The Defensive Role of the Interferon System

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ABSTRACT The evidence relating the interferon system to the infectious process has been examined. The available evidence supports the view that the interferon system is an important component of the body's nonimmune defenses, which are probably the major causes of recovery from already established virus infections of body tissues. The interferon system can also serve to limit virus spread through the bloodstream. Factors which may influence the interferon system and thereby influence virus infection have been considered. Finally, evidence is presented which indicates that the interferon system is one of the determinants of virulence of certain viruses and is one of the determinants of some persistent virus infections.

The discovery of interferons by Isaacs and Lindenmann (1) led, within a short time, to major revisions in concepts of cellular immunity and recovery of multicellular organisms from infection. The significance of the antiviral effect of the interferon system extends to virus infections of the acute, chronic, and oncogenic varieties. More recent evidence suggests that the interferon system may play a role during infection by Chlamydia and certain protozoal parasites. This section will consider the implications of the interferon system as a host defense during infection. Several reviews contain related information (2–9). A more detailed consideration of the various host defenses during viral infection will be published (10).

COMPONENTS OF THE INTERFERON SYSTEM

The term "interferon system" is used because this anti-infectious mechanism is now thought to be divisible into several components. For the present purposes we will refer to interferon as a protein(s) which is produced or released by cells following viral infection and certain other stimuli. Available evidence suggests that interferon is not itself directly antiviral, but rather, it reacts with cells to induce the formation of a new intracellular substance which mediates the antiviral activity. This antiviral component of the interferon system may be a polypeptide or a protein.
Production of interferon by the infected cell is thought to be preceded by derepression of the interferon cistron, leading to formation of interferon messenger RNA which then results in production of interferon protein. Completed interferon is rapidly released by cells. Production of the proposed antiviral substance, after reaction of cells with interferon, is similarly thought to be preceded by derepression of another cistron and formation of messenger RNA which is then translated into a polypeptide. There is little evidence to help determine whether the polypeptide is itself the antiviral substance in the resistant cell, or whether it controls formation of an antiviral substance. Fig. 1 summarizes these interactions.

The interferon system is the earliest appearing of the known host defenses in that it can be detected to be operative within hours after infection (3). Most viruses are able to induce interferon to a greater or lesser extent, and most viruses are sensitive to its antiviral action also to a greater or lesser extent.

**Figure 1.** How interferon works. Current concepts of the mechanisms of the interferon system.

The antiviral action of interferon is intracellular and may relate to an inhibition of the functioning of the viral messenger RNA with the cells ribosomes. The duration of activation of the interferon system (interference) is from 1 to 3 wk during acute virus infections in vivo (11–13).

The concepts of the sequential formation of the components of the interferon system are presented so they may serve as the basis for some of the subsequent interpretations.

**ROLE OF INTERFERON DURING ESTABLISHMENT OF VIRAL INFECTION AT THE IMPLANTATION SITE**

Successful infection at the implantation site requires that viruses replicate in the initially infected cell and then spread to infect other cells within the same tissue. The first host defense to make its appearance is the interferon system (2, 3). It is produced by infected cells at about the same time as virus is produced. Replication of virus in the initially infected cell is probably not
affected by the interferon system. The interferon mechanism which is activated within the infected cell probably does not inhibit virus infection within that cell. This comes from the finding that inhibition of interferon production by metabolic inhibitors in virus-infected cells does not significantly increase the virus yield during a one-step growth cycle (14).

The interferon protein is released from infected cells as it is produced and diffuses to surrounding cells where it activates the production of the antiviral state. In this way spreading virus meets an intracellular barrier to its continued replication. The degree of antiviral activity is probably dependent on the extracellular concentration of interferon (15), so the cells in closest contact with the infected, interferon-producing cells become most resistant to virus. Protection of more distant cells does occur but to a lesser degree (16, 17). The interferon defense functions in this manner not only in infected tissues at the portal of entry, but in any infected tissue as considered below.

Successful establishment of viral infection at the implantation site sometimes leads to disease in that same tissue (e.g., influenza infection of the lung, rhinovirus infection of the nasal tract, and wart virus infection of the skin). For other viruses the established infection at the portal of entry serves as a dissemination site for spread to other organs and tissues where the disease symptoms originate.

**ROLE OF INTERFERON DURING SPREAD OF VIRUS TO DISTAL TISSUES AND ORGANS**

Virus may spread from the portal of entry to target organs by means of body fluid (serum or lymph) or by means of infected cells. Interferon appears in serum within a few hours after the onset of viremia (17). Experiments utilizing passive transfer of interferon indicate that the circulating interferon can act to both reduce the viremia and to reach target organs where it protects cells against subsequent seeding of virus from the bloodstream and lymph (17–19).

Spread of virus may also occur via infected cells such as those in nerves and via white blood cells. Spread of infection along a nerve has not been studied in terms of the interferon defense. However the possible role of the interferon mechanism may be surmised from other knowledge. Spread of virus along the sheath surrounding the axon would be expected to be resisted in the same way as is virus spread during early infection of any tissues (see above). Spread of virus within a nerve axon could be retarded only by intracellularly active defense mechanisms. The interferon defense might be less effective in this situation because activation of the interferon system would be delayed until virus or interferon reaches the distant nucleus of the nerve cell to derepress the cistron encoded for antiviral protein.

Virus may also spread by infected white blood cells, which, due to their mobility, could deposit infectious virus in target organs. Several of the host
defenses have been shown to affect the ability of leukocytes to support virus
growth. The lymphoid series of cells in the body are particularly sensitive to
the induction of interferon in that a broad range of viral and nonviral stimuli
can induce these cells. The ready response of interferon production has also
provided the first known bridge between the immunological system and the
interferon system and will be considered in the section by Dr. L. Glasgow.

**ROLE OF INTERFERON DURING RECOVERY FROM
THE FULLY ESTABLISHED VIRUS INFECTION OF
BODY TISSUES AND ORGANS**

Virus may establish an infection in various tissues within the body including
the implantation site, tissues in contact with the vascular system, and target
organs. It seems probable that the mechanisms which govern the recovery
from the fully infected tissue apply at these diverse sites of established infec-
tion. The recovery process may not occur simultaneously within the various
infected tissues in the body because the time of onset of infection and time of
production of localized host defenses is usually different for the different
tissues. In this way, tissues at the implantation site or tissues in contact with
the vascular system may be undergoing recovery at the time that virus infec-
tion is being established within the target organs (20–22).

The finding that a major characteristic of the recovering tissue is nonspecific
resistance to viral superinfection indicates that nonimmune defenses like
interferon are correlated temperally with recovery from the established infec-
tion. Fig. 2 schematizes the relative occurrences of virus growth, disease,
interferon, and antibody during the first and during a repeat infection. Sup-
porting evidence comes from many sources.

