 virus was added to cultures of hamster-kidney cells no marked changes in the appearance of the cells were seen during periods ranging

from four to six weeks or longer. Appropriate tests for the presence of the virus made throughout this period indicated that for a while it multiplied to a moderate extent, but then multiplication apparently ceased, since the virus in its complete infectious form could no longer be detected by the ordinary procedures. This failure to detect complete virus, however, did not signify that it had become inactive, for it later proved possible to show by special technics that it was still in a masked or hidden state.

As incubation of the cultures was continued, the growth rate of the cells accelerated as indicated by an increase in the number of mitotic figures. After four to six weeks of incubation cells or groups of cells were seen here and there throughout the main population that had not previously been present and could be readily distinguished by their round or polygonal shape from the original population, which was composed of cells similar to fibroblasts. These newly appearing cells multiplied very rapidly, piling up one over the other to form heaped-up colonies or masses, an arrangement that contrasted sharply with the regular monolayer pattern presented by the original normal cells. When subcultured, these newly appearing epithelioid cells continued to grow very fast, easily outstripping the other forms. In this way apparently pure cultures of the new cells were obtained. Indeed, the growth potential of these cells was so high that single cells when placed on the surface of a petri dish formed colonies, from which clonal lines were readily obtained in the same way that one would culture a colony of bacteria.

Detailed studies of three such clones have established a number of interesting facts regarding the biologic properties of the transformed cells and their relation to the virus.

It was first found that complete infectious virus particles were not produced by the cells of any of these lines in quantities detectable by routine methods of assay. However, when special technics were applied, virus was intermittently demonstrated. The results indicated that under these special conditions, a single cell among several million will suddenly begin to manufacture complete virus. Since the cells in each line were all derived from a single parent it may be concluded from these results that every cell in the clonal line carries the viral genome, and that in the cell population as a whole, the process of viral synthesis is suppressed, although rarely it may go to completion under circumstances that cannot yet be precisely defined.

Secondly, it was determined, by the introduction of different numbers of cells from these clonal lines into the hamster cheek pouch, that they were highly oncogenic. With two of the lines between 10 and 100 cells, and with the third less than 1000 cells produced tumors. Histologically, the tumors were varied, often consisting of adenocarcinomatous elements intermingled with areas of fibrosarcoma. Some of the neoplasms appeared to be fibrosarcomas in which no epithelial elements were found.

Since we are confident that in these clones the cell population consists entirely of the descendants of a single cell, these findings strongly suggest that the transformed cells are multipotential and when acted upon by unknown factors operating in the animal and within the growing tumor can differentiate into epithelial cells or forms similar to fibroblasts.

Thirdly, and perhaps most significantly, an antigen that is not present in the normal hamster cell has been demonstrated in all three cloned lines by the results of experiments that we have carried out in collaboration with Dr. Albert Sabin. This new antigen, which was first shown by Huebner and his associates to appear in the cells of tumors induced by inoculation of hamsters with SV40 virus, appears to be a new type produced by the cell itself since it is unrelated to any of the known antigens present in the virus particle. In tumor-bearing animals antibodies develop that react specifically in complement-fixation tests with the new cellular antigen. It is virus dependent, however, since it is found only in cells transformed by SV40 virus and not in those transformed by other agents such as the polyoma virus or in the cells of other tumors not associated with a virus. Thus, we have found, again in collaboration with Dr. Sabin, that a cellular antigen of the same specificity is present in human-kidney cells transformed in vitro by SV40, and Black and his associates have demonstrated the same antigen in cultures of cells of mice, rabbits and pigs exposed to this agent. Cellular complement-fixing antigens also develop in cells transformed by polyoma virus and the oncogenic adenoviruses Types 12 and 18 that are also virus dependent, as demonstrated by Huebner and his group. We have, therefore, considerable reason to conjecture that the development of a new cellular antigen may be a regular effect of the temperate virus-cell relation irrespective of whether it is associated with the neoplastic transformation.

It now remains to point out by way of peroration a few of the ways in which I can imagine that these findings and many other related observations by others working with comparable phenomena may contribute in the future to the advancement of virology and medicine.

