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ANTIVIRAL ACTIVITIES OF INTERFERONS

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Interferons are a group of proteins produced by eucaryotic cells when they are stimulated by virus infection, double-stranded RNA and various other inducers. Cells, when treated with interferons, exhibit a number of responses, the principal action of interest in this review being the establishment of virus resistance. There are however a number of other responses that have been described, such as inhibition of non-viral agents; priming; blocking; cell-multiplication-inhibition; toxicity enhancement; enhanced synthetic activities; surface alteration; enhanced immunolysis; enhanced phagocytosis and various immune modulations. In this survey we will first discuss the antiviral action of interferon both in vitro and in vivo and describe the non-antiviral activities, as these are likely to contribute to virus resistance mechanisms in the animal.

1. GENETICS OF INTERFERON ACTION

The antiviral action of interferon is under cellular genetic control: interferon must induce new cellular messenger RNA and protein synthesis for the cell to become resistant to viruses (Lockart, 1964; Taylor, 1964); the cell nucleus must be present at the time of interferon treatment but not afterwards (Radke et al., 1974; Young et al., 1975). The difficulties in genetic analyses of interferon actions were first overcome by using somatic cell hybridization of human and mouse cells, where there is little cross-species activity of the interferons produced. Human–mouse cell hybrids are produced by fusion of the two cell types using inactivated Sendai virus. These hybrids preferentially lose human chromosomes and their human phenotypes. Thus, it is possible to correlate the loss of a human phenotype with the concomitant loss of a particular human chromosome. Results from these experiments enable gene dosage and other genetic experiments to be performed on aneuploid cells with abnormal numbers of certain chromosomes. It must be emphasized that numerous epigenetic factors can contribute to modulations of sensitivity to interferon and/or the ability of cells to express antiviral and non-antiviral activities. These epigenetic factors can exert their modulating capacity at any stage, from the binding of interferon to cell surface, to the translation of antiviral protein, to its expression. Thus, the action mechanism of interferon is best understood by a breakdown of each step of its action and analysis of the data pertaining to each step.

1.1. HYBRID CELL ANALYSES

Using monkey–mouse cell hybrids, Chany and his associates (Cassingena et al., 1971; Chany et al., 1973, 1975; Chany, 1976) showed that genes for the production and action of interferon are asyntenic in mice (not present on the same chromosome). This was also found to be the case in the human interferon system (Tan et al., 1973, 1974). Tan and his colleagues used a large number of human–mouse hybrid cells, which gradually lost human chromosomes while retaining mouse chromosomes, and demonstrated a correlation of residual human chromosomes with sensitivity to antiviral activity of human interferon: a positive correlation was found between sensitivity to human interferon, expression of a human isozyme indophenolozidase A, and presence of human chromosome 21. This observation was confirmed in a number of subclones.
where indophenoloxidase A and human antiviral action segregated concomitantly (Tan et al., 1973; Tan, 1975; Cregan et al., 1975). Morgan and Faik (1977) found the same phenomenon by using human–hamster hybrids, where human interferon antiviral activity is dependent on the presence of human chromosome 21. Revel et al. (1976) confirmed the same involvement of human chromosome 21 with the antiviral activities of human interferon using human–mouse hybrids. Chany et al. claimed that, if only human chromosome 21 were present in human–mouse hybrids, there was no response to human interferon; the response depended upon the presence of other human chromosomes in the hybrid as well (Chany et al., 1975; Chany, 1976). However, Slate et al. (1978) found that the mere presence of human chromosome 21 was sufficient to elicit an antiviral response to human interferon, whereas presence of other human chromosomes in the hybrid elevated the sensitivity to human interferon.

1.2. CHROMOSOMAL ASSIGNMENTS FOR INTERFERON ACTION IN ANEUPLOID CELLS

1.2.1. Dosage Effect of Chromosome 21 on Antiviral Activities of Human Interferon

The assignment of human interferon antiviral activities to chromosome 21 has been confirmed in a number of studies by using cells containing abnormal copies of specific chromosomes. Human cells from the genetic disorder of Down's syndrome (trisomic 21) are the most common. Tan et al. (1974) found the sensitivity to human interferons exhibits a hierarchy corresponding to the number of chromosome 21, i.e. trisomy over normal diploid over monosomic aneuploid cells. This observation has been confirmed repeatedly in a number of laboratories (Chany et al., 1975; Tan et al., 1975, 1977; Revel et al., 1976; Wiranowska-Stewart and Stewart II, 1977; Slate et al., 1978). Trisomic 21 human cell lines are now routinely used for human interferon assays in numerous laboratories for higher sensitivities.

This relationship of interferon sensitivity with the number of chromosome 21 also extends to antiviral action induced by human type II interferons, human leukocyte interferons and human fibroblast interferons (Tan, 1977; Slate et al., 1978; Wiranowska-Stewart and Stewart II, 1977), and by each of the molecular size-forms of human leukocyte interferons isolated from SDS-polyacrylamide gels (Stewart II et al., 1977). The same hierarchy was found to exist when human cells were exposed to mouse (heterologous) interferon (Wiranowska-Stewart and Stewart II, 1977). It was shown that the increased sensitivity was a specific response to the increased number of chromosomes 21, where cells with a loss or gain of other human chromosomes do not exhibit such an increase or decrease in sensitivity (Tan, 1977; Epstein and Epstein, 1976). Furthermore, at least two separate laboratories have been able to localize the interferon sensitivity gene at the distal portion of the long arm of human chromosome 21 (Tan and Greene, 1976; Epstein and Epstein, 1976).

1.2.2. Non-antiviral Activities of Interferon and Human Chromosome 21

There are opposing claims as to the relationship of human chromosome 21 and sensitivities to the non-antiviral activities of interferon. DeClercq et al. (1975a) claimed that there was no correlation between the antiviral, double-stranded RNA toxicity enhancement and priming activities of interferon to human cells which are monosomic, disomic and trisomic for chromosome 21. They thus concluded that the non-antiviral activities of interferon are not controlled by chromosome 21. Several other workers have shown results to the contrary. Tan (1976, 1977) has shown that the sensitivity of cells to the cell-multiplication-inhibitory actions of interferon is controlled by chromosome 21. Cupples and Tan (1977) further demonstrated that chromosome 21 determines the sensitivity to inhibition of mitogen-induced lymphoblastogenesis by human interferon. Frankfort et al. (1978) recently demonstrated that the priming activity of interferon is controlled by human chromosome 21. In view of the amount of data supporting the correlation of non-antiviral activities of interferon and chromosome 21, we conclude that DeClercq and his associates might have erred in their interpretations.
1.2.3. Regulatory Chromosomes for Interferon Actions

It has been observed that the increase in sensitivity to interferon increases exponentially with the increase of number of chromosome 21, and not linearly (Tan, 1977; Wiranowska-Stewart and Stewart II, 1977). It is therefore possible that the regulatory genetic control of interferon action is located on separate chromosome(s) and the increase in chromosome 21 creates an imbalance between the product of the action gene and its regulator. Chany et al. (1975) showed that human triploid cells were normal in their response to interferon, suggesting that a full complement of chromosome offsets the increased sensitivity to interferon conferred by increased numbers of chromosome 21. These investigators also found that human cells trisomic for chromosome 16 were less sensitive than normal diploid cells to human interferon. This suggests that the regulatory control of interferon sensitivity might be on chromosome 16. Blach-Olszewska et al. (1977) postulated that the disproportionate number of these regulatory chromosomes in HeLa cells makes this cell line insensitive to interferon.

1.3. Role of Chromosome 21 in the Binding of Interferon

In the previous section we have presented data showing that the increased sensitivity to human interferon antiviral and non-antiviral actions is determined by chromosome 21. We now present data to show that this increase in sensitivity is due to an interferon receptor component coded by chromosome 21.

1.3.1. Interaction of Interferon with Cells

The exact nature of the initial interaction of interferon with cells remains unknown. It had been suggested that membrane component(s) bind interferon but the exact mode of binding remains speculative. It has been shown by a number of laboratories that interferon is capable of strong and highly selective adsorption to a number of unrelated substances. These include proteins, simple hydrocarbons, or polyribo-nucleotides. Thus, it is no simple task to determine the receptor component of the cell surface by interference from simple binding studies to isolated components.