A sufficient quantity of interferon can inhibit the multiplication of most
viruses in various animal tissues in vivo and in vitro (3). Interferon is generally
present in infected tissues of animals prior to the onset of recovery from diverse
virus infections (23–33). Similar results have been obtained in studies in man
(8, 34). These studies have demonstrated that interferon can be produced as
early as 1 hr after virus infection and is generally demonstrable in high titer
within 1–2 days. In comparison, recovery, as measured by decreasing virus
in the infected tissue, usually begins 1 or more days after interferon is first

![Figure 2. Host reaction to viral infection. Appearance of virus, interferon, and antibody during virus infection.](image-url)
detected. The presence of interferon in target organs during recovery is evidenced by these same studies and also by others (35–37). Apparently, inconsistent findings are the low or undetectable levels of interferon in organs of mice during certain nonlethal infections (38–43). But some of these viruses may have been very sensitive to interferon. Hence, interferon produced by cells originally infected may have so reduced virus multiplication that little or no detectable amounts of interferon were formed (44). The finding that tissues of mice which were chronically infected with lymphocytic choriomeningitis virus manifested interference in the absence of detectable interferon (38) suggests either the possibility of another antiviral factor, or that the antiviral portion of the interferon system may have been functioning despite the absence of detectable interferon as discussed above.

Further evidence relating the interferon system to recovery comes from the expectation that decreased function of the interferon mechanism would increase the severity of those virus infections in which it contributes significantly towards recovery. Such were the findings in young chick embryos with an “immature” interferon system (45). More recent studies have extended the evidence. Decreased function of the interferon system, as caused by altered temperature, psychological stress, chemical inhibitors, and different virus strains, led to impaired recovery of animals (30, 46–49). Carefully controlled studies of tissue cultures infected with vaccinia, herpes, measles, or arboviruses also indicate that impairment of the interferon mechanism hinders recovery (50–54).

The effect of specific decrease in the functioning of the interferon mechanism is clearly demonstrated in studies of arbo B virus infection of two strains of C3H mice (44). C3H and C3H RV mice are known to differ only at the genetic locus which determines resistance to infections with arbo B viruses. They produce equal amounts of interferon after arbo B virus infection, but the virus-resistant C3H RV cell cultures and the intact mice were much more sensitive to the inhibitory effect of interferon when tested with arbo B viruses than were the C3H cultures or mice. The increased effectiveness of interferon was limited to arbo B viruses. Thus a genetic difference in interferon responsiveness determined the severity of virus infection both in tissue culture and in the intact mouse. This study also points out the problem in interpreting the role of interferon only from interferon production findings (55), since cell responsiveness to interferon can also be a determining factor.

Another test of the relationship of the interferon system to recovery is the transfer of presently available amounts of interferon to animals. These early studies demonstrated greatest protection when interferon was given prior to or at the same time as infection and not when interferon was given significantly after infection (56–63). More recently treatment with large amounts of interferon or inducers of interferon was shown to retard the development of estab-
lished infections with encephalomyocarditis virus, leukemia virus, herpes simplex virus, and other viruses. Analogously, production of interferon by virus-resistant cells in a mixed tissue culture can protect the virus-susceptible fraction of the cell population (64). The failure of interferon to protect man against subsequent rhinovirus infection (65), unlike the previously reported protection against subsequent vaccinia virus infection (59), may have been due to dosage problems.

Taken together most of the available evidence does support a causal relationship between the interferon system and recovery from established infections. The available evidence also indicates that interferon is not the sole factor which influences recovery, and in certain virus infections it may not be the most important factor (10).

INTERPLAY OF INTERFERON WITH OTHER FACTORS DURING INFECTION

The possibility has been raised that nonimmune antiviral factors may affect the interferon system as well as directly inhibit virus multiplication (66). Certain ones will be briefly considered here in relation to recovery from virus infection. For example, lowered or raised temperature may respectively depress or enhance the interferon system during infections in vitro and in vivo (47, 53, 66, 67). Changes in pH and oxygen tension have been reported to enhance or retard production of the interferon system in certain, but not all, virus infections in vitro (68-72).

Other mechanisms may also affect the interferon system. Corticosteroids have been reported to inhibit the interferon system in several, but not all, virus infections in ovo and in vitro (73-75). The effect of psychological stress on inhibiting production of interferon and increasing the severity of vesicular stomatitis virus and polyoma virus infections of mice may have a hormonal basis (48).

It has been observed that cells and animals which have yielded interferon may not yield again for a period of time on restimulation by virus (76-79). Hyporeactivity to release of interferon by endotoxin may be due to a circulating inhibitor of endotoxin in the rabbit (77, 80). The significance or hyporeactivity during virus infection is yet to be determined.

Another factor which has been reported to influence the interferon system is the age of the animal. Tissues from young chick and mouse embryos were generally found to have a poorly functioning interferon system (45, 81-83), and this system has been shown in mice to continue to develop through the neonatal period (84-85). Several of these investigators have suggested that lack of effectiveness of the immature interferon system may be one factor which contributes to the malforming effects of some virus infections of the fetus and to unusually severe infections during the neonatal period (7). In-
consistent is the finding that lymphocytes from young human embryos have been found to produce normal amounts of interferon (K. Cantell and H. Strander, 1969, personal communication.).

Results of several studies have indicated that pretreatment of cells with interferon influences the subsequent production of interferon by infected cells (86–88). Chicken and mouse cells treated with small amounts of interferon and then infected with virus produce substantially more interferon than do cells not previously treated with interferon. Pretreatment with large amounts of interferon has the reverse effect of decreasing subsequent production of interferon. It was also observed that chicken cells pretreated with small amounts of interferon not only produced increased amounts of interferon after infection, but they produced interferon and its messenger RNA substantially earlier than cultures which had not been pretreated (89, 90). Such an enhanced response bears a superficial resemblance to an immunological booster effect and may similarly act to amplify the interferon defense mechanism.

Some viruses may inhibit the interferon system by causing a general depression of the cellular RNA or protein synthesis which seems to be required for production of both interferon and the proposed antiviral substance. For example, mengo virus has been reported to produce two distinct proteins which respectively inhibit cellular synthesis of RNA and protein (91). Similar inhibition of cellular RNA synthesis following infection of cells by herpes simplex and vesicular stomatitis viruses has been correlated with decreased production of interferon (92, 93). Inhibition of the interferon system before production of the antiviral substance could act to prevent the action of this antiviral mechanism. However, prior establishment of the antiviral effect has been reported to retard the virus-induced inhibition of cellular synthesis of RNA (94, 95). The significance of these phenomena in relation to virulence of viruses and pathogenesis of infection deserves further study. It also raises the possibility that infection of an animal by a virus which inhibits synthesis of components of the interferon system could increase the severity of a subsequent infection by another virus.

A natural experiment which illustrated an interplay of these host defense factors is the human disease syndrome hypogammaglobulinemia (see reference 7). Impairment of production of normal amounts of antibody by these patients is believed to result in increased frequency and severity of certain pyogenic bacterial infections as well as a lesser increase in severity of certain virus infections. The small amount of antibody produced by these patients is sufficient to account for a resistance to the spread of many viruses through the bloodstream and, therefore, can account for the immunologically specific resistance to reinfection observed in these patients. Since the nonimmune and nonspecific defense factors are largely independent of the immune response, the ability of hypogammaglobulinemic patients to recover normally from
established virus infection is probably due to normally functioning cellular immunity (see reference 7), interferon (96), body temperature control, inflammatory responses, etc. The occasionally observed increased severity of virus infections in these patients (e.g. vaccinia virus and poliomyelitis infections) might be explained by impaired antibody production during the viremic spread of virus in the primary infection with resulting prolonged viremia and increased seeding of target organs.

THE INTERFERON SYSTEM AS A FACTOR IN THE VIRULENCE OF VIRUSES

If the interferon system plays an important role in the body's defense against virus infection, then it should be an important determinant of virus virulence (97). A virulent virus will be considered as one which causes relatively more damage to the infected host system than do other strains of the same virus type.

The definition of virus sensitivity to the antiviral action of interferon becomes critical in any comparison with virulence of viruses. Certain viruses like adenoviruses (98, 99), herpes viruses, including cytomegaloviruses (100, 101), have been considered to be relatively resistant to the antiviral action of interferon. It recently has been found however that cell-free human cytomegalovirus is highly sensitive to the antiviral action of human interferon (D. Lang, M. T. Thomas, and I. Gresser, 1969, personal communication). Similarly, in the mouse, it has been found that induction of interferon protects against very small challenge doses of herpes simplex virus as well as it does against small or large doses of the highly sensitive encephalomyocarditis virus. However, there is no protection against moderate to high doses of herpes virus (102). These findings indicate that under certain experimental conditions cytomegalovirus and herpes simplex virus may be highly sensitive to the antiviral action of interferon. It has been suggested that the production of anti-interferon factors (D. Lang, M. T. Thomas, and I. Gresser, 1969, personal communication; 103, 104) (see below) could account for the difference in sensitivity under different experimental conditions.

A highly virulent virus should not be significantly inhibited by any natural defense factors (including the interferon system) which are active during infection, and/or the virulent virus should not elicit these defensive responses. Consistent with this interpretation are the observations that the interferon system is relatively ineffective in infections with more virulent strains of certain viruses, and conversely, the interferon system is often more effective during infections with less virulent viruses. Supporting data have been obtained with strains of Newcastle disease virus (67, 105), vesicular stomatitis virus (106), Semliki Forest virus (107), rubella virus (108), mumps virus (G. Sharamek, H. Reploh, and F. Deinhardt, 1969, personal communication),
various other arboviruses (44, 67), foot-and-mouth disease virus (109), and polyoma virus (30).

It has recently been found that virulent strains of Newcastle disease virus induce little interferon during infection of chickens, but that avirulent strains induce larger amounts of interferon during infection and at the same time manifest a resistance to superinfection with Newcastle disease virus (110).

As might be anticipated from the existence of a large number of virus inhibitory factors in addition to the interferon system (111-113), there is not always such a correlation between the response of the interferon system and virulence, e.g., with strains of influenza virus (40, 42), Sindbis virus (39), Newcastle disease virus (105), and vaccinia virus (41). These reports are consistent with multiple determinants of virus virulence.

Taken together, the findings are consistent with the interpretation that the interferon system may be an important determinant of relative virulence of certain virus strains. However, definitive studies must await development of techniques for the simultaneous measurement of yield of virus, interferon, and antiviral activity per infected cell, in vitro and at different stages of infection in the intact animal.

Recent observations indicate two additional mechanisms whereby a virus may avoid the inhibitory effect of the interferon system and, perhaps, thereby manifest increased virulence. First, conditions of infection by herpes simplex virus (92) and vesicular stomatitis virus (93), which lead to inhibition of cellular RNA synthesis, suppress the synthesis of components of the interferon system while enhancing yields of virus. The phenomenon of “inverse interference” (114) may have a similar basis. That inhibition of cellular RNA synthesis is not the sole means by which virus may cause decreased production of interferon is suggested by the findings that avirulent strains of Newcastle disease virus and parainfluenza type 3 virus failed to induce interferon production in cells, although no cytopathology occurred (105, 115, 116). Absence of cytopathology suggests that there was no significant inhibition of RNA synthesis during the growth of these viruses. Mouse leukemia virus and mouse cytomegalovirus infections are other examples (117, 118). These findings indicate that certain cell–virus interactions do not lead to production of much interferon, as a result either of inhibition by virus of cellular synthetic processes or of unknown mechanisms. The relationship between ability of virus to inhibit the response of the interferon system and virulence merits further study.

A second mechanism whereby virus may overcome the inhibitory effect of the interferon system is the reported existence of a fraction of virus populations which is resistant (104, 119). It was observed that a fraction of an encephalomyocarditis virus population, varying from 10 to 15% of the input virus, was capable of multiplying in interferon-treated mouse embryo cultures (104). The resistance of this “persistent fraction” to interferon was not due
to a genetic property of the virus, and superficially it resembled similar phenomena observed with most other virus-inactivating agents (120). Vesicular stomatitis virus and vaccinia virus were also shown to contain interferon-resistant persistent fractions. The magnitude of the persistent fraction may vary depending on the virus, type of cell, as well as on the cellular environment. A large persistent fraction of this type could exert an important influence on virulence of infection, but such studies are yet to be carried out in vivo.

ROLE OF THE INTERFERON SYSTEM IN PERSISTENT INFECTIONS

Persistent infection in vitro and in vivo may result from infection of genetically resistant cells, from antibody or other virus inhibitors in extracellular fluids, from interference and interferon, and from unknown factors (121). Several persistent infections of tissue cultures are thought to be caused by the interferon system, although only a few definitive studies have been reported. Interferon has been detected at very early and at advanced stages of persistent infection of mouse L cells with Newcastle disease virus (122–124), human amnion and KB cells with poliovirus (125), calf kidney cells with the WS strain of influenza virus and with foot-and-mouth disease virus (126, 127), KB cells with parainfluenza type 3 virus (128), mouse embryo cells with vaccinia virus (50), human amnion and mouse L cells with tick-borne encephalitis virus (53, 129), mouse 23 P cells with polyoma virus and with herpes simplex virus (90), and monkey cells with rubella virus (130). Similar results have been observed during the early period of infection of mice with lactic dehydrogenase virus (32). Interferon was found during the later stages of persistent infection of mouse cell cultures with polyoma viruses; tests for it were not made during the early stages (131). Neither interferon nor significant interference of the interferon type was detected in mouse L-cell cultures persistently infected with polyoma virus (123, 132), in chicken cells infected with RAV leukemia virus (133), or in mouse cells infected with murine leukemia viruses (134), suggesting that the interferon system did not participate in the maintenance of these carrier cultures. Persistent infections of mice or of mouse L-cell cultures with lymphocytic choriomeningitis virus did not give rise to detectable interferon but did result in interference (38). However, the precise times of sampling of these persistently infected mice were not stated, and it is possible that interferon was produced during the initial stages of infection as it is during infection with lactic dehydrogenase virus. The demonstration of interference when no or only low levels of interferon can be detected does not exclude an important role for the interferon system during these persistent infections. It is conceivable that (a) the rapid turnover rate of interferon in vivo (17, 19, 135) reduces levels below detectability, or (b) intracellular inter-
feron in amounts which cannot be detected may still be highly effective (53, 136).

Further evidence linking the interferon system to persistent infections comes from studies of inhibition or enhancement of the interferon system during persistent infections. Enhancement of the interferon mechanism retarded multiplication of vaccinia virus, herpes simplex virus, and tick-borne encephalitis virus during persistent infections in mouse cell cultures (50, 53, 88). Similarly in mice, stimulation of the interferon system inhibited the growth of lactic dehydrogenase virus (137). Conversely, inhibition of the interferon mechanism by several techniques was followed by enhanced virus growth and increased cell destruction in persistently infected mouse cell cultures (50, 53, 88). In general, the resistance of persistently infected cultures was nonspecific for virus—a property coinciding with that of the interferon system. The quantity of interferon was shown to be sufficient to account for the observed inhibition of herpes simplex virus during persistent infection of mouse cell cultures with both herpes simplex and polyoma viruses (88). Studies with other viruses and cells are needed to establish that the antiviral activity of the interferon system is quantitatively sufficient to account for persistent infections. Another difficulty is that certain persistently infected cell cultures which manifest interference produce interferon but are not sensitive to the action of exogenous interferon (53, 125, 128, 129). It is possible that the interferon produced within the infected cells is better able to induce the antiviral state than is exogenous interferon.

Several of these investigators and others (138) have suggested that those persistent infections which are dependent upon the interferon system may result from a shifting balance between antiviral activity and virus multiplication. Specifically, increasing multiplication of virus in a persistently infected system induces increased production of interferon and antiviral activity, which prevents further increase of virus. Conversely, decreasing multiplication of virus results in decreased interferon and antiviral activity, which then permits increase of virus multiplication.

That the interferon system may be participating in naturally occurring persistent infections comes from several studies. Interferon was produced by cultured cells from three different cases of human malignant lymphoma (139, 140). Herpes simplex virus-like particles are frequently found in these cells by electron microscopy (141). Another example is the observation that cultures from normal chick embryos can initiate production of interferon (R. Z. Lockart, Jr., and T. Sreevalsan, 1965, personal communication). Since many flocks of chickens are persistently infected with leukosis viruses (142) and perhaps other viruses, it is possible that the interferon production resulted from a persistent infection in ovo.

Taken together, the available evidence favors the view that the interferon
system is an important determinant of certain persistent infections in vitro and in vivo. However, further studies are needed to determine what proportion of persistent infections it influences.

**APPLICATION TO CONTROL OF VIRAL DISEASE**

Medical science has very effectively adapted the natural antibody defense against viral spread and reinfection to prevent but not to treat viral infections. The natural antibody defense is nontoxic, and so application has been achieved with minor problems of toxicity. Antibody has been applied to disease prophylaxis both by passive transfer of antibody and by vaccine stimulation of antibody. However, a major limitation of the application of the antibody defense is a lack of effectiveness of antiviral antibody after the establishment of infection of the target organs. A classic example is the ability of antibody to prevent measles infection of children when the antibody is given early after exposure to virus, but as the incubation period of measles progresses the amount of antibody required to influence the oncoming disease increases rapidly. Towards the end of the incubation period of measles no amount of antibody provides protection. Thus antibody against measles virus loses its effectiveness as the onset of the established disease approaches.

By analogy it had been predicted that the interferon defense system which is thought to naturally promote recovery could be applied to both prevent and treat virus infection (c.f. 2, 3, 7, 9, 143–145). Also, as a natural defense mechanism, toxicity should be minimal. It has already been demonstrated that interferon can prevent a broad range of virus infections. However, until recently the limitation of the quantity of interferon which could be produced and the species barrier to the action of interferon have prevented therapy of established infections (145). These limitations have also prevented practical prophylaxis of viral infections of man. As a result many studies have concentrated on the development of chemicals which induce the body to produce large amounts of its own interferon. Beginning with Isaacs and his coworkers (68), it has been shown that such inducers can be found and that some of them are relatively nontoxic and inexpensive. These inducers include extracts of microorganisms, such as statolon (146). Also included are the synthetic pyran copolymers (147) and natural and synthetic ribonucleic acids (148, 149). Certain of the RNA inducers of the interferon mechanism are extremely potent. The therapeutic efficacy of RNA inducers of interferon in herpes keratoconjunctivitis has been studied (150) (Fig. 3). Fig. 3 shows that rabbits with herpes infections of the eye may be treated with interferon inducers after establishment of the disease with resulting enhanced recovery from the infection.

Quite recently it has been found that inducers of interferon will protect against certain protozoal parasites (151–153). This aspect will be considered in this session by Dr. Jahiel.
It has been reported that the interferon inducer, polyinosinic: polycytidylic acid (154) inhibits the growth of a number of experimental tumors in animals. Most of the tumor types were not deliberately induced by virus, but rather, they were transplanted tumors of spontaneous origin or induced by chemical carcinogenesis (154–158). This compound, in addition to inducing interferon, enhances cell mediated graft vs. host reactions and may have direct specific chemotherapeutic action against some of the tumors. It is not yet clear how much of the antitumor action is attributable to the interferon system, but it should be pointed out that it has also been shown that interferon preparations exert strong antitumor action when tested against tumors of virus origin (159), and even against tumors induced by a chemical carcinogen (160).

REFERENCES

1. ISAACS, A., and J. LINDENMANN. 1957. Virus interference. I. The interferon. Proc. Roy. Soc. Ser. B Biol. Sci. 147:258.
2. BARON, S. 1963. Mechanism of recovery from viral infection. Advan. Virus Res. 10:39.
3. ISAACS, A. 1963. Interferon. Advan. Virus Res. 10:1.
4. RITA, G., M. RUSI, F. BIANCHI BARDINELLI, and F. DIANZANI. 1963. Fattori biologici della interferenza virale: L'interferone. Atti Congr. Naz. Microbiol., 12th, Perugia. 12:9.
5. GLASGOW, L. A. 1965. Interferon: a review. J. Pediat. 67:104.
6. WAGNER, R. R. 1965. Interferon. A review and analysis of recent observations. Amer. J. Med. 38:726.
7. BARON, S. 1967. Host defenses during virus infection. In Modern Trends in Medical Virology. Butterworth & Co. Ltd., London. 77.
8. WHEELOCK, E. F., R. P. LARKE, and N. L. CORSLINE. 1968. Interference in human viral infections: Present status and prospects for the future. Progr. Med. Viral. 10:236.
9. LEVY, H. B., S. BARON, and C. E. BÜCKLER. 1969. Biochemistry of interferon. In Biochemistry of Viruses. H. B. Levy, editor. Marcel Dekker, Inc., New York. 579.
10. BARON, S. 1970. The defensive and biological roles of the interferon system. In The Interferons. N. Finter, editor. North Holland Publishing Co., Amsterdam. In press.
11. SCHLESINGER, R. W., P. K. OLITSKY, and I. M. MORGAN. 1943. Observations on acquired cellular resistance to equine encephalomyelitis virus. Proc. Soc. Exp. Biol. Med. 54:272.
12. SCHLESINGER, R. W., P. K. OLITSKY, and I. M. MORGAN. 1944. Induced resistance of the central nervous system to experimental infection with equine encephalomyelitis virus. III. Abortive infection with Western virus and subsequent interference with the action of heterologous viruses. J. Exp. Med. 80:197.
13. DUFFY, C. E., and P. N. MORGAN. 1953. Interval between inoculations as a factor in interference between neurotropic viruses. Proc. Soc. Exp. Biol. Med. 84:298.
14. Friedman, R. M. 1964. Role of interferon in viral interference. Nature (London). 201:848.
15. Baron, S., C. E. Buckler, H. B. Levy, and R. M. Friedman. 1967. Some factors affecting the interferon-induced antiviral state. Proc. Soc. Exp. Biol. Med. 125:1320.
16. Grossberg, S. E., E. W. Hooke, and R. R. Wagner. 1962. Hemorrhagic encephalopathy in chick embryos infected with influenza virus. III. Viral interference at a distant site induced by prior allantoic infection. J. Immunol. 88:1.
17. Baron, S., C. E. Buckler, R. V. McCloskey, and R. L. Kirschstein. 1966. Role of interferon during viremia. I. Production of circulating interferon. J. Immunol. 96:12.
18. Baron, S., C. E. Buckler, R. M. Friedman, and R. V. McCloskey. 1966. Role of interferon during viremia. II. Protective action of circulating interferon. J. Immunol. 96:17.
19. Finter, N. B. 1966. Interferon as an antiviral agent in vivo: Quantitative and temporal aspects of the protection of mice against Semliki Forest virus. Brit. J. Exp. Pathol. 47:261.
20. Hurst, E. W. 1936. Infection of the rhesus monkey (Macaca Mulatta) and the guinea-pig with the virus of equine encephalomyelitis. J. Pathol. Bacteriol. 42:271.
21. Fenner, F. 1965. In Viral and Rickettsial Infections of Man. F. L. Horsfall and I. Tamm, editors. J. B. Lippincott Co., Philadelphia, Pa. 356.
22. Wenner, H. A., C. Bolano, C. T. Cho, and P. S. Kamitsuka. Monkey Pox. IV. Modification of disease pattern by antilymphocytic sera. J. Infe. Dis. 120:318.
23. Isaacs, A., and G. Hitchcock. 1960. Role of interferon in recovery from virus infections. Lancet. II:69.
24. Hitchcock, G., and J. S. Porterfield. 1961. The production of interferon in brains of mice infected with an arthropod-borne virus. Virology. 13:363.
25. Line, F., and J. Raub. 1961. Multiplication of mouse-adapted influenza virus in mouse lungs after infection with very low doses. Nature (London). 192:478.
26. Wagner, R. R. 1961. Biological studies of interferon. I. Suppression of cellular infection with Eastern equine encephalomyelitis virus. Virology. 13:323.
27. Friedman, R. M., S. Baron, C. E. Buckler, and R. I. Steinmuller. 1962. The role of antibody, delayed hypersensitivity and interferon production in recovery of guinea pigs from primary infection with vaccinia virus. J. Exp. Med. 116:347.
28. Verlinde, J. D., and A. Kret. 1963. On the formation of a substance with the characteristics of interferon in the brains of mice infected intracerebrally with vaccinia virus. Acta Leidensia Scholae Medicinae Tropic. 32:297.
29. Baron, S., and C. E. Buckler. 1963. Circulating interferon in mice after intravenous injection of virus. Science (Washington). 141:1061.
30. Friedman, R. M., and A. S. Rabson. 1964. Possible role of interferon in determining the oncogenic effect of polyoma virus variants. J. Exp. Med. 119:71.
31. Mallucci, L. 1964. Mouse hepatitis virus and interferon production in normal and regenerating liver. Arch. gesamte Virusforsch. 15:91.
32. Baron, S., H. G. duBoy, C. E. Buckler, and M. L. Johnson. 1964. Relationship of interferon production to virus growth in vivo. Proc. Soc. Exp. Biol. Med. 117:238.
33. Force, E. E., R. C. Stewart, and R. F. Haff. 1965. Development of interferon in rabbit dermis after infection with herpes simplex virus. Virology. 25:322.
34. Jao, R. L., E. F. Wheeler, and G. G. Jackson. 1965. Interferon study in volunteers infected with Asian influenza. J. Clin. Invest. 44:1062.
35. Grether, I., and H. B. Dull. 1964. A virus inhibitor in pharyngeal washings from patients with influenza. Proc. Soc. Exp. Biol. Med. 115:192.
36. Wheeler, E. F. 1964. Interferon in dermal crusts of human vaccinia virus vaccinations. Possible explanation of relative benignity of variolation smallpox. Proc. Soc. Exp. Biol. Med. 117:650.
37. Knight, V., W. F. Fleet, and D. J. Lang. 1964. Inhibition of measles rash by chickenpox. J. Amer. Med. Ass. 188:690.
38. Wagner, R. R., and R. M. Snyder. 1962. Viral interference induced in mice by acute or persistent infection with the virus of lymphocytic choriomeningitis. Nature (London). 196:393.
39. VILŽEK, J. 1964. Production of interferon by newborn and adult mice infected with Sindbis virus. *Virology.* 22:651.
40. LINK, F., D. BLASKOVIC, and J. RAUS. 1965. Relationship between virus multiplication and interferon production in mouse lungs after infection with adapted and unadapted influenza. *Acta Virol.* 9:295.
41. LINK, F., D. BLASKOVIC, J. RAUS, and P. ALBRECHT. 1965. Investigations into the adaptation of a Neurovaccinia virus to mouse lungs. *Acta Virol.* 9:323.
42. INGLOT, A. D., M. LOBODZINSKA, I. BIERNACKA, and E. NIEDZWIEDZKA. 1966. Changes in the production of interferon in the process of adaptation of influenza type A5 virus to the mouse lung. *Arch. Immunol. Ther. Exp.* 14:333.
43. POLLIKOFF, R., M. LIEBERMAN, and N. E. LEM. 1965. Role of interferon and partial immunity in influenza virus infection of mouse lung. *Proc. Soc. Exp. Biol. Med.* 119:790.
44. HANSON, B. H., KOPROWSKI, S., BARON, and C. E. BUCKLER. 1969. Interferon-mediated natural resistance of mice to arbo B virus infection. *Microbios.* IB:51.
45. BARON, S., and A. ISAACS. 1961. Mechanism of recovery from viral infection in chick embryo. *Nature (London).* 191:97.
46. POSTIC, B. 1965. Studies of the role of interferon in experimental infections of mice with Sindbis virus. Doctoral Dissertation. University of Pittsburgh, Pittsburgh, Pa. 1.
47. RUIZ-GOMEZ, J., and J. SOSA-MARTINEZ. 1965. Virus multiplication and interferon production at different temperatures in adult mice infected with coxsackie B1 virus. *Arch. gesamte Virusforsch.* 17:295.
48. CHANG, S. S., and A. F. RASMUSSEN, JR. 1965. Stress-induced suppression of interferon production in virus-infected mice. *Nature (London).* 205:623.
49. SoLovYov, V. D., and L. M. MENTKEVICH. 1965. The effect of colchicine on viral interference and interferon formation. *Acta Virol.* 9:298.
50. GLASGOW, L. A., and K. HABEL. 1962. The role of interferon in vaccinia virus infection of mouse embryo tissue culture. *J. Exp. Med.* 115:503.
51. WADDELL, G. H., M. M. SIGEL, and M. WRYK. 1963. Factors associated with the response of the cell to herpes simplex virus. *Bacteriol. Proc.* 1963:150.
52. ANDERSON, C., and J. ATHERTON. 1964. Effect of actinomycin D on measles virus growth and on interferon production. *Nature (London).* 203:571.
53. STANCEK, D. 1965. The role of interferon and tick-borne encephalitis virus-infected L-cells. 3. The effects of temperature on the production of virus and interferon by L cells during acute and persistent infection. *Acta Virol.* 9:298.
54. FAUCONNIER, B. 1968. Stimulation of viral multiplication by antiinterferon serum influence on the number of plaques. *C. R. Hebld. Sances Acad. Sci. Paris.* 267:2241.
55. VANNO, T., R. Gwatkin, and H. Koprowski. 1961. Production of interferon by brains of genetically resistant and susceptible mice infected with West Nile virus. *Virology.* 14:385.
56. ISAACS, A., and M. A. WESTWOOD. 1959. Inhibition by interferon of the growth of vaccinia virus in the rabbit skin. *Lancet.* II:324.
57. Hitchcock, G., and A. ISAACS. 1960. Protection of mice against the lethal action of an encephalitis virus. *Brit. Med. J.* II:1268.
58. CANTHEL, K., and V. TOMMILA. 1960. Effect of interferon on experimental vaccinia and herpes simplex virus infections in rabbits' eyes. *Lancet.* II:682.
59. SCIENTIFIC COMMITTEE ON INTERFERON. 1962. Effect of interferon on vaccination in volunteers. *Lancet.* 1:873.
60. Denys, P., Jr. 1963. Protective effect of interferon in rats infected with Sindbis virus. *Lancet.* II:174.
61. Lampson, G. P., A. A. TYTELL, M. M. NEMES, and M. R. Hilleman. 1963. Purification and characterization of chick embryo interferon. *Proc. Soc. Exp. Biol. Med.* 112:463.
62. Finter, N. B. 1964. Protection of mice by interferon against systemic virus infections. *Brit. Med. J.* II:931.
63. BOUDREAULT, A., and V. PAVILANS. 1964. Observations on the protective action of interferon in vivo. *Rev. Can. Biol.* 23:277.
64. Gresser, I., and J. F. Enders. 1962. Alteration of cellular resistance to Sindbis virus in mixed cultures of human cells attributable to interferon. *Virology*. 16:428.

65. Scientific Committee on Interferon. 1965. Experiments with interferon in man. *Lancet*. 1:1055.

66. Isaacs, A. 1962. Production and action of interferon. *Cold Spring Harbor Symp. Quant. Biol.* 27:343.

67. Ruiz-Gomez, J., and A. Isaacs. 1963. Optimal temperature for growth and sensitivity to interferon among different viruses. *Virology*. 19:8.

68. Isaacs, A., S. Baron, and A. C. Allison as cited in: Isaacs, A. 1961. Interferon. *Sci. Amer.* 204:51.

69. DeMaeyer, E., and P. DeSomer. 1962. Influence of pH on interferon production and activity. *Nature (London)*. 194:1252.

70. Gifford, C. E. 1963. Effect of environmental changes upon antiviral action of interferon. *Proc. Soc. Exp. Biol. Med.* 114:844.

71. Burke, D. C., and A. Buchan. 1965. Interferon production in chick embryo cells. I. Production by ultraviolet-inactivated virus. *Virology*. 26:28.

72. Hallum, J. V., J. S. Youngner, and N. J. Arnold. 1968. Effect of pH on the protective action of interferon in L cells. *J. Virol.* 2:772.

73. Kilbourne, E. D., K. M. Smart, and B. A. Pororny. 1961. Inhibition by cortisone of the synthesis and action of interferon. *Nature (London)*. 190:650.

74. Reinske, V. 1965. The influence of steroid hormones and growth hormones on the effect of interferon in tissue culture. *Acta Pathol. Microbiol. Scand.* 64:167.

75. Mendelson, S., and L. A. Glasgow. 1966. The in vitro and in vivo effects of cortisol on interferon production and action. *J. Immunol.* 96:343.

76. Cantell, K., and K. Paucker. 1963. Quantitative studies on viral interference in suspended L cells. IV. Production and assay of interferon. *Virology*. 21:11.

77. Ho, M., Y. Kono, and M. K. Breeng. 1965. Tolerance to the induction of interferons by endotoxin and virus: Role of a humoral factor. *Proc. Soc. Exp. Biol. Med.* 119:1227.

78. Youngner, J. S., and W. R. Senebring. 1965. Interferon appearance stimulated by endotoxin, bacteria, or viruses in mice pre-treated with Escherichia coli endotoxin or infected with Mycobacterium tuberculosis. *Nature (London)*. 208:456.

79. Van Rossu, W., and P. DeSomer. 1965. Some aspects of the interferon production in vivo. *Life Sci.* 5:103.

80. Ho, M., and Y. Kono. 1965. Tolerance to the induction of interferons by endotoxins and virus. *J. Clin. Invest.* 44:1059.

81. Isaacs, A., and S. Baron. 1960. Antivilal action of interferon in embryonic cells. *Lancet*. 2:946.

82. Cantell, K., M. Valle, R. Schakir, J. J. Suusen, and E. Uroma. 1965. Observations on production, assay and purification of chick embryo interferon. *Ann. Med. Exp. Biol. Fenn.* 43:123.

83. Grossberg, S. E. Inducible antiviral resistance during embryogenesis. In The Proceedings of the International Symposium on Interferon, Held in Lyon, France, in 1969. C. Chany, editor. In press.

84. Sawicki, L. 1961. Influence of age of mice on the recovery from experimental Sendai virus infection. *Nature (London)*. 192:1258.

85. Heineberg, H., E. Gold, and F. C. Robbins. 1964. Differences in interferon content in tissues of mice of various ages infected with Coxsackie B3 virus. *Proc. Soc. Exp. Biol. Med.* 115:947.

86. Isaacs, A., and D. C. Burke. 1958. Mode of action of interferon. *Nature (London)*. 182:1073.

87. Lockart, R. Z., Jr. 1963. Production of an interferon by L cells infected with Western Equine encephalomyelitis virus. *J. Bacteriol.* 85:536.

88. Glasgow, L. A., and K. Habel. 1963. Role of poliovirus and interferon in a herpes simplex virus infection in vitro. *Virology*. 19:328.