In the first place I believe that it will be demonstrated that the temperate relation between virus and host cell is a common event. Already, there are a number of clinical and epidemiologic observations that favor this view. Thus, the persistence of virus in a latent form in herpes-simplex infections has long been recognized. One can now, I think, visualize a bit more clearly how such infection is maintained. It also seems likely that the genome of the virus of varicella remains in certain cells in which little or no complete virus is produced and so is able to persist for years. Alteration of the virus-cell equilibrium by

factors as yet unknown may suddenly occur. As a result, complete virus is formed that causes cellular damage expressed by the clinical manifestation of herpes zoster. The long lasting immunity conferred by an attack of many acute viral infections has long been held by some to depend upon the continuous presence of virus in the tissues. We are now in a position to suggest a mechanism by which this durable immunity might be maintained. We can also account theoretically for the failure to support this hypothesis by isolation of virus from the tissues of persons who have previously undergone an attack, since unless we know exactly how to proceed to upset the cell-virus equilibrium and thus to allow synthesis of complete virus to proceed we shall fail to detect the presence of the viral genome.

The implications of these findings in the future exploration of the possibility that viruses cause cancer in man are obvious and so require little comment. If these agents are etiologically involved we probably should not expect to find them in the complete state in tumor tissue — in fact they have not been found in spite of many attempts. Rather than continue to look for agents in this form a more promising approach would consist in exploring a variety of conditions that might release the full capacity of the viral genome. Already, investigations are proceeding along these lines. These efforts may fail, but at least they are proceeding logically from an established experimental basis. The discovery of the new cellular antigens in cells transformed by virus seems to provide a means of determining whether some of the known viruses oncogenic in lower animals have caused tumors in man. I believe that such surveys are already in progress. The results will be awaited with interest, especially in patients known to have been exposed to one of these agents.

Finally, one may speculate, and I admit I am now speculating very wildly, that in certain degenerative diseases, such as multiple sclerosis and Parkinson's disease, viral agents may ultimately be found to be involved. For it does not seem impossible from what is now known that infection in certain persons, perhaps with common viruses like those of measles or mumps or herpes simplex, might be followed by the establishment of the sort of virus-cell relation that I have been talking about. As a result, new antigens might appear. The cells bearing them would become immunologically foreign and eventually might be injured and destroyed either by the development of humoral antibodies specific for the new antigen or by a cellular reaction of the homograft-rejection type. Since I am now speculating without restraint it may not be too fantastic also to suggest that a mechanism of this sort might even condition some of the autoimmune diseases.

But I shall go no further with these imaginings and end here, realizing that I have already indulged too long in the pleasant but quite unscientific pastime of "calling spirits from the vasty deep."

HEMODYNAMIC EFFECTS OF BLOOD TRANSFUSION IN CHRONIC ANEMIA*

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IN patients with severe chronic anemia, whether or not it is amenable to treatment with specific therapy, the administration of blood transfusions is often necessary to provide immediate symptomatic improvement and to prevent potential irreversible anoxic damage to tissues. The slow administration of packed red blood cells with the patient in a semiupright position is often well tolerated. Not infrequently, however, congestive heart failure may supervene during or after the transfusion.[2,3] The hematology literature is replete with caution against transfusion, especially in patients with pernicious anemia, and a number of fatal cases have been observed with pulmonary edema found at post-mortem examination.[4-7]

Fullerton and Turner[8] have commented on the development of severe congestive heart failure and a high mortality after blood transfusions in patients with severe anemia of pregnancy with or without clinical evidence of heart failure initially. They described a marked decrease in mortality rate when an exchange transfusion was carried out in these patients. Hemodynamic measurements were not reported in these cases. Sharpey-Schafer[3] has observed a rise in venous pressure and a fall in cardiac output after transfusions in anemic patients, and has suggested that the heart in severe anemia be-

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Supported in part by grants (HE-00442 and HTS-5244) from the National Heart Institute, National Institutes of Health, United States Public Health Service.

Presented in part at a meeting of the New England Cardiovascular Society on February 11, 1963.[1]

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