1.3.1.1. Indirect studies. Early attempts to demonstrate binding of interferon to cells by measuring the decrease of interferon from medium were conflicting. Some investigators found that interferon activity disappeared from the medium after cell contact (Burke and Buchan, 1965; Gifford, 1963a; Lindenmann et al., 1957; Merigan, 1964; Sellers and Fitzpatrick, 1962, Wagner, 1961). However, such losses could be attributed to inactivation of interferon (Merigan et al., 1965) or to its adhesion to various surfaces (Lampson et al., 1963). Other investigators have reported that interferons could repeatedly induce antiviral activity in cultures without appreciable loss of activity (Buckler et al., 1966; Friedman, 1967). It was also found that interferon-induced resistance in cells by binding in the cold was not removed by washing. However, treatment of cells with trypsin after exposure to interferon in the cold prevented development of interferon-induced virus resistance (Friedman, 1967; Goldsby, 1967; Levine, 1966; Vilcek and Lowy, 1967; Berman and Vilcek, 1974; Stewart II, 1975a). These data suggest that interferon first binds to cells at a superficial site. There are reports that interferon treatment of cells alters the subsequent binding to these cells of cholera toxin and thyrotropin (Kohn et al., 1976). Interferon-treated cells are also less sensitive to the toxicity of diphtheria toxin (Yabrov, 1966; 1967; T. J. Moehring et al., 1971). The data suggest that either interferons share the same receptor sites with cholera toxin, diphtheria toxin and thyrotropin, or that interferon binding alters the cell membrane in such a way as to decrease the binding of these substances. The data of Knight and Korant (1977), demonstrating that interferon-treated cells are electrophoretically different from normal cells, tend to support the hypothesis that interferon binding does induce cell alterations.

Gangliosides have been suggested to play a role in receptor or receptor-like binding
of interferon. Receptors are inferred as gangliosides, or ganglioside-like structures, or as receptor-activator of ganglioside-glycoprotein complexes (Besancon and Ankel, 1974a, 1976; Vengris et al., 1976; Pitha et al., 1976a; Kohn et al., 1976; Pittha, 1977; Friedman, 1977). Gangliosides were also reported to be able to coat interferon bound to agarose, and conversely gangliosides bound to agarose were able to bind interferon (Besancon and Ankel, 1974a; Besancon et al., 1976a). Besancon and Ankel also reported that pretreatment of cells with plant lectins can block the action of interferon (1974b, 1976). Addition of gangliosides to certain mouse cells that are deficient in these structures increases their sensitivities to interferon (Pitha et al., 1976a). Interpretation of these data is difficult in view of the known host-range specificities of interferons and the affinity exhibited by interferons for numerous structurally unrelated substances, e.g. polyribonucleotides, blue dextran, glass beads, immobilized L-tryptophan, etc. Interferon immobilized on agarose beads had been used to demonstrate that the induction of antiviral (Ankel et al., 1973; Chany et al., 1975; Knight, 1974a) and non-antiviral (Knight, 1974b) activities are triggered from the exterior of the cell. This is rather tenuous since it is impossible to exclude the possibility of interferon leakage from the agarose bead, or removal of interferon from the agarose beads after cell contact.

1.3.1.2. Direct studies. There should be a positive correlation between the sensitivity of cells to interferon and the amount of interferon bound to cell surfaces, if the sensitivity level is determined by the number of interferon receptors on the cell surface. Wagner (1961) was unable to recover any detectable antiviral activities after he treated chick cells with 64 units of interferon. Levine (1966) was also unable to detect interferon activities when he treated cells with 180 units of interferon, but was able to detect 10 units from cells treated with 900 units of interferon. Friedman (1967) was also able to recover trace levels of antiviral activities from chick cells treated with 2000 units/ml interferon. There were, however, no attempts made to correlate the binding with sensitivities of the cells to the interferon they bound. Stewart II et al. (1972c) found that mouse interferon could be recovered from mouse cells treated with mouse interferon, but were unable to detect any antiviral activity when heterologous cells were treated with mouse interferon. The amount of interferon recovered from three different types of mouse cells correlated directly with the sensitivity they exhibit to the antiviral activities of interferon. Mouse interferon was found to bind to cells from 4 to 37°C, though with slower kinetics at the lower temperature. Those interferons that were bound at 4°C were sensitive to trypsin treatment, whereas interferon binding at higher temperature (37°C) was insensitive to trypsin digestion (Stewart II, 1975a). Using human interferons, Berman and Vilcek (1974) confirmed these observations: interferon could be recovered from heterologous cells and not homologous cells; interferon binds to cells at 37°C and at 4°C; interferon that binds at 4°C remains sensitive to treatment with trypsin, whereas that binding at 37°C is not. Stewart II (1975a) also found that the applied interferon rapidly became internalized in cell-sap and nuclear membrane fragments. It was not known, however, if such uptake of interferon was necessary for the activities induced. Kohno et al. (1975a, b) found that cell-bound interferon eluted from cells after the removal of unbound interferon, and later reported that the binding of interferon to cells determine the antiviral activities by using two rodent interferons (mouse and hamster) and a variety of rodent cell lines (Umino and Khomo, 1976). Gresser et al. (1974) found that murine leukemia L1210 cells which are resistant to the antiviral and cell-multiplication-inhibitory actions of interferon did not bind mouse interferon, whereas L1210 cells that are sensitive to these actions of interferon did bind mouse interferons. These cells were later found to be resistant and sensitive, respectively, to the double-stranded RNA toxicity-enhancing effect of interferon (Werenne and Rousseau, 1976a; Gresser and Stewart II, unpublished data).

In certain instances, the binding of interferon does not correlate with the subsequent induction of interferon actions. Chany and Vignal (1968) described a mouse
embryo line transformed by murine sarcoma virus which became completely resistant to the antiviral action of interferon after more than 200 passages in the continued presence of interferon. These cells have been found to bind interferon to the same extent as parental, interferon-sensitive mouse cells (Stewart II, unpublished data). Kuwata and co-workers (Kuwata et al. 1976a, b; Fuse and Kuwata, 1976) have described two lines of transformed human cells which were both sensitive to the antiviral effects of interferon but were different in their sensitivities to the cell-multiplication-inhibitory actions of interferon. The cells which are resistant to this effect bound appreciably less amounts of interferon than those cells sensitive to the cell-multiplication-inhibition action of interferon. These reports suggest that there are other control mechanisms subsequent to the binding of interferon which can also affect the actions of interferon.

1.3.2. Interferon Binding and Chromosome 21

There are a number of proposed roles for chromosome 21 in sensitivity to interferon actions. Tan (1975) suggested that chromosome 21 codes for the synthesis of an intracellular antiviral protein; Chany et al. (1975) and Revel et al. (1976) suggested that chromosome 21 carries the structural gene for human interferon receptors. This is based on their observation that cells which are sensitive to interferon became resistant when treated with antiserum prepared against chromosome 21-directed cell surface components. Chany and his colleagues (Chany et al., 1975; Chany, 1976) have suggested that interferon host-specificity is due to interferon–receptor interactions. This is determined by chromosome 21 in human cells whereas in human-mouse hybrids, the receptor is of human origin and the antiviral machinery is of mouse origin. Slate et al. (1978) have shown that human–mouse hybrids containing only human chromosome 21 as the detectable human genetic component were sensitive to human interferons (fibroblast and leukocyte) but the antiviral mechanisms were due to mouse chromosome-directed products. All the above data indicate that human chromosome 21 codes for an interferon receptor. DeClercq et al. (1976) claimed that cells with different numbers of copies of chromosome 21 (tri-, di-, and monosomic) were, in addition to being equally sensitive to the non-antiviral actions of interferon, all able to bind the same amount of human interferon. This claim was however, refuted by Wiranowska-Stewart and Stewart II (1977) who found that human cells with one, two or three copies of human chromosome 21 bound increasing amounts of interferon.

1.4. Physiological and Other Factors Which Influence Interferon Actions

The action of interferons can be modulated by factors other than the genetic influence of specific chromosomes. Events subsequent to interferon binding (transcription and translation) can be affected to give altered interferon-induced products. These complications further contribute to the difficulties in understanding the actions of interferon and assigning the genetic elements which control these actions.