89. Friedman, R. M. 1966. Effect of interferon treatment on interferon production. *J. Immunol.* 96:872.
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90. LEVY, H. B., C. E. BUCKLER, and S. BARON. 1966. Effect of interferon on early interferon production. Science (Washington). 152:1274.
91. FRANKLIN, R. M., and D. BALTIMORE. 1962. Patterns of macromolecular synthesis in normal and virus-infected cells. Cold Spring Harbor Symp. Quant. Biol. 27:175.
92. AURELIAN, L., and B. ROIZMAN. 1965. Abortive infection of canine cells by herpes simplex virus. II. Alternative suppression of synthesis of interferon and viral constituents. J. Mol. Biol. 11:339.
93. WAGNER, R. R., and A. S. HUANG. 1966. Inhibition of RNA and interferon synthesis in Krebs-2 cells infected with vesicular stomatitis virus. Virology. 28:1.
94. LEVY, H. B. 1964. Studies on the mechanism of interferon action. II. The effect of interferon on some early events in Mengo virus infection in L cells. Virology. 22:575.
95. HAASE, A. T., S. BARON, H. B. LEVY, and J. A. KASAL. 1969. Mengovirus-induced cytopathic effect in L-cells: Protective effect of interferon. J. Virol. 4:490.
96. GRESSER, I. 1961. Production of interferon by suspensions of human leucocytes. Proc. Soc. Exp. Biol. Med. 108:799.
97. ENDERS, J. F. 1960. A consideration of the mechanisms of resistance to viral infection based on recent studies of the agents of measles and poliomyelitis. Trans. Stud. Cell. Physicians Philadelphia. 28:68.
98. GALLAGHER, J. G., and N. KHOBYARIAN. 1969. Adenovirus susceptibility to interferon: sensitivity of types 2, 7, and 12 to human interferon. Proc. Soc. Exp. Biol. Med. 130:137.
99. OXMAN, M. N., W. P. ROWE, and P. H. BLAKL. 1967. Studies of adenovirus-SV40 hybrid viruses. VI. Differential effects of interferon on SV40 and adenovirus T antigen formation in cells infected with SV40 virus, adenoviruses, and adenovirus-SV40 hybrid viruses. Proc. Nat. Acad. Sci. U.S.A. 57:941.
100. GLASGOW, L. A., J. B. HANSHAW, T. C. MERRIAN, and J. K. PETRALI. 1967. Interferon and cytomegalovirus in vivo and in vitro. Proc. Soc. Exp. Biol. Med. 125:843.
101. RABON, A. S., S. A. TYRELL, and H. B. LEVY. 1969. Inhibition of human cytomegalovirus in vitro by double-stranded polyribocytidylicinosinic acid (Poly I-C). Proc. Soc. Exp. Biol. Med. 131:495.
102. CATALANO, L., and S. BARON. 1970. Protection against herpes virus and encephalomyocarditis virus encephalitis with a double-stranded RNA inducer of interferon. Proc. Soc. Exp. Biol. Med. 133:648.
103. CHANY, C. 1969. Cellular regulation of the interferon mechanism-viral antagonists. Proceedings of the Second Conference on Antiviral Substances. Ann. N. Y. Acad. Sci. In press.
104. TAKEMOTO, K. K., and S. BARON. 1966. Passive interferon protection in mouse influenza. Proc. Soc. Exp. Biol. Med. 121:5670.
105. BARON, S. 1964. Relationships of interferon and temperature to virulence of Newcastle disease virus. In Newcastle disease virus: An evolving pathogen. R. P. Hansson, editor. University of Wisconsin Press, Madison, Wis. 205.
106. WAGNER, R. R., A. H. LEVY, R. M. SNYDER, G. A. RATSFLLE, and D. F. HYATT. 1963. Biologic properties of two plaque variants of vesicular stomatitis virus (Indiana Serotype). J. Immunol. 91:112.
107. FINTER, N. B. 1964. Interferon production and sensitivity of Semliki Forest virus variants. J. Hyg. 62:237.
108. PARKMAN, P. D., H. M. MEYER, R. L. KIRSCHSTEIN, and H. E. HOPPS. 1966. Attenuated rubella virus. I. Development and laboratory characterization. N. Engl. J. Med. 275:569.
109. WATANABE, M. Proceedings of the Japan-American Conference on Interferon, 1969. In press.
110. SELLSERS, R. F. 1963. Multiplication, interferon production and sensitivity of virulent and attenuated strains of the virus of foot-and-mouth disease. Nature (London). 198:1228.
111. BURNET, F. M. 1959. In The Viruses. F. M. Burnet and W. M. Stanley, editors. Academic Press, Inc., New York. 3:275.
112. FINNER, F., and J. CAHAN. 1959. In The Viruses. F. M. Burnet and W. M. Stanley, editors. Academic Press, Inc., New York. 3:225.
113. Lwoff, A., and M. Lwoff. 1960. Factors in viral development and their role in the evolution of infection. *Ann. Inst. Pasteur (Paris)*. 98:173.

114. Lindemann, J. 1960. Interferon and inverse interferenz. *Z. Hyg. Infektionskr. Med. Mikrobiol. Immunol. Virol.* 146:237.

115. Hermodsson, S. 1964. Role of interferon in the autointerference of Newcastle disease virus (NDV). *Acta Pathol. Microbiol. Scand.* 62:133.

116. Hermodsson, S. 1964. Action of parainfluenza virus type 3 on synthesis of interferon and multiplication of heterologous virus. *Acta Pathol. Microbiol. Scand.* 62:224.

117. Vandeputte, M., J. Delafonteyne, A. Billiau, and P. DeSomer. 1967. Influence and production of interferon in Rauscher virus infected mice. *Arch. gesamte Virusforsch.* 20:235.

118. Osborn, J. F., and D. N. Medearis. 1967. Suppression of interferon and antibody and multiplication of Newcastle disease virus in cytomegalovirus infected mice. *Proc. Soc. Exp. Biol. Med.* 124:347.

119. Gauntt, C. J., and R. Z. Lockart, Jr. 1966. Inhibition of Mengo virus by interferon. *J. Bacteriol.* 91:176.

120. Dulbecco, R., M. Vogt, and A. Strickland. 1956. Study of basic aspects of neutralization of 2 animal viruses, Western equine encephalitis virus and poliomyelitis virus. *Virology.* 2:162.

121. Walker, D. L. 1964. The viral carrier state in animal cell cultures. *Progr. Med. Virol.* 6:111.

122. Henle, W., G. Henle, F. Deinhardt, and V. V. Beres. 1959. Studies on persistent infections in tissue cultures. IV. Evidence for the production of an interferon in MCN cells by myxoviruses. *J. Exp. Med.* 110:525.

123. Henle, W. 1963. Interference and interferon in persistent viral infections of cell cultures. *J. Immunol.* 91:145.

124. Rodríguez, J. E., and W. Henle. 1964. Studies on persistent infections of tissue cultures. V. The initial stages of infection of L (MCN) cells by Newcastle disease virus. *J. Exp. Med.* 119:895.

125. Ho, M., and J. F. Enders. 1959. Further studies on an inhibitor of viral activity appearing in infected cell cultures and its role in chronic viral infections. *Virology.* 9:446.

126. Tyrrell, D. A. J. 1939. Interferon produced by cultures of calf kidney cells. *Nature (Washington).* 184:452.

127. Philipson, L., and Z. Dinter. 1963. The role of interferon in persistent infection with foot and mouth disease virus. *J. Gen. Microbiol.* 32:277.

128. Chaney, C. 1961. An interferon-like inhibitor of viral multiplication from malignant cells (the viral autoinhibition phenomenon). *Virology.* 13:465.

129. Mayer, V. 1962. Interactions of mammalian cells with tick-borne encephalitis virus. *Acta Virol.* 6:217.

130. Wong, K. T., S. Baron, and T. G. Ward. 1967. Rubella virus: Role of interferon during infection of African green monkey kidney tissue cultures. *J. Immunol.* 99:1140.

131. Barski, G., and F. Cornewert. 1962. Response of different mouse cell strains to polyoma infection in vitro. Latency and self-inhibition effect in infected cultures. *J. Nat. Cancer Inst.* 28:823.

132. Hare, J. D., and H. R. Morgan. 1964. Polyoma virus and L cell relationship. II. A curable carrier system not dependent on interferon. *J. Nat. Cancer Inst.* 33:765.

133. Hanafusa, H., T. Hanafusa, and H. Rubin. 1964. Analysis of the defectiveness of Rous Sarcoma virus. I. Characterization of the helper virus. *Virology.* 22:391.

134. Sarma, P. S., M. P. Chrono, J. W. Hartley, and R. J. Huesner. 1967. A viral interference test for mouse leukemia viruses. *Virology.* 33:180.

135. Subrahmanyan, T., and C. Mims. 1966. Fate of intravenously administered interferon and the distribution of interferon during virus infections in mice. *Brit. J. Exp. Pathol.* 47:168.

136. Dianzani, F., S. Gagnoni, C. E. Buckler, and S. Baron. Studies of the induction of interferon system by non-replicating Newcastle disease virus. *In The Proceedings of*
the International Symposium on Interferon Held in Lyon, France, in 1969. C. Chany, editor. In press; and 1970. Proc. Soc. Exp. Biol. Med. 133:322.

137. DuBu, H. G., and M. L. Johnson. 1965. Some properties of the lactic dehydrogenase agent of mice. J. Exp. Med. 122:587.

138. Wagner, R. R. 1969. Viral interference. Some considerations of basic mechanisms and their potential relationship to host resistance. Bacteriol. Rev. 24:151.

139. Henle, G., and W. Henle. 1965. Evidence for a persistent viral infection in a cell line derived from Burkitt's lymphoma. J. Bacteriol. 89:222.

140. Rabon, A. S., G. T. O'Connor, S. Baron, J. J. Wang, and F. Y. Legallais. 1966. Morphologic, cytogenetic and virologic studies in vitro of a malignant lymphoma from an African child. Int. J. Cancer. 1:89.

141. Epstein, M. A., J. P. Woodall, and A. D. Thomson. 1964. Lymphoblastic lymphoma in bone marrow of African green monkey inoculated with biopsy material from a child with Burkitt's lymphoma. Lancet. II:238.

142. Ruben, H. 1962. The immunological basis for noninfective Rous sarcomas. Cold Spring Harbor Symp. Quant. Biol. 27:441.

143. Baron, S., and A. Isacss. 1961. Interferon and natural recovery from virus diseases. New Sci. 11:81.

144. Baron, S., and H. B. Levy. 1966. Interferon. Ann. Rev. Microbiol. 20:291.

145. Finter, N. B. 1966. Interferons. North Holland Publishing Co., Amsterdam.

146. Kleenschmidt, W. J., J. C. Crine, and E. B. Murphy. 1964. Interferon production induced by statolon. Proc. Nat. Acad. Sci. U.S.A. 52:741.

147. Reclaval, W. 1967. In The Reticuloendothelial System and Atherosclerosis. N. R. Siluzio and R. Pacleti, editors. Plenum Publishing Corporation, New York. 315.

148. Lampson, G. P., A. A. Tytell, A. K. Field, M. M. Nem, and M. R. Hilleman. 1967. Inducers of interferon and host resistance. I. Double-stranded RNA from extracts of penicillium funiculosum. Proc. Nat. Acad. Sci. U.S.A. 58:782.

149. Field, A. K., A. A. Tytell, G. P. Lampson, and M. R. Hilleman. 1967. Inducers of interferon and host resistance. II. Multistranded synthetic polynucleotide complexes. Proc. Nat. Acad. Sci. U.S.A. 58:1004.

150. Park, J. H., and S. Baron. 1968. Herpetic keratoconjunctivitis: therapy with synthetic double-stranded RNA. Science (Washington). 162:811.

151. Jahiel, R. I., J. Vincz, R. Nussenzweig, and J. Vanderberg. 1968. Interferon inducers protect mice against plasmodium berghei malaria. Science (Washington). 161:802.

152. Schultze, W. N., K. Y. Huang, and F. B. Gordon. 1968. Role of interferon in experimental mouse malaria. Nature (London). 220:709.

153. Remington, J. S., and T. C. Mergan. 1968. Interferon: Protection of cells infected with an intracelllular protozoan (Toxoplasma Gondii). Science (Washington). 161:804.

154. Levy, H. B., L. W. Law, and A. S. Rabon. 1969. Inhibition of tumor growth by polynosinic-polycytidylic acid. Proc. Nat. Acad. Sci. U.S.A. 62:357.

155. Zeleznyk, L. D., and B. K. Bhuyan. 1969. Treatment of leukemic mice with double-stranded polynucleotides. Proc. Soc. Exp. Biol. Med. 120:126.

156. Gelboin, H., and H. B. Levy. 1969. Effect of polynosinic-polycytidylic acid on DMBA carcinogenesis. Science (Washington). In press.

157. Sarma, P. S., G. Shih, R. H. Neubauer, S. Baron, and R. J. Huenner. 1969. Virus-induced sarcoma of mice: Inhibition by a synthetic polynucleotide complex. Proc. Nat. Acad. Sci. U.S.A. 62:1046.

158. Haim, J. S., C. Greenewalt, and R. J. Huenner. 1969. Synthetic double-stranded RNA: Inhibitory effect on murine leukemia and sarcoma viruses in cell cultures. Nature (London). 222:1116.

159. Gresser, I., J. Coppey, D. Fontaine-Brouty-Boy, R. Falcoff, E. Falcoff, and A. Zapela. 1967. Interferon and murine leukemia. IV. Efficacy of interferon preparations administered after inoculation of Friend virus. Nature (London). 215:174.

160. Gresser, I., C. Bourall, J. P. Levy, D. Fontaine-Brouty-Boy, and M. R. Thomas. 1969. Increased survival in mice inoculated with tumor cells and treated with interferon preparations. Proc. Nat. Acad. Sci. U.S.A. 63:51.