all modify the reflectivity of the flint. Chemical changes involving the pigments, their dispersal along intergranular surfaces, or removal by leaching modify both reflectivity and capacity to preferentially absorb.

Attempts to correlate patina thickness with age, and thus to use flint patinae chronometrically, have proven unsatisfactory because other factors, whose importance in some cases exceeds that of age, have not been taken into account. The texture and microstructure of flint, its permeability, and the kind, proportion, and distribution of impurities can be evaluated by regular petrographic techniques. Environmental factors can be assumed constant for artifacts from the same types of soil in a given climatic region. Only after allowances have been made for these additional variables does the age-dependence of flint patination become clear.

References

1. A. R. Kelly, "Age measurements in decomposed flint," *Georgia Dept. of Mines, Mining and Geol., Geol. Survey Bull. No. 60* (1953), pp. 321–330; ——— and V. J. Hurst, *Am. Antiquity* **22**, No. 2 (1956).
2. I. Friedman and R. L. Smith, *Am. Antiquity* **25**, 476 (1960).

Infectious Nucleic Acids, a New Dimension in Virology

Their release from infected tissues and resistance to antibodies may explain some anomalous conditions.

Roger M. Herriott

In the last few years a new dimension in virology was discovered by finding that naked, or free viral nucleic acids are infectious (*1–12*) and that they are not affected by antisera which neutralize whole virus (*3, 5, 8*). Discovered first in plant viruses (*1*), the infective nature of viral nucleic acids was soon afterwards demonstrated for poliomyelitis (*2, 3*), eastern equine and West Nile encephalitis (*2, 4*), Semliki Forest encephalitis (*12*), foot-and-mouth disease (*10*), influenza (*5, 11*), a bacterial virus disease (*7*), and a viral-induced tumor disease (*6*), to mention some representative cases (*31*). Both ribose and deoxyribose-type nucleic acids are among the examples, so there is every reason to believe this is a general phenomenon. Only the efficiency of infection is lower in the nucleic acid preparations than in the case of intact viruses. In all cases the nucleic acid produced the usual disease with the release of whole virus particles.

This capacity of nucleic acid to breach the main defense mechanism of animals led me to several questions and to some speculation which may be worth examining in detail in order to determine the degree to which infective nucleic acids of viruses play an unrecognized role in natural diseases.

The questions which follow serve as the nucleus around which this article is organized.

1) If the viral nucleic acids are released from diseased tissues and if antibodies do not react with nucleic acids, what stops a viral infection?

2) Is the persistence of some infective agents for long periods in the blood of infected subjects—as in serum hepatitis or infectious anemia of horses—due to an infective nucleic acid?

3) Are infectious nucleic acids, either free or in an unreactive envelope, responsible for reports of infectivity in the presence of antibodies?

4) Can the long immunity imparted by infection with certain viral agents be attributed to the maintenance of a low-grade infection, perpetuated by infectious nucleic acid?

5) What will infectious nucleic acids do in an individual vaccinated with a "killed" virus preparation?

6) Since viral nucleic acids can infect hosts not infectible with whole virus, does the search for insect vectors and susceptible hosts which might serve as reservoirs or intermediate hosts need reinvestigation?

7) Do these properties account for the failure to find transmissible agents in human tumors?

While the answers to all or even most of these questions may not lie in the existence of free infectious nucleic acid, the phrasing of the questions deliberately focuses attention on the unusual properties of viral nucleic acids. Questions of a similar nature have been raised briefly by others (*14, 15*).

Viral Nucleic Acid in Infected Cells

Let us first consider the likelihood that free or naked nucleic acid may be present in infected cells and may be liberated to infect surrounding tissues. If there is evidence against such a possibility, it would suggest that the infectious nucleic acids are artificial products of the laboratory and play no part in natural diseases. In two instances in which this point has been examined, free viral nucleic acid has been found or implicated.

Phage-infected *Escherichia coli* have been studied most intensively. In this system, infection is initiated by injection of viral nucleic acid into the host cell (*16*). This is soon followed by synthesis of a "pool" of viral nucleic acid from which progeny virus is formed (*17*). This pool of nucleic acid is maintained essentially constant during intracellular phage formation. At lysis, presumably, the viral nucleic acid from the pool which had not been enclosed in the protein coat is released along with whole virus.

In the case of tissues infected with animal viruses, the evidence is more pertinent to the present discussion. Wecker (*18*) reported that cold phenol, which does not separate viral nucleic

The author is professor of biochemistry in the Johns Hopkins University School of Hygiene and Public Health, Baltimore, Md.

acid from the protein of whole virus, will release infectivity from chick allantoic membranes infected with equine encephalitis virus. No infectivity was released, however, if the infected membranes were first treated with ribonuclease. Since whole virus was not affected by this enzyme, these observations suggest that the infectious nucleic acid is free in the cells and is liberated by cold phenol.

Others (*19*) have found that early treatment of influenza-infected allantoic membranes with ribonuclease reduced the infectivity of the tissue contents; but when the same was found to be true for tissues infected with DNA virus (*20*) as well, it was clear that the action was not necessarily exerted on the viral nucleic acid. This observation is not evidence *against* the presence of free viral nucleic acid in tissues, it merely indicates the difficulty of interpreting complex experiments.

The report of Huppert and Sanders (*9*) is important in the present discussion. These workers reported that they obtained infective ribonuclease-resistant units from tissue infected with encephalomyocarditis virus. These units sedimented much more slowly than whole virus. It will be interesting to know the nature of the material protecting the nucleic acid from the nuclease.

The studies of phage-infected cells and Wecker's report (*18*) are less equivocal than some of the others. They leave little doubt that there is free viral nucleic acid in the particular systems examined.

Infectivity in the Presence of Antibodies

If, as some of the above studies indicate, infective nucleic acid is present in infected cells, then it should sometimes be detectable in extracellular fluids. However, since whole virus may also be present, some means of separating whole virus and viral nucleic acid, or of distinguishing between them, is necessary. The presence of both infectivity and neutralizing antibodies in the same fluid would be highly suggestive, and if the infectivity should then be destroyed by a nuclease, this would be decisive, for no structures other than nucleic acids would react in this way. A search of the literature has turned up a few cases in which the first criterion is satisfied, but no such case has appeared since the infectious nature of viral nucleic acids has been recognized.

Andrewes (*21*) and Todd (*22*) noted many years ago that antivaccinia serum failed to inactivate virus preparations totally, and Smith (*23*) observed that, for a period of several days, rabbits infected with vaccinia had both virus and antibodies in their blood. Berry and Kitchen (*24*) carefully examined a laboratory worker who became accidentally infected with yellow fever virus. They reported that on the fourth and fifth days the blood of this individual contained neutralizing antibodies, as tested in mice, yet showed infectivity for rhesus monkeys. Unfortunately, a close examination of the details surrounding each of these experiments shows that in no instance is the interpretation unequivocal.

Sabin (*25*), however, in a series of papers on the mechanism of immunity to viruses, showed quite clearly that virus preparations mixed with immune serum were noninfectious when inoculated by one route but readily infectious when inoculated by other routes, yet the tissues infected by the several routes were essentially equally susceptible to limiting doses of virus. In rabbits, more than 100 times the concentration of immune serum needed to neutralize 50 to 500 minimal infective doses of B virus inoculated by the intracutaneous route failed to protect against a single minimal infective dose inoculated by the intracerebral route, although the rabbits were found to be equally susceptible by both routes. Similar results were obtained with vaccinia, herpes, or pseudorabies viruses and suggest that this observation is not just an isolated exception. If it is assumed that the viral preparations contained some infectious nucleic acid, then the results become explicable as follows: the immune serum neutralized whole virus and left the infectious nucleic acid, which is destroyed by nucleases before it can infect when inoculated by the cutaneous route but not when inoculated intracerebrally. In this connection it is of interest that the route of inoculation of nucleic acid from foot-and-mouth-disease virus was found to be important (*10*). Inoculation intraperitoneally failed to produce infection, in sharp contrast with the high infectivity of nucleic acid inoculated by the intramuscular pathway. Sabin has suggested (*26*) that his experiments should be repeated in the light of the present hypothesis, and that addition of nucleases to the viral preparations might lead to decisive results.

More recently Dulbecco, *et al.* (*27*) have reported that excess antibody failed to reduce below a minimum the infectivity titer of either western equine encephalomyelitis virus or poliomyelitis virus. Their failure to observe a drop in infectivity with time of incubation suggests that either the serum ribonuclease was ineffective or the viral nucleic acid was protected.

At this point the puzzling character of the disease produced by herpes simplex virus is worthy of discussion. A fraction of the individuals with a history of this disease suffer recurrent episodes which may be initiated by unusual stresses, including fever. In an analysis of this syndrome, Andrewes and Carmichael (*28*) and Brain (*29*) observed that the disease reappeared only in those individuals having neutralizing antibodies. Burnet and Williams (*30*) also studied this problem and confirmed these observations. This conclusion virtually rules out reinfection from an external source and suggests recrudescence. Either the primary infection is kept submerged in the interim and flares up when the control mechanism is altered, or, as in lysogenic bacteria (*31*), an inactive form must be induced or activated. Unless it is assumed that the antibodies cannot reach the reactivated "virus," the latter must be serologically unreactive, a property associated with the free nucleic acids. If the hypothesis thus far is correct, then responsibility for submergence of activity between episodes could be attributed to the humoral nucleases. Under stresses such as fever, which precede recurrence of the disease, the nucleases may become inhibited and may thereby permit the infectious nucleic acid from the low-level infection to enlarge the area of infection and produce symptoms —all this in the presence of antibodies. White blood cells, which release a deoxyribonuclease inhibitor in vitro (*32*), accumulate in the blood during fever, so that if the nucleic acid of herpes is of the deoxyribonucleic acid type, as appears plausible (*33*), the model is complete.

Nonantigenic Viral Agents

At this point I shall consider a few specific diseases, each of which has an anomalous facet suggesting either that the infective agent is nonantigenic or that at some stage it is nonantigenic.

The anomalies range from "carrier" states where no antibody is demonstrable to recrudescence in the presence of antibodies, as in the already discussed example of herpes simplex.

The viral agent that causes serum hepatitis is not known to infect animals other than man, a fact which seriously limits our ability to obtain reliable information about its properties. The disease is distinguished by a long period (up to 50 days) of viremia preceding the onset of symptoms, which in some instances may not develop for three to four months after exposure (*34*). If there were a protein component of this agent, antibody would be expected to form and neutralize the agent in this time interval. There are also reports of repeated attacks of the disease (*34*). These reports, supported by one that gamma globulin from convalescent patients has failed to prevent infection with known infective material (*24*, *35*), are evidence for an immunologically unreactive agent. However, the stability of the agent for long periods in serum requires that the viral nucleic acid must be protected from the nucleases by a membrane of nonantigenic material, perhaps lipid. The report by Huppert and Saunders (*9*) of finding a ribonuclease-resistant infective encephalomyocarditis particle that sediments more slowly than the usual virus particles may be pertinent.

Other diseases in which the viral agent persists for very long periods in the blood without antibody formation include infectious hepatitis of mice (*36*), infectious anemia of horses (*37*), and lymphocytic choriomeningitis in mice (*38*), although in the last instance other explanations have been offered (*39*).

To imply that all nonantigenic disease agents are free nucleic acids is not my intent, and to draw such a conclusion would be to disregard the fact that free nucleic acids are extremely vulnerable to nucleases of blood (*32*). Since the infectious agents persist for long periods in the blood, it is necessary to suppose that either (i) the infective nucleic acid is released by the tissues more rapidly than it is being removed or digested, or (ii) the nucleases are suppressed in these cases by inhibitors (*32*), or (iii) the nucleic acid is surrounded by a nonantigenic membrane which protects it from nucleases (*9*). At the present time there are too few data for us to decide among these possibilities, although decisive experiments are feasible.

Increased Host Range of Nucleic Acid

A certain property of viral nucleic acid which was discovered independently in three different laboratories (*40*, *41*) will have particular importance if subsequent work shows it to be a general property of viral nucleic acids. It was found that the range of cell hosts for viral nucleic acids is greater than for the whole virus. Thus, Syverton's group (*40*) showed that rabbits, hamsters, and guinea pigs, as well as certain of their tissues, were infectable by a variety of enteric virus nucleic acids, including poliomyelitis, but not by whole viruses. A somewhat similar case has recently been found for a bacterial virus (*7*). In the light of this remarkable discovery, tests for susceptible tissues or hosts, which in the past were made with whole virus, will in many instances need re-examination with viral nucleic acids.

Tumor Agents

Despite an ever-increasing list of viral agents shown to initiate tumor formation in animals, some of which become malignant (see *42* for a more complete discussion), few such agents, if any, have been found associated with malignant growth in man. Questions naturally arise concerning the reason for this difference. If human tumors are caused by viral agents, are these agents in a masked form, like the papilloma virus in the domestic rabbit (*43*), or is the tumor agent a viral nucleic acid which functions *in situ* but, when transferred to another host, is so slow in infecting other cells that it is destroyed by the nucleases? The failure to find viral antigen in the basal germinal layer of the rabbit papilloma where neoplasia is occurring, in contrast to the easily observable quantities of antigen higher in the wart, led Noyes and Mellors (*44*) to suggest that it is the nucleic acid that is infectious, and led Shope (*15*) to wonder if the more labile viral nucleic acid is responsible for the neoplasia.

In recent years the production of myxomatosis in rabbits through the combined action of avirulent Shope fibroma virus and heat-killed myxoma virus [the Berry-Dedrick phenomenon (*45*)] has been clarified somewhat. Shack and Kilham (*46*) have shown that the nuclease-sensitive nucleic acid and a small quantity of protein from the myxoma virus must be included with the fibroma virus. The nucleic acid is not infectious alone, but requires the supporting action of the fibroma virus, either to change the permeability of the host cell to nucleic acid or because the nucleic acid is incomplete as prepared and must acquire some missing part from the related strain before it can infect. Similar "transformations" have been reported for other pox viruses (*47*).

In the case of the polyoma virus, a nuclease-sensitive infective nucleic acid has been reported (*6*) which produces typical tumors, so it is not unreasonable to look for such an agent in those instances where the classical type of search for whole virus has failed, but where success in looking for an infectious nucleic acid may depend on the suppression of the naturally occurring nucleases.

Nucleases as a Defense Mechanism

In general, the initiation of an infection depends on whether at least one viral particle can penetrate a susceptible cell where it is safe from the usual host defense mechanisms. Once a cell is infected, the spread of the infection in the tissues is determined by the same forces plus the added, but little understood, feature of cell-to-cell transmission of the infective agent, possibly without its exposure to extracellular insults. The concentration (titer) of virus, number of susceptible cells, and time of penetration are on the side of infection and against the forces tending to inhibit the process. In general, this inhibition of infection by whole virus is due to antibodies, although there may be other deterrents, such as interferon (*48*). Since nucleic acids are not influenced by antibodies to whole virus (*3*, *5*, *8*), the possibility that nucleases which are known to be highly destructive of nucleic acids (*49*) might serve as an additional defense mechanism deserves consideration.

My colleagues and I have determined blood levels in human beings of both deoxyribonuclease and ribonuclease (*32*). We found that the active nuclease in the blood of the average adult reduced the infectivity of a deoxyribonucleic acid agent to 10 percent (a 1-log drop) in 12 minutes at 37°C, whereas a ribonucleic acid agent was reduced to the same level in 2 to 3 seconds. This information shows that, other things being equal, an infective deoxyribonucleic acid would have 100 times as great a chance of initiating an infection as would ribonucleic acid of

viral origin. Virologists working with tissue cultures have recognized that the nucleases of serum (*2, 3, 11*) rapidly destroy viral nucleic acid infectivity. On the other side, nucleic acids are taken up by susceptible, or "competent," cells in less than a minute or two (*3, 50*), and there are, of course, many instances (noted earlier) of infections produced in animals by inoculating only the viral nucleic acid. It may be considered as established, therefore, that for nonimmune animals the normal nuclease levels are not high enough to prevent infection, although there is one report (*10*) that the route of inoculation of viral nucleic acid was critical. It is possible, however, that in these instances of infection the concentrations of nucleic acid inoculated were inordinately high relative to those that might develop in infected tissues.

Considerable variation in the blood nuclease levels of individuals, due, perhaps, to a release in vivo of either enzymes or their inhibitors from the cellular elements of blood (*32*), has been observed. Such variations, enhanced perhaps by the effects of a specific disease or physiological condition, might well produce wide differences in the response of individuals to infectious nucleic acids.

The balance between nuclease destruction and infectivity may be so fine in some instances that failure to find infective agents when their existence had been suspected—as in cancer research—might be due to an increase in nuclease concentration. This increase need not be excessive by ordinary standards. In looking for infectious nucleic acids, utilization of the nuclease inhibitors found in certain cells of blood (*32*) should prove of value.

Permanent Immunity

It is generally agreed (*51*) that after recovery from certain viral diseases such as poliomyelitis or yellow fever, individuals are permanently immune to the agent. To account for this it has sometimes been thought that perhaps in these cases there is a very low level infection maintaining a stimulus for antibody formation, but no very appropriate model for maintaining an infection in the presence of antibodies has been suggested. The infectious nucleic acid provides just such a model. The whole virus, released by tissues, would be rapidly neutralized by humoral antibodies and would provide an anamnestic stimulus, while released nucleic acid would infect a few susceptible cells and maintain the infection. The larger range of cell hosts for the nucleic acid (*40, 41*) may be particularly important in this connection.

Does a "Killed" Vaccine Protect against Infective Nucleic Acid?

Perhaps many of the questions raised in the earlier sections of this article can be tested by challenging, with viral nucleic acid, animals vaccinated with a "killed" whole virus preparation. Since the vaccinated animal presumably has no tissue or local immunity and possesses only antibodies which do not inhibit the free nucleic acid, there is every reason to expect some cells to become infected. Then, depending on whether infectious nucleic acid is thereafter released by infected cells and on how cell-to-cell infection takes place, any of several possible results may be anticipated.

If only whole virus is released, the antibodies induced by the vaccine should stop the infection promptly, and the animal should show little or no effect. If the tissues release infectious nucleic acid which spreads the infection to other cells and tissues, then symptoms may be observed.

It would be important in any event to examine these animals for a viremia by making undelayed inoculation of blood samples into unvaccinated susceptible animals by the route most sensitive to low levels of viral nucleic acid. A delay in transfer might permit nucleases of the blood to destroy any nucleic acid. There is considerable individual (*32, 52*) and species (*52*) variation in nuclease levels, so that extrapolations are at best only suggestive. The success of such an experiment might also depend on the particular disease agent.

It may be argued that observations from a vast number of neutralization studies of viremic agents virtually eliminate the possibility that an infective nucleic acid phase is present in blood or comparable fluids. This objection would be difficult to answer were it not customary for virologists to use serum samples in their tests; the time consumed in preparing the sample might well be sufficient for nuclease destruction of the infectivity, especially since deoxyribonuclease levels in serum are ten times higher than in blood, because of the release of this enzyme from platelets during clotting (*32*).

It is clear from the protection afforded by passive immunization and the correlation between rise in the level of antibodies and reduction in the intensity of symptoms that the whole virus plays the major role in most diseases. There are, however, exceptions, or features which do not fit such a simple picture, and it is these that are being viewed in the light of the recently discovered properties of viral nucleic acids. The true significance of infectious nucleic acids in natural infections will not be known until many carefully planned experiments have been performed which take into consideration some of the properties which have been described.

The control of viral infections by nonspecific mechanisms such as inflammatory reactions and interferon formation (*48*) has recently been emphasized (*53*). Nuclease action may be included among the nonspecific mechanisms. One or more of these mechanisms could interfere with the disease produced by a viral nucleic acid and explain the observed recovery, but it is not now known which mechanism is responsible for this action.

Summary

Viral nucleic acids have been found to be infectious for tissues and animals, yet are nonantigenic and resistant to antibodies against whole virus. Other unique properties, such as their host range and their susceptibility to nuclease action, render them a wholly new dimension to be reckoned with in virology.

These properties may explain a number of conditions which at present are considered anomalous. The release from infected tissues of even a small proportion of total virus as free nucleic acid could, in an otherwise immune individual, lead to a low level of infection which would, perhaps, explain permanent immunity. If the proportion of nucleic acid is higher, or if the nucleic acid is resistant to nucleases because of an inert envelope, such conditions as "carrier" states—that is, viremias with or without antibodies—are possible.

Note added in proof: The recent article by J. D. Ebert and F. H. Wilt (*54*) came to my attention after the present article was written. Ebert and Wilt's excellent article indicates the impact of the newer knowledge of viral nucleic acids on the ideas developing in the field of embryology.

References and Notes

1. H. Fraenkel-Conrat, *J. Am. Chem. Soc.* **78**, 802 (1956) ➡ A. Gierer and G. Schramm, *Nature* **177**, 702 (1956); ———, *Z. Naturforsch.* **11b**, 138 (1956).
➡ J. S. Coulter, H. M. Bird, R. A. Brown, *Nature* **179**, 859 (1957).
➡ H. E. Alexander, G. Koch, I. M. Mountain, O. Van Damme, *J. Exptl. Med.* **108**, 493 (1958).
4. E. Wecker and W. Schafer, *Z. Naturforsch.* **12b**, 415 (1957).
5. H. F. Maassab, *Proc. Natl. Acad. Sci. U.S.* **45**, 877 (1959).
6. G. A. DiMayorca, B. E. Eddy, S. E. Stewart, W. S. Hunter, C. Friend, A. Bendich, *ibid.* **45**, 1805 (1959).
7. G. D. Guthrie and R. Sinsheimer, *J. Mol. Biol.* **2**, 297 (1960).
➡ F. Sokol, H. Libikova, J. Zemla, *Nature* **184**, 1581 (1959).
➡ J. Huppert and F. K. Sanders, *ibid.* **182**, 515 (1958).
➡ F. Brown, R. F. Sellers, D. L. Stewart, *ibid.* **182**, 535 (1958).
➡ G. L. Ada and S. G. Anderson, *ibid.* **183**, 799 (1959).
➡ P. Y. Cheng, *ibid.* **181**, 1800 (1958).
13. For a more complete listing, s ➡ L. M. Kozloff, *Ann. Rev. Biochem.* **29**, 475 (1960).
14. A. B. Sabin, in *Rept. Proc. Intern. Congr. Microbiol. 7th Congr. Stockholm* (1958), p. 253.
15. R. E. Shope, personal communication.
➡ A. D. Hershey and M. Chase, *J. Gen. Physiol.* **36**, 39 (1952).
➡ A. D. Hershey, J. Dixon, M. Chase, *ibid.* **36**, 777 (195 ➡ A. D. Hershey, *ibid.* **37**, 1 (1953).
➡ E. Wecker, *Virology* **7**, 241 (1959).
➡ J. LeClerc, *Nature* **177**, 578 (195 ➡ F. M. Burnet, P. Lind, B. Perry, *Australian J. Exptl. Biol. Med. Sci.* **35**, 517 (1957).
➡ I. Tamm and R. Bablanian, *J. Exptl. Med.* **111**, 351 (1960).
➡ C. H. Andrewes, *J. Pathol. Bacteriol.* **31**, 671 (1928).
22. C. Todd, *Brit. J. Exptl. Pathol.* **9**, 247 (1928).
23. W. Smith, *ibid.* **10**, 93 (1929).
24. G. P. Berry and S. Kitchen, *Am. J. Trop. Med.* **11**, 365 (1931).
25. A. B. Sabin, *Brit. J. Exptl. Pathol.* **16**, 169 (1935); I am grateful to Dr. Sabin for calling my attention to this article.
26. ———, personal communication.
➡ R. Dulbecco, M. Vogt, A. G. R. Strickland, *Virology* **2**, 162 (1956).
➡ C. H. Andrewes and E. A. Carmichael, *Lancet* **1**, 857 (1930).
29. R. B. Brain, *Brit. J. Exptl. Pathol.* **13**, 166 (1932).
30. M. F. Burnet and S. W. Williams, *Australian J. Med.* **1**, 637 (1939).
31. A. Lwoff, *Bacteriol. Revs.* **17**, 270 (1953).
➡ R. M. Herriott, J. H. Connolly, S. Gupta, *Nature* **189**, 817 (1961).
➡ A. Newton and M. G. P. Stoker, *Virology* **5**, 549 (1948); S. Osterhout and I. Tamm, *Federation Proc.* **18**, 590 (1959).
34. W. P. Havens and J. R. Paul, in *Viral and Rickettsial Infections of Man*, T. M. Rivers and F. L. Horsfall, Jr., Eds. (Lippincott, Philadelphia, ed. 3, 1959), chap. 27, p. 570.
35. M. E. Drake, J. A. Barondess, W. J. Bashe, Jr., G. Henle, W. Henle, J. Stokes, Jr., R. B. Pennell, *J. Am. Med. Assoc.* **152**, 690 (1953); G. S. Mirick has obtained some evidence which suggests that gamma globulin may be protective (personal communication).
36. A. W. Gledhill and C. H. Andrewes, *Brit. J. Exptl. Pathol.* **32**, 554 (1951 ➡ A. W. Gledhill, G. W. A. Dick, C. H. Andrewes, *Lancet* **2**, 509 (195 ➡ J. S. F. Niven, A. W. Gledhill, G. W. A. Dick, C. H. Andrewes, *ibid.* **2**, 1061 (1952).
37. M. N. Dreguss and L. S. Lombard, *Experimental Studies in Equine Infectious Anemia* (Univ. of Pennsylvania Press, Philadelphia, 1954).
➡ E. Traub, *J. Exptl. Med.* **63**, 847 (1936); **68**, 229 (1938).
39. F. M. Burnet *Principles of Animal Virology* (Academic Press, New York, 1955), p. 244.
40. J. J. Holland, L. C. McLaren, J. T. Syverton, *Proc. Soc. Exptl. Biol. Med.* **100**, 843 (195 ➡ *J. Exptl. Med.* **110**, 65 (1959).
41. I. M. Mountain and H. E. Alexander, *Proc. Soc. Exptl. Biol. Med.* **101**, 527 (195 ➡ P. De Somer, A. Prinzie, E. Schonne, *Nature* **184**, 652 (1959).
42. *Cancer Research* **20**, 669 (1960).
43. R. E. Shope, *Proc. Soc. Exptl. Biol. Med.* **32**, 830 (1935).
➡ W. F. Noyes and R. C. Mellors, *J. Exptl. Med.* **106**, 555 (1957).
45. G. P. Berry and H. M. Dedrick, *J. Bacteriol.* **32**, 356 (1936).
46. J. Shack and L. Kilham, *Proc. Soc. Exptl. Biol. Med.* **100**, 726 (1959).
➡ F. Fenner, I. H. Holmes, W. K. Joklik, G. M. Woodroofe, *Nature* **183**, 1340 (1959);
➡ T. Hanafusa, H. Hanafusa, J. Kamahora, *Virology* **8**, 525 (1959).
48. A. Isaacs, *Symposium Soc. Gen. Microbiol. 9th* (1959), p. 102; R. R. Wagner, *Bacteriol. Revs.* **24**, 151 (1960).
➡ M. McCarty and O. T. Avery, *J. Exptl. Med.* **83**, 89 (1946); G. Schramm and A. Gierer in *Cellular Biology, Nucleic Acids and Viruses* (New York Academy of Sciences, New York, 1957), vol. 5, p. 2 ➡ K. Sprunt, S. Koenig, H. E. Alexander, *Virology* **13**, 135 (1961); J. Polatnick and H. L. Bachrach, *Proc. Soc. Exptl. Biol. Med.* **105**, 486 (1960).
50. H. H. Henstell, R. L. Freedman, B. Ginsburg, *Cancer Research* **12**, 346 (1952); S. H. Goodgal and R. M. Herriott, *Federation Proc.* **15**, 1923 (195 ➡ L. Lerman and L. Tolmach, *Biochim. et Biophys. Acta* **26**, 68 (195 ➡ M. Fox and R. D. Hotchkiss, *Nature* **187**, 1002 (1960); S. H. Goodgal and R. M. Herriott, *J. Gen. Physiol.*, in pre ➡ F. M. Sirotnak and D. J. Hutchinson, *Biochim. et Biophys. Acta* **36**, 246 (195 ➡ S. M. Gantler, *Nature* **184**, 1505 (1959); E. Borenfreund and A. Bendich, *J. Biophys. Biochem. Cytol.* **9**, 81 (1961).
51. J. E. Smadel, in *Viral and Rickettsial Infections of Man*, T. M. Rivers and F. L. Horsfall, Jr., Eds. (Lippincott, Philadelphia, ed. 3, 1959), chap. 1.
➡ N. B. Kurnick, *Arch. Biochem. Biophys.* **43**, 97 (1953).
53. A. Lwoff, *Bacteriol. Revs.* **23**, 109 (1959).
54. J. D. Ebert and F. H. Wilt, *Quart. Rev. Biol.* **35**, 261 (1960).

Financing Scientific Research in Australia

Federal funds and research agencies play a dominant role in the national research effort.

S. Encel

The character of scientific research in Australia must be understood in relation to a continent presenting enormous natural difficulties for European settlement. It is far from Europe and North America (Sydney, the largest city, is 12,000 miles from London). Two-thirds of its area of nearly 3 million square miles is virtually uninhabitable. In 1939 the population was close to 7 million; in 1959, after a decade of the most rapid growth in its history, the figure reached 10 million—less than that of Greater New York. The combination of geographical remoteness, difficult terrain, limited rainfall, limited natural resources, and sparse population has meant a slow rate of growth. In particular, it meant a slow rate of industrialization up to 1939, with primary production (of minerals and of pastoral and farm products) greater than the total output of secondary industry. Since World War II, secondary industry has come to account for a higher proportion of gross national product than primary industry, but Australia's prosperity still depends heavily on exports of wool and farm products, which provide 75 to 80 percent of export income. This income has generally been sufficient to support a high standard of living, especially since it has occurred in conjunction with a pattern of governmental economic intervention sometimes described as "state socialism" (*1*), whose effect has been to maintain a high level of wages (surpassed only in North America).

Industrial growth, hampered by the small internal market, by limitations in raw materials, and by remoteness from possible export markets, has been particularly dependent on high tariffs and on the large-scale investment of

The author is a senior lecturer in political science and public administration at the Australian National University, Canberra City, in the School of General Studies.