1.4.1. Effects of Age on Interferon Action

Tissues from very young chick embryos were much less sensitive to interferon than were tissues from older embryos (Isaacs and Baron, 1960; Cantell et al., 1965; Grossberg and Morahan, 1971). Similar differences were found with human embryonic tissues (Siewers et al., 1970). Several laboratories have found that cultures of the same cell line exhibit different sensitivities to interferon when cultures of different ages were compared, the older cultures being more sensitive (Cantell and Paucker, 1963; Carver and Marcus, 1967; Lockart, 1963, 1968; Rossman and Vilcek, 1969; Billiau and Buckler, 1970; McLaren, 1970; Korsantiya et al., 1967; Lvovsky and Levy, 1976). The differences in sensitivities ranged from ten-fold to 100-fold. These differences are clearly not due to genetic differences. At least three mechanisms have
been suggested to account for this aging effect and interferon sensitivity. 

(a) Cells may continue to accumulate interferon receptors as they age, hence the cell surface becomes increasingly saturated with these receptor molecules. There is no direct evidence for this possibility, and efforts are made to perform binding experiments with fixed numbers of cells at similar culture age (Wiranowska–Stewart and Stewart II, 1977).

(b) Younger cells may have a repressor of interferon action. Several reports of such substances have appeared in the literature, referred to by various names: 'stimulons' (Chany and Brailovsky, 1965, 1967; Brailovsky and Chany, 1965); or 'interferon antagonists' (Truden et al., 1967; Fournier et al., 1968, 1969, 1974; Galliot et al., 1973; Rytel, 1975; Lidin and Adams, 1975; Cembrzynska–Nowak, 1977). Grossberg and Morahan (1971) have reported that younger cells elaborate more of this type of factor which, when added to older cells, was antagonistic to interferon actions.

(c) Younger cells may be more able to inactivate interferons (Korsantiya et al., 1967).

1.4.2. Cell Density Effects

Rossman and Vilcek (1969) reported that interferon sensitivities are influenced by cell densities. Dianzani and his colleagues have demonstrated that antiviral resistance develops more rapidly and to higher levels in more concentrated cultures. This could be due to higher levels of localized interferon which can be transferred from one cell to another when the cells are packed closer to each other (Dianzani et al., 1975, 1976, 1977; Dianzani and Baron, 1975, 1977). Blalock and Baron (1977) recently reported that interferon-treated cells can apparently elaborate part of the antiviral machinery which could be transferred from one cell to another. It is feasible that dense cultures could better transfer this antiviral machinery between adjacent cell via a more efficient cell–cell information transfer.

1.4.3. Variations in Interferon Sensitivities of Diploid Cells

There are variations even among diploid human cells with respect to their sensitivities to interferon (J. M. Moehring et al., 1971). Gifford (1974) reported that mouse spleen cells were about 500 times less sensitive to the antiviral effects of mouse interferon than L929 cells, which in turn are somewhat less sensitive than primary mouse embryo fibroblast or mouse kidney cultures (DeMaeyer–Guignard et al., 1977; Stewart II et al., 1972c).

1.5. OTHER FACTORS MODULATING INTERFERON ACTIONS

There are a number of other factors which have been reported to influence the apparent sensitivities of cells to interferon. They are discussed here to emphasize the difficulties in unravelling the genetic components responsible for interferon action mechanisms. Each of these variables must be considered and carefully controlled in experiments designed to understand the mechanism of action of interferon.

1.5.1. Antagonists

A number of factors have been reported to be inhibitory to the actions of interferon. These factors were assumed to stimulate virus growth but have been subsequently shown to enhance virus growth by decreasing interferon production (Kato and Eggers, 1969; Kato and Ohta, 1966; Kato et al., 1965a,b, 1966, 1969). Other factors have been shown to enhance virus growth by the stimulation of some mechanism totally unrelated to interferon action.

Chany and his associates have described a protein isolated from virus-infected or uninfected tissues which, when added to cells before or after interferon treatment, lowers the virus resistance of these tissues (Brailovsky and Chany, 1965; Chany and Brailovsky, 1965, 1967; Chany et al., 1969; Galliot et al., 1973; Fournier et al., 1968,
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1969, 1972, 1974; Chany–Fournier et al., 1977). Other laboratories have similarly isolated such factors from various sources (Ghendon, 1965; Ghendon et al., 1966; Truden et al., 1967; Brodeur et al., 1973; Rytel, 1975; Cembrzynska–Nowak, 1977). Recently, Chany and his co-workers have reported that plant lectins eliminate the antiviral state established by interferon treatment and suggest that the tissue antagonist of interferon is a mammalian lectin-like substance (Chany–Fournier et al., 1977; Pauloin et al., 1977).

1.5.2. Factors Influencing Early Interferon–Cell Interactions

Factors which are known to alter the cell surface (structural integrity of the cell membrane) have been shown to change the cellular response to interferon. This alteration is presumed to be due to altered interferon binding and/or activation of events subsequent to interferon–cell contact (Chany, 1976; Bourgeade and Chany, 1976). Various substances with affinity for ganglioside, and gangliosides themselves, have been shown to affect interferon sensitivities in cells. Since this is a rather general phenomenon with no specificity of cell origin, it is assumed that these substances lower interferon adhesion to the cell surface rather than affect specific interferon receptors (Besancon and Ankel, 1974b; Besancon et al., 1976; Vengris et al., 1976).

Friedman and Kohn (1976) have shown that cholera toxin is capable of inhibiting the development of antiviral activity if the toxin is added at the same time with interferon. There is, however, no effect if toxin was added after interferon treatment. Similar effects were demonstrated for gonadotropin by Besancon and Ankel (1976) and for thyrotropin by Kohn et al. (1976). These findings suggest a two-step binding-initiation event or a mutually exclusive binding of these substances and interferon to the cell surface.

Isoprinosine (para-acetamidobenzoic acid salt of N, N-dimethylamino-2-propanolinosine), an agent which affects cell membrane, has been reported to increase the antiviral potency of interferon in mice, but was not active in vitro (Chany and Cerutti, 1977a, b). Cytochalasin B, colchicine and vinblastine, which affect microtubule and microfilament development in cells, have been shown to decrease the action of interferon (Soloviev and Mentkevich, 1965; Bourgeade and Chany, 1976). Other chemicals which have been demonstrated to inhibit the action of interferon are: ouabain (inhibitor of membrane adenosine triphosphatase, Lebon et al., 1975), mercaptopyridethylbenzimidazole (inhibitor of nucleosides transport across cell membranes; Friedman and Pastan, 1969), and vitamin A (Blalock and Gifford, 1974), apparently by the direct inactivation of interferon by vitamin A (Blalock and Gifford, 1975, 1976a, b, 1977). Agents which have been reported to enhance interferon actions are: dibazole (a benzimidazole derivative; Yabrov et al., 1971); poly-l-ornithine (increases adsorption and uptake of macromolecules into cells; Kleinschmidt and Ellis, 1967; Tilles, 1967); histone (Stancek and Matisova, 1968); and extracts from Escherichia coli (Vilcek and Ng, 1967). Steroid hormones, through some unknown mechanism, have been reported to enhance, not affect, and decrease interferon actions (Kilbourne et al., 1961; Reinicke, 1964, 1965a, b; Mendelson and Glasgow, 1966; DeMaeyer and DeMaeyer, 1963). It is evident from the above lists that agents exhibiting effects on interferon action are wide and varied. There is no common trend and they probably act through different mechanisms which remain to be elucidated.

1.5.3. Miscellaneous Factors

(a) Temperature: there is apparently no effect on the actions of interferon within the range of 31–39°C (Gifford, 1963b, Ruiz–Gomez and Isaacs, 1963; Stewart II and Desmyter, unpublished data).

(b) Oxygen tension: the reported effects of oxygen tension on interferon action are contradictory. Isaacs et al. (1961) reported oxygen tension influence on interferon
action, whereas other investigators have been unable to determine any effects (Gifford, 1963a; Burke and Buchan, 1965; Zemla and Schramek, 1962).

(c) pH: there are contradictory claims with respect to the effect of pH on interferon actions. Gifford (1963a) and Burke and Buchan (1965) reported no effect of pH changes on interferon titers with a range of pH 6.6-8.1. DeMaeyer and DeSommer (1962) reported that lower bicarbonate concentrations gave elevated interferon titers. Hallum et al. (1968) found that below pH 6 interferon was unable to induce virus resistance, and suggested this could be due to dissociation of polysomes. Brown and Besancon (1972) and Brown et al. (1973) also found an inhibitory effect of pH 6 on interferon actions, and attributed this to membrane transport arrest rather than solely to the inhibition of cellular metabolism.

(d) Ions of heavy metals: Gainer (1972) reported that high concentrations of arsenicals added to cultures shortly before or after interferon treatment inhibited interferon action, whereas low concentrations of the same ions increased the activity of interferon. He also reported (1977) that near toxic concentrations of cadmium, mercuric, and nickel salts reduced the actions of interferon in cell cultures.

(e) Cyclic AMP: Friedman and Pastan (1969) reported that cyclic AMP slightly increases the sensitivity of chick cells to interferon, but there were no effects observed with several analogs of cyclic AMP. Allen et al. (1974) reported a two-fold increase of interferon action in mouse cells (L,929); other related cyclic nucleotides had a more pronounced effect (9-MT-PRcP, 6-methylthio-9-β-d-ribofuranosylpurine 3', 5' cyclic phosphate, at a concentration of 10^-2 M, increases interferon action by sixteen- to thirty-two-fold. It was suggested that the cyclic nucleotides affect cells such that they behave as aged cultures. Weber and Stewart (1975) also reported that vitamin C slightly enhanced the antiviral activity of human leukocyte interferon in human fibroblast cells and suggested that this increase was due to elevated production of cyclic AMP. Meldolesi et al. (1977) demonstrated that interferon induced an increase in cyclic AMP levels in interferon-sensitive cells but not in interferon-resistant cells. This elevation of cyclic AMP preceded the induction of antiviral activities. Mecs et al. (1974) reported that interferon elevates the level of cyclic AMP in L cells, but this increase does not parallel antiviral activities.

(f) Viruses: Various investigators have reported that a number of viruses are capable of aborting the effects of interferons in cell cultures from various animals. These include: calf kidney cultures infected with parainfluenza virus (Hermodsson, 1963, 1964); newborn calf kidney cultures infected with bovine diarrhea virus (Diderholm and Dinter, 1966); chick cells infected with mumps virus (Frothingham, 1965); chick cells infected with tick-borne encephalitis virus (Libikova, 1965); L cells infected with tick-borne encephalitis virus (Vilcek and Stancek, 1963); and HeLa cells infected with Sendai virus (Maeno et al., 1966). This had been suggested as a mechanism whereby the growth of one virus enhances the growth of another (Paucker and Henle, 1958; Cantell, 1968). Thacore and his co-workers have also been able to demonstrate that one virus can rescue another from interferon-induced inhibition (Thacore and Youngner, 1970, 1972, 1973a, b, 1975; Thacore, 1976).

In view of the number of complications and contributions from various factors which affect virus infection and growth in interferon-treated cells, it is not possible to attribute all the many fluctuations in interferon response to any genetic determinants in the treated cells, nor is it an easy task to investigate any particular genetic influence on interferon actions.

2. MECHANISMS OF ANTIVIRAL ACTIONS OF INTERFERONS

The antiviral activities of interferons will be treated both at the cellular level and at the molecular level. The non-antiviral activities of interferon will then be discussed and the antiviral activities of interferons in the intact animal will be considered last, as it seems likely that the action of interferon in host recovery processes from virus infections involves both antiviral and non-antiviral activities.
2.1. GENERAL CONSIDERATIONS OF ANTIVIRAL ACTIVITIES OF INTERFERONS

The antiviral activities of interferon in cells have been examined extensively. This antiviral activity does not result from a non-specific toxic effect on the cells; rather it inhibits the replication of a wide range of viruses through processes which require de novo cellular protein synthesis. An initial interaction of cells with interferon is essential to the subsequent development of virus resistance; the establishment of the antiviral state is achieved slowly (over several hours) though interferon-binding is complete within minutes (Stewart II, 1975a; Berman and Vilcek, 1974). The antiviral state, once established, is maintained for several hours to several days, depending on such variables as the physiological state of the cells, after which the cells return to their previous virus-sensitive state. This section will describe the events after binding of interferon to cells, the development of the antiviral state, the mechanisms by which interferons exert these inhibitory effects on viruses and the decay of the antiviral state.

2.1.1. Conversion to the Antiviral State

2.1.1.1. Kinetics of the development of antiviral activity. Lindenmann et al. (1957) observed that there was no detectable development of virus resistance in chick cells that were exposed to interferon and virus simultaneously. Some virus resistance was found in cells exposed to interferon 6 hr before virus infection, and maximal resistance to virus infection was found in cells exposed to interferon for 24 hr. Some investigators found that a short treatment with interferon can often inhibit virus replication (Vilcek, 1969) and others have found inhibition by interferon treatment even when interferon was added after virus exposure (Wagner, 1961; DeSomer et al., 1962; Grossberg and Holland, 1962; Lerner and Bailey, 1974). However, usually several hours of exposure and incubation after initial treatment with interferon was necessary for the development of full antiviral activity.

The time required, after exposure to interferon, for the full establishment of the antiviral state in cells was found by several investigators to be independent of interferon concentration used for induction of viral resistance (Lockart, 1966; Baron et al., 1967). The response rate for the development of resistance to several viruses in interferon-treated chick cells was found to be the same; however, the development of resistance to these same viruses was slower in interferon-treated mouse cells (Jordan, 1972). Dianzani et al. (1976) reported that in most strains of human foreskin cells, viral resistance reached a maximum 6 hr after exposure to interferon (3–10 units/ml), whereas some human fibroblasts did not develop maximum resistance until 17–20 hr after interferon treatment.

Recently, Dianzani and his associates (Dianzani et al., 1976, 1977; Dianzani and Baron, 1975, 1977) investigated the effects of high concentrations of local interferon on development of virus resistance. They found a drastic difference in cellular response to interferon preparations kept at different temperatures (namely, prewarmed interferon preparations at 37°C and interferon preparations kept at room temperature). Antiviral resistance developed fully within a few minutes when cells were treated with prewarmed interferon preparations, whereas with lower temperature interferon preparations, several hours were required. Cells treated with warmed interferon for 15 min develop full antiviral activities even after washing and exposure to anti-interferon antiserum. Dianzani et al. (1977) also reported that cells exposed to high concentrations of interferon (about 300 units/ml) developed antiviral activities much more rapidly than those exposed to low levels (2–4 units/ml) of interferon. This report, although in conflict with earlier reports (Lockart and Horn, 1963; Baron et al., 1967; Dianzani et al., 1968), does shed light on the implication of interferon involvement in pathogenesis. DeClercq (1977) has suggested that the antitumor effects of interferon induced by poly(rI)-poly(rC) can be discounted in mice. He based his reasoning on the fact that administration to mice of amounts of exogenous interferon, at levels equal to those found in blood of mice injected with poly(rI)·poly(rC), failed.
to duplicate the same antitumor effect of poly (rI)·poly (rC) injection. These interpretations are unfortunate as they tend to confuse the evaluation of interferon as an antitumor agent by assuming that circulating interferon represents the total production level, and disregards the fact pointed out by Dianzani et al. (1977) that locally produced interferon induces significantly higher antiviral states in surrounding cells than those induced by circulating interferon.

It should be emphasized in the evaluation of kinetic data of the development of interferon-induced antiviral effects that metabolic processes may occur in the lag period of virus replication (several hours). These metabolic processes may be required for the development of the antiviral states. The true assessment of the involvement of these metabolic events in the establishment of the antiviral state and their timing can only be achieved if specific blocks (inhibition) of these events are available.

2.1.1.2. Metabolic requirements for the development of virus resistance. That interferons are not themselves antiviral substances but induce cells to produce such an antiviral substance was inferred from the observation that DNA-dependent RNA transcription (actinomycin D inhibition) and de novo protein synthesis (puromycin inhibition) are required for cells to become resistant to viruses (Lockart, 1964; Taylor, 1964; Friedman and Sonnabend, 1965a).

A number of RNA-transcription and protein synthesis inhibitors have been shown by various investigators to block the development of the antiviral state in interferon-treated cells: 6-azauridine and 5-fluorouracil (Nichols and Tershak, 1967); p-fluorophenylalanine (Friedman and Sonnabend, 1964; Sonnabend and Friedman, 1973); cycloheximide (Stewart II et al., 1971a). Using actinomycin D, Dianzani et al. (1976) concluded that the messenger RNA coding for the 'antiviral protein' was synthesized within 1 hr after initial interferon-cell contact. Enucleated cells were demonstrated by two groups to be incapable of developing antiviral activity (Radke et al., 1974; Young et al., 1975). These results clearly show that cellular RNA and protein synthesis are required for cells to develop virus resistance after exposure to interferon. Most investigators assumed that these data demonstrate that interferon induces the transcription of a cellular mRNA which codes for the antiviral protein (or its precursor), with subsequent translation of this mRNA giving rise to the development of the antiviral state. This model is rather simplistic, but to date has not been testable, for no mRNA coding for the antiviral protein has been isolated (though one was recently suggested; Ershov et al., 1976, 1977), nor has the antiviral protein been identified. Other alternative models have been put forward to account for the dependence of 'antiviral state' development on de novo RNA and protein synthesis. One such model proposed that interferon may itself be involved in the antiviral machinery and that de novo synthesis of RNA and protein served for the production of a permease which transports interferon from the exterior binding site to within the cell (Sheaff and Stewart, 1969, 1970a, b, c; Stewart and Sheaff, 1972). Since interferon-producing cells themselves only become resistant to virus after exposure to interferon from without (Vengris et al., 1975), the interferon induction of such a permease must therefore be inducible only on the exterior cell surface. This model does not seem likely.

2.1.1.3. Stability of the antiviral state. Cells are capable of sustaining the antiviral state over extended periods of time, provided the interferon level remains stable in the extracellular environment. Removal of the extracellular interferon causes decay of the antiviral state. The rate of this decay of the antiviral state depends on a number of factors such as the metabolic state of the population and the concentration of interferon used for induction of the antiviral state.

Isaacs and Westwood (1959a) reported that chick cells sustained the antiviral state for several days if incubated in serum-free maintenance medium but rapidly lost viral resistance when incubated in growth medium. Paucker and Cantell (1963) found a complete decay of viral resistance in L cells only after several cell generations following removal of interferon from the medium. Friedman and Sonnabend (1964)
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observed partial loss of antiviral activity after chick embryo cells were incubated in an interferon-free medium for 14 hr. It is important to realize that bound interferon can elute from cells. Thus, low levels of such eluted interferon in the fresh culture medium may delay the decay of the antiviral state in 'interferon-free' medium. The true decay rate of the antiviral state may be arrived at by incorporating antibodies to interferon in the fresh medium. The variation of the decay rates in some cultures may be due to the difference in interferon concentrations used to induce the antiviral state, suggesting either a variation in the magnitude of the antiviral state or the level of released (eluted) interferon in the washed cultures. Variation exists even for experiments reported by the same investigators (albeit over 10 years later). Baron et al. (1968) reported that interferon-treated mouse embryo cells lost their virus resistance gradually over a 48 hr period; later, Dianzani et al. (1976) reported that viral resistance remained at maximal levels for about 12 hr after removal of interferon, then rapidly decayed to undetectable levels over the next 2 hr.

Baron et al. (1968) found that addition of actinomycin D, cycloheximide or fluorophenylalanine to the medium after the removal of interferon resulted in an increased decay rate of the antiviral state. Since then, several other investigators have reported contradicting results. Chany et al. (1971) reported a potentiation of the antiviral state by actinomycin D treatment of L cells; Lab and Koehren (1972) obtained similar results in chick cells. Radke et al. (1974) found that enucleated chick cells sustained virus resistance significantly longer than did normal chick cells. Lab and Koehren (1976) reported that the antiviral state decays rapidly after removal of interferon from chick cell cultures, and completely disappears within 72 hr. Addition of cycloheximide at 18, 32, 48 or 72 hr after removal of interferon partially or fully restores the antiviral state, depending on the time of addition of the inhibitor. These authors suggest that cycloheximide acts by blocking synthesis of a postulated regulatory protein which reversibly inactivates the antiviral protein or its expression. It is possible that the induction of virus resistance by interferon, like the induction of interferon itself, is under post-transcriptional control and can similarly be 'superinduced'.

Another factor which contributes to the apparent variation in the decay rate of the antiviral state is the type of virus used. Virus having essential components of replication with rapid turnover rates would not be able to restore production of virus if these components are destroyed during the antiviral state, thus a false indication of a prolonged antiviral state. However, viruses with more stable essential replicative components would be capable of virus production once the antiviral state fades (Marcus and Sekellick, 1976; Friedman and Costa, 1976).

2.1.2. Character of Interferon-induced Virus Resistance

Viral resistance induced in cells by interferon is capable of inhibiting viruses of every known type, in contrast to the specificity of antibodies to the virus used for its production. There are, however, differences in degrees of inhibition of different viruses. A generalization of data has led some investigators to infer that some viruses are 'interferon sensitive' while others are 'interferon resistant' (Grossberg, 1972). Rather, for each cell species, a spectrum of virus inhibition develops when treated with interferon (Stewart II et al., 1969). Some authors have attempted to compare interferon sensitivities of different viruses using data collected by different virus assay methods, e.g. single-cycle virus yield reduction; multiple-cycle virus yield reduction; plaque reduction; cytopathic-effect inhibition (Rodgers et al., 1972; Hilfenhaus et al., 1975b; Adams et al., 1975; DuBuy et al., 1973; Harris et al., 1974); such comparisons are meaningless (Stewart II and Sulkin, 1968). The virus resistance established in interferon-treated cells is characteristic of the cell type and does not depend on the type of interferon used. Stewart II and Lockart (1970) first demonstrated that monkey interferon induced in human cells a virus resistance spectrum of human cells. Other investigators have also found the same cell species-related virus resistance phenomenon (Ahl and Rump, 1976; Ito and Montagnier, 1977). Further evidence that the interferon-
action mechanism is determined by the treated cell, and not the origin of interferon species, was provided by the observation that human interferon induces mouse-type phosphorylated protein in human–mouse hybrid cells which contain only human chromosome 21 (proposed to code for interferon receptor) and complete mouse genetic material. Hallum et al. (1970) suggested that the differential decay rates of the antiviral state against viruses might produce artifactual differences in virus resistance if the assay method used was plaque reduction; other investigators, using all the above mentioned techniques of virus assay simultaneously, have obtained similar spectra of resistance to different viruses regardless of the virus assay method (Stewart II et al., 1969; Stewart II and Lockart, 1970; Gallagher and Khoobyarian, 1971, 1972; Ito and Montagnier, 1977). Some relative virus-sensitivity spectra to interferon-induced resistances are listed in Table 1.

**Table 1. Relative Sensitivities of Viruses to Different Species of Interferons**

| A. Human Interferon on Human Cells |
|-----------------------------------|
| **(1) Cytopathic-effect inhibition assay:** |
| Sindbis > VSV > RhIno-HGP > Corona 229E > Vaccinia > Herpes simplex > Adeno 2 = CMV (Ho and Enders, 1959; Glasgow et al., 1967; Smorodintsev et al., 1971; Stewart II and Desmyter, unpublished data) |
| **(2) Plaque-reduction assay:** |
| Sindbis > VSV = Rubella > Rhino > SFV > Vaccinia = Adeno 2, 7, 12 > Adeno 1, 3, 4, 11, 18 > Adeno 8, 5 (Armstrong and Merigan, 1971; Came et al., 1976; Desmyter et al., 1967; Gallagher and Khoobyarian, 1969, 1971; Stewart II et al., 1969) |
| **(3) Single-cycle yield reduction:** |
| Influenza A 1968 > Influenza A 1974 > Influenza A 1972 = Sindbis > Parainfluenza-1 > VSV > SFV > Vaccinia = Parainfluenza-3 = Coxsackie B-1 > SV40 > Adeno 1 (Came et al., 1976; Marchenko et al., 1976; Murphy et al., 1975; Oie et al., 1972; Stewart II and Lockart, 1970) |

| B. Chicken Interferon on Chicken Cells |
|---------------------------------------|
| **(1) Cytopathic-effect inhibition assay:** |
| WEE = EEE > Vaccinia > Fowl plague > NDV > Pseudorabies = Herpes simplex (Vilcek, 1962; Vilcek and Rada, 1962) |
| **(2) Plaque-reduction assay:** |
| Onyong-nyong > Chikungunya > Vaccinia = Japanese encephalitis > SFV > VSV = Fowl plague > NDV (Friedman, 1964; Gifford et al., 1964; Grossberg and Scherer, 1964; Hallum et al., 1970; Portnoy and Merigan, 1971; Ruiz-Gomez and Isaacs, 1963) |
| **(3) Yield-reduction assay:** |
| Sendai > Influenza-PR8 > Mel-influenza > Fowl plague (Burke and Isaacs, 1960) |

| C. Mouse Interferon on Mouse Cell |
|-----------------------------------|
| **(1) Plaque-reduction assay:** |
| Vaccinia > Sindbis > EMC = EEE = Herpes simplex = VSV > SFV (Glasgow and Habel, 1962; Stewart II et al., 1969) |

* Viruses are listed in decreasing order of sensitivity to interferon.

Abbreviations: EEE, eastern equine encephalitis; CMV, cytomegalovirus; EMC, encephalomyocarditis; NDV, Newcastle disease virus; SFV, Semliki Forest virus; VSV, Vesicular stomatitis virus.

The relative sensitivities of viruses to the resistance induced by interferon have also been used to characterize different molecular species of interferons. Vilcek et al. (1977) found that human leukocyte and human fibroblast interferon induced similar spectra of virus resistances and each of the molecular species of human leukocyte interferons isolated in SDS-polyacrylamide gels induce the same order of relative virus resistance, as did the size-species of mouse interferons isolated in SDS-polyacrylamide gels (Stewart II, unpublished data).
2.2. ANTIVIRAL MECHANISMS: SITES OF INTERFERON ACTIONS AGAINST VIRUSES

During the past decade, various models have been proposed to describe the mechanism of action of interferon (Colby and Morgan, 1971; Kleinschmidt, 1972; Sonnabend and Friedman, 1973; Metz, 1975a, b; Friedman, 1977; Joklik, 1977; Friedman and Chang, 1977; Lewis et al., 1977); progress has been slow. With the proposal of each new model, there are a rash of experiments attempting to either substantiate or disprove the particular model in vogue. It is quite possible that the contradictions in published data have been partly due to the crude preparations of interferons used. With the advances of interferon purification techniques, recent studies have been performed with interferon preparations with high specific activities. Voluminous information on the ability of interferon to inhibit virus-specific protein synthesis (Joklik and Merigan, 1966; Marcus and Salb, 1966, 1968; Carter and Levy, 1967a, b; 1968; Levy and Carter, 1968; Kerr et al., 1970; Kerr, 1971; Esteban and Metz, 1973; Metz and Esteban, 1972; Friedman, 1968; Friedman et al., 1972) indicates clearly that at least one of the mechanisms of interferon actions is at the translational level. Actions of interferon at the transcriptional level have also been reported, with inhibition of viral mRNA synthesis in polymerase-containing viruses (Marcus et al., 1971; Oxman and Levin, 1971; Bialy and Colby, 1972; Manders et al., 1972), perhaps through an inhibition of the viral polymerase function. There are reports claiming the inhibitory action of interferon at each of the steps of virus infection and multiplication subsequent to the initial states of virus attachment and penetration, through uncoating, viral mRNA and protein synthesis, maturation and finally release of mature viruses (Billiau, 1977). One school of thought maintains that all of these effects are merely multiple expressions of a single interferon action mechanism, namely translation inhibition, while others have suggested that there are multiple mechanisms of interferon action (Stewart II et al., 1969; Stewart II and Lockart, 1970; Hallum et al., 1970; Stewart II et al., 1973a; Marcus et al., 1971; Friedman, 1977; Friedman and Chang, 1977). The evidence for interferon action on each of the events or viral replication will be discussed in the following section.

2.2.1. Viral Attachment, Penetration and Uncoating

Early experiments with a few viruses have shown that virus adsorption was unaffected by treating cells with interferon (Ho and Enders, 1959; Wagner, 1960; Cantell and Paukker, 1963; Stewart II and Sulkin, 1966; Morgan et al., 1973); and it was then generalized that viral adsorption is unaffected. However, the many facets of interferon action on various viruses, and the reported alterations of cell membranes after interferon treatment, dictate a closer look into the influence of interferon on virus adsorption before this generalized statement can be substantiated.

It has been widely believed that interferon does not inhibit uncoating of virus. This stems from some indirect data and very limited direct data. The indirect evidence is based on the fact that interferon inhibits virus replication in cells infected with either intact virion or infectious RNA extracted from certain viruses (Ho, 1961, 1962; DeSomer et al., 1962; Mayer et al., 1961, 1962; Grossberg and Holland, 1962; Stewart II et al., 1971a). These data thus supposedly prove that interferon action must be at a step beyond the uncoating of virus (Sonnabend and Friedman, 1973; Friedman, 1977). However, the interferon effect may be at more than one step. Direct studies showing the lack of effect of interferon on virus uncoating have only been reported for reovirus (Wiebe and Joklik, 1975; Galster and Lengyel, 1976). Recent data suggest that, in certain virus infections, virus uncoating may be affected by interferon treatment. Yamato (1975) reported that virus infection initiated by infectious SV₄₀ viral DNA was only slightly sensitive to interferon treatment, whereas infection initiated by intact SV₄₀ virion was quite sensitive to interferon inhibition, as demonstrated repeatedly by Oxman and his colleagues (Oxman and Black, 1966; Oxman and Levin, 1971; Oxman et al., 1967a, b, 1974; Metz et al., 1976, 1977), and other
investigators (Yakobson et al., 1977a, b). Again a spectrum of interferon actions at different steps of replication in different viruses may be a plausible explanation.

2.2.2. Inhibition of Virus Transcription

The first evidence for interferon action on inhibition of primary transcription was reported by Marcus et al. (1971) with vesicular stomatitis virus infection of chick cells. A similar effect was later seemingly confirmed in human cells (Manders et al., 1972), and subsequently in monkey cells (Marcus and Sekellick, 1976). Other investigators found significant discrepancies between interferon sensitivities of early VSV transcription products and those resulting from secondary transcriptions (Baxt et al., 1977) and suggested that the apparent primary transcription effect of interferon was due to trivial effects. Similarly, Wiebe and Joklik (1975) found that, while reovirus yields were inhibited significantly by interferon, primary reovirus transcription was only slightly depressed. Repik et al. (1974) also discounted the differences in primary inhibition in influenza viral RNA transcription between interferon- and non-interferon-treated cells and concluded that there is no inhibition of transcription. Bialy and Colby (1972) reported transcription inhibition in vaccinia virus-infected chick cells treated with interferon, but this could possibly be due to the effect of cycloheximide and not interferon treatment (Jungwirth et al., 1977). In fact, analysis of poxvirus infection in interferon-treated cells revealed that all 'early' RNAs of vaccinia virus are synthesized and, rather than at inhibited levels, RNAs are synthesized at enhanced levels in interferon-treated cells (Joklik and Merigan, 1966; Jungwirth et al., 1972a, b; Osterhoff et al., 1976; Esteban and Metz, 1973; Horak et al., 1971; Metz et al., 1975b; Metz and Esteban, 1972; Metz, 1975). There are no clear explanations for this discrepancy.

The most convincing evidence for primary inhibition of transcription by interferon treatment comes from the SV40 virus studies by Oxman and his colleagues, who demonstrated that early SV40 RNA synthesis in monkey cells was markedly inhibited (Oxman and Levin, 1971), whereas virus adsorption, penetration and uncoating were not affected (Metz et al., 1976). This was contradicted by Yamamoto et al. (1975) who showed that uncoating inhibition may be responsible for the apparent transcription-inhibitory activity of interferon treatment. Metz et al. (1976) suggested that inhibition of SV40 RNA transcription could be due to either a reduced level of transcription of the viral genome, or an elevated level of degradation of viral RNA within the nucleus. However, their report of reversing the blockage of viral RNA release from the nucleus with 300 mM KCl suggests a physiological blockage rather than a true reflection on the action of interferon treatment. Marcus et al. (1975) reported a membrane-bound ribonuclease in chick cells treated with interferon, and suggested that this nuclease activity could be the mechanism of interferon action. However, this nuclease activity could not be found in hamster or monkey cells and was present in chick cells not treated with interferon (Maenner and Brandner, 1976).

To date, there is no clear-cut evidence for or against the inhibitory action of interferon on viral RNA transcription; it appears, though, that the low inhibition reported in various cell–virus systems is not sufficient to account for the inhibition of virus replication.

2.2.3. Inhibition of Virus Translation

Considerable data have been gathered on the inhibitory action of interferon at the translation level. There are two approaches: (a) studies of the message function of the input viral RNA in interferon-treated cells, and (b) studies of messenger RNA translations in cell-free protein synthesizing systems prepared from interferon-treated cells. Using either or both approaches, it is possible to show that translation of viral messages is inhibited by interferon treatment, but this does not prove that the inhibitory interferon action is only at this stage of virus replication.
2.2.3.1. Inhibition of viral message translation in cells. Extensive published results showing that interferon treatment inhibits early viral message translation all agree that this is a significant action mechanism for inhibition of virus replication. Several early studies have shown that early viral RNA synthesis was inhibited in interferon-treated cells (Lockart et al., 1962; DeSomer et al., 1962; Taylor, 1965; Friedman and Sonnabend, 1965b; Gordon et al., 1966; Mees et al., 1967) and, with a particular virus, some classes of RNA are more susceptible to interferon-induced inhibition than others. In these cases viral RNA replications were dependent on the synthesis of a viral RNA polymerase. Thus, the inhibition of viral RNA synthesis could result from the primary inhibition of viral RNA polymerase synthesis (Friedman et al., 1967; Friedman and Sreevalsan, 1970). A similar depression of viral polymerase synthesis was found in Semliki Forest virus infection of chick cells (Martin and Sonnabend, 1967; Sonnabend et al., 1967) and in Mengovirus infection of L cells (Miner et al., 1966).

Speculation on the mechanism of interferon action based on these findings included that of Levy and Carter (1968) who claimed that, in the case of mengovirus, inhibition resulted from the inability of viral ribosomes to associate with viral mRNA to form functional translational units, whereas Friedman and Sreevalsan (1970) found no such inhibition of polysome formation.

In the case of reovirus infection, a strong inhibition of viral protein synthesis was observed with a minimal level of inhibition of viral RNA transcription (Wiebe and Joklik, 1975).

Studies with vaccinia virus infection have indicated that thymidine kinase induction by vaccinia virus was inhibited by interferon treatment in chick cells (Bodo and Jungwirth, 1967; Ghosh and Gifford, 1965; Levine et al., 1967; Ohno and Nozima, 1964) but not in mouse cells (Barban and Baron, 1968). It was suggested by Magee et al. (1968) that while cell-directed primary uncoating of vaccinia virus proceeds normally, the viral-directed secondary uncoating of virus is inhibited by interferon, and the virus remains in core particles. Even though the vaccinia viral mRNA formed an interferon-treated cells are polyadenylated (Klesel et al., 1974), they are unable to form stable polysomes (Bodo et al., 1972; Joklik and Merigan, 1966; Metz and Esteban, 1972; Metz et al., 1975).

There is, however, one non-antiviral effect of interferon (double-stranded RNA-toxicity-enhancement, Stewart II et al., 1972a) which complicates the results obtained from the vaccinia virus studies. During vaccinia virus infection, interferon-treated cells are destroyed more rapidly than control, untreated cells (Joklik and Merigan, 1966; Horak et al., 1971; Stewart II et al., 1973a). This is most likely due to double-stranded RNA synthesized in vaccinia virus-infected cells (Colby and Duesberg, 1969); thus, this rapid inhibition of both cellular and viral protein synthesis in interferon-treated cells could be due to polysome breakdown and/or total cell destruction.

Another virus studied extensively with respect to interferon action is SV40. It was suggested that the inhibition of SV40 T antigen synthesis in interferon-treated cells (Oxman and Black, 1966) may be due either to uncoating inhibition (Yamamoto et al., 1975) or to transcription inhibition (Oxman and Levin, 1971). The findings of Grassmann et al. (1974), showing that SV40 cRNA microinjected into interferon-treated cells was also inhibited in its translation, strongly suggest that the primary inhibitory action of the interferon mechanism is at the translational level. More recently, Yakobson et al. (1977b) demonstrated that interferon is able to fully induce the antiviral state in monkey cells preinfected with SV40 and actively synthesizing SV40 T antigen. By 18-24 hr after addition of interferon, both early and late SV40 protein synthesis is completely arrested, even though viral mRNA synthesis continues at an unaltered rate (Yakobson et al., 1977a). During SV40 infection, host cellular protein synthesis continues unchanged; thus, it is easier to draw the conclusion that interferon treatment inhibits viral mRNA translation in this system than in the vaccinia virus system where total cell destruction takes place.
A rather different approach to explain the action of interferon-induced selective inhibition of viral mRNA translation was taken by Levy and Riley (1973) and Riley and Levy (1977). They proposed that interferon-treated cells are able to differentiate between cellular and viral messages by synthesizing modified mRNA which is larger than normal, and that interferon-treated cells are capable of making the enzymes required to effect these modifications to cellular mRNA. These puzzling data await confirmation.

2.2.3.2. Inhibition of viral mRNA translation in cell-free systems. The study of interferon action-mechanism in cell-free systems was started over a decade ago. The early studies, however, were performed prior to the refinement of techniques in cell-free translation systems. Although some interest was aroused by these pioneering experiments, they can, at best, be considered imaginative.

Marcus and Salb (1966, 1968) proposed that interferon induced a 'translational inhibitory protein' that combined with ribosomes and inhibited their ability to bind and translate viral mRNA but not cellular mRNA; treatment of these inhibited ribosomes with trypsin restored their ability to translate viral mRNA. Carter and Levy (1967a, b, 1968) supported this idea with their claims that ribosomes of interferon-treated L cells do not bind Mengovirus mRNA. They further reported that translation of polyuridylic acid and of tobacco mosaic virus RNA was not inhibited in interferon-treated cell systems. Other laboratories have been unable to substantiate the difference in binding of viral mRNA to ribosomes from control or interferon-treated cells (Kerr et al., 1970) or the selectivity of translation of different mRNAs (Friedman, 1977). However, the advent of many refinements of techniques in cell-free protein synthesis has enabled investigators to realistically study the effect of interferon treatment on viral RNA translation.

(i) Infection-activation of antiviral action. Friedman et al. (1972) found that viral mRNA translation was the same in cell-free extracts prepared from normal and interferon-treated cells; however, extracts prepared from vaccinia or EMC virus-infected interferon-treated cells would not translate viral messages, although polyuridylic acid translation was uninhibited. Kerr et al. (1973, 1974b) then concluded that interferon-induced antiviral action requires virus infection to activate translation inhibition. Other investigators studying different systems have reported that virus infection was not necessary for the inhibition of translation of viral message in interferon-treated cells; polyuridylic acid, however, was translated with no inhibition. An unidentified factor which inhibits viral mRNA was proposed to reside on ribosomes. This factor could be removed by salt-washing the ribosomes (Falcoff et al., 1972, 1973; Gupta et al., 1973, 1974; Samuel and Joklik, 1974; Samuel, 1976; Mayr et al., 1977; Hiller et al., 1976; Zilberstein et al., 1976a).

There are, however, disagreements among these investigators as to the specificity of this translation inhibition. Falcoff et al. (1973), Gupta et al. (1973, 1974) and Hiller et al. (1976) reported a non-specific inhibition of both viral and cellular (hemoglobin) mRNA translation in the interferon-treated cell extracts, whereas Samuel and Joklik (1974) reported that their translation system was capable of discerning viral mRNA from cellular mRNA with no inhibition of the latter. The unidentified factor was found to be a 48,000 dalton protein isolated from salt-washes of interferon-treated ribosomes. This factor was able to inhibit translation of viral mRNA when it was added to normal cell extracts. This translation-inhibiting protein does not exhibit any species specificity as observed with interferons in host cells; it is active whether added to homologous or heterologous cell extracts (Samuel and Farris, 1977). It also possesses a nucleolytic activity (Eppstein and Samuel, 1977). This lack of host-range specificity is similar to the transfer of virus resistance from interferon-treated cells to non-treated cells by close contact (Blalock and Baron, 1977).

(ii) Antiviral action activated by double-stranded RNA. There are at least three antiviral actions activated by double-stranded RNA (dsRNA); these are phosphoryl-
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Kerr and his co-workers (Kerr et al., 1974a, 1976) reported the viral infection-dependent interferon-induced inhibition of translation in cell extracts; this inhibitory activity was also observed when dsRNA and adenosine-5'-triphosphate (ATP) were added to the system. After a period of incubation in the cell extract, both dsRNA and ATP could be removed without loss of translation-inhibitory action, suggesting the synthesis of a translation-inhibitory factor, apparently via phosphorylation of an existing protein (Roberts et al., 1976a). During RNA- or DNA-containing virus replication, dsRNA can be formed (Colby and Duesberg, 1969); it is, thus, very plausible that the inhibitory action dependent on virus infection is due to the presence of dsRNA.

Further studies of this particular translation-inhibition cell-free system (which contains in the reaction mixture: dsRNA, ATP and interferon-treated cell extract) by many investigators revealed a number of events upon the addition of dsRNA. Although minor differences exist in some of the reports (e.g. slight differences in molecular weights determined), it is surprising to note the degree of agreement (Brown et al., 1976; Lebleu et al., 1976; Sen et al., 1976; Zilberstein et al., 1976a, b; Roberts et al., 1976b; Revel et al., 1977; Galster and Lengyel, 1976; Kerr et al., 1976; Ratner et al., 1977; Yakobson et al., 1977a, b; Revel, 1977; Lieberman et al., 1974; Swetly and Ostertag, 1974; Shaila et al., 1977; Rossi et al., 1977a, b, c). A summary of these reports shows that two major proteins are phosphorylated in the reaction mixture; the molecular weight of the larger one ranges between 60,000 and 67,000 daltons and the smaller one between 30,000 and 37,000 daltons. These were proposed to be Ml and eIF-2 initiation factors of the ribosome translation complex by Revel (1977).

An endonuclease activity was observed which degrades both cellular and viral mRNAs. In the studies with reovirus mRNAs it was found that this endonuclease degrades larger mRNAs faster than smaller mRNAs, and that dsRNA isolated from reovirus subparticles in interferon-treated cells contains shorter dsRNAs, suggesting an interferon-induced endonuclease-generated degradation. This endonuclease activity apparently is not limited to one cell type since it is found in many species.

A low molecular weight inhibitor of translation (LMWIT) was found in extracts of interferon-treated cells when dsRNA and ATP were added (Roberts et al., 1976b). This LMWIT was identified to be an unusual oligonucleotide with the following structural formula:

$$\text{pppA}^2\text{P}^\gamma\text{A}^2\text{P}^\delta\text{A}$$

(Kerr and Brown, 1978; Ball and White, 1978). This LMWIT did not appear to be an inhibitor itself as there was a lag period of about 15 min after its addition to a translating system (rabbit reticulocyte) before termination of translation. It seemed likely that it induces (or regulates) the formation of other inhibitors (Hovanessian et al., 1977). Kerr et al. (1977) reported that LMWIT was synthesized by enzymes present in interferon-treated cell extracts. The inhibitor was found to be sensitive to alkali, alkaline phosphatase, and snake venom phosphodiesterase, but was resistant to various nucleases (micrococcal, P1, T2 and U2). LMWIT is a very active compound capable of inhibiting translation at nanomolar concentration. An apparent action of LMWIT was reported to be an activator of an endonuclease (Clemens and Williams, 1978). It will be interesting to see if this inhibitor exerts a selective translation inhibition against viral RNA in intact cells and whether it will enhance toxicity of dsRNA to intact cells.

It is apparent that interferon treatment of many types of cells induces enzyme(s) which, in the presence of dsRNA and ATP, will phosphorylate proteins and LMWIT (Werenne and Rosseau, 1976b). This phosphorylation phenomenon is also found in cells treated with type II interferon (Wietzerbin et al., 1977) and in dsRNA- and ATP-treated extracts of virus-resistant mouse cells which are apparently spontaneous.
producers of low levels of mouse interferon (Jarvis and Colby, 1978). Treating cell extracts from human-mouse hybrids (containing only chromosome 21 of human origin) with dsRNA and ATP, Slate et al. (1978) found that the mouse 67,000 dalton protein marker was phosphorylated. Human protein marker similarly obtained from human cell extracts was reported to be slightly larger (Lebleu et al., 1976). A compound apparently identical to LMWIT is synthesized by enzymes from rabbit reticulocytes (Hovanessian and Kerr, 1978). It was also found by Cooper and Farrell (1977) that a cytoplasmic extract of interferon-treated L cells, when mixed with dsRNA and ATP, will inhibit protein synthesis in the rabbit reticulocyte system. This inhibition is apparently due to the phosphorylation of met-tRNA binding factor resulting in a defect of peptide chain initiation. Addition of initiation factor eIF2 reduces this inhibition of translation, suggesting that interferon may inhibit translation via the phosphorylation of eIF2.

Other actions of interferon treatment on translation inhibition were investigated by addition of components essential for protein synthesis to the cell-free extracts and observing for relief of translation-inhibition. Transfer RNA was the obvious component to be investigated in detail. Addition of tRNA was found to alleviate translation-inhibition in interferon-treated cell extracts by many investigators (Gupta et al., 1973, 1974; Content et al., 1974, 1975; Hiller et al., 1976; Weissenbach et al., 1977; R. Falcoff et al., 1976; Zilberstein et al., 1976a; Mayr et al., 1977). This reversal effect could be detected with different tRNAs for viral and cellular mRNAs. Falcoff et al. (1976) reported that tRNA<sup>hu</sup> was responsible for the reversal of translation inhibition of polyuridylic acid; whereas with Mengo mRNA, tRNA<sup>hu</sup> only partially reversed the inhibition. Polycytidylic acid was found not to be translation-inhibited by interferon but, surprisingly, translated better in interferon-cell extracts than in normal cell extracts, an interesting but puzzling observation. Several investigators suggest that perhaps tRNA in interferon-treated cell extracts is more labile (Sen et al., 1976), but Colby et al. (1976) found that tRNA from control and interferon-treated mouse L cells had the same number of tRNA<sup>hu</sup> isoacceptors and that tRNA from both reversed translation-inhibition of reovirus mRNA equally. Content et al. (1974) made similar observations, thus negating the suggestive difference in tRNA lability. Other parameters of translation-inhibition found to be inhibited in interferon-treated cell extracts were methylation of reovirus mRNA (Sen et al., 1975, 1977; Shaila et al., 1977) and the identification of an inhibitor of the discharge of amino acid previously esterified to a viral mRNA (Sela et al., 1976). The significance of either of the above described effects with respect to mechanism of interferon action still remains to be elucidated.

2.2.4. Inhibition of Maturation and Release

Evidence from studies of RNA-tumor viruses has shifted some of the attention on mechanism of action of interferon from the early stages of virus infection (described above) to the later stages of virus replication—maturation and release (Billiau et al., 1974, 1975; Friedman and Ramseur, 1974; Friedman et al., 1975). Investigators from these two laboratories observed an accumulation of RNA-tumor virus components in interferon-treated cells which also released significantly less C-type particles than normal cells. This late arrest of virus replication apparently is not the only mechanism of action of interferon against tumor viruses. Other replication inhibition mechanisms against both RNA- and DNA-tumor viruses by interferon have been reported (Bader, 1962; Birg and Meyer, 1975; Fitzgerald, 1969; Gottlieb-Stematsky et al., 1966; Oxman et al., 1967b; Peries et al., 1968; Van Griensven et al., 1971).

In tumor virus replication the viral genome is duplicated and incorporated into the cell genome, at which state the cell can become a chronic pro-virus carrier and is capable of producing virus either spontaneously or can be induced to do so. Treatment of cultures with interferon (which is then retained in culture medium) prior to infection with murine sarcoma virus prevents transformation of the culture
and virus production; however, interferon treatment after infection was not effective, suggesting an inhibition of virus production but not synthesis and incorporation of proviral RNA (Fitzgerald, 1969; Peries et al., 1968; Pitha et al., 1976b; Sarma et al., 1969).

Cultures infected with oncornaviruses, but not producing viruses, can be induced by treating the cultures with pyrimidines, cycloheximide and glucocorticoids. Treatment of such induced cultures with interferon decreases the amount of virus released (Blaineau et al., 1975; Lieberman et al., 1974; Pitha et al., 1976b; Ramoni et al., 1977; Ramsaur and Friedman, 1976; Rossi et al., 1977a, b, c; Swetly and Ostertag, 1974; Wu et al., 1975, 1976). The amount of intracellular gs-antigen produced in cultures induced by iododeoxyuridine is not affected by interferon treatment.

With murine leukemia virus the following observations were reported with interferon treatment: (a) upon removal of interferon, virus production rapidly resumed; (b) viral protein p30, reverse transcriptase unchanged (Friedman and Ramsaur, 1974; Friedman et al., 1975; Pitha et al., 1976b; Shapiro et al., 1977); (c) no cleavage inhibition of several precursors of major viral protein (Pitha et al., 1977; Shapiro et al., 1977); (d) number of virus particles budding on surfaces of cells greatly increased while extracellular virus decreased by 90–95% (Chang et al., 1977a); (e) these budding particles are disproportionately high in transcriptase-to-infectivity ratios (Pitha et al., 1976b).

In the case of C-type particles, it was found that upon interferon treatment of cultures chronically producing these particles the number of particles associated with cultures is not reduced but increased, whereas the extracellular virus was markedly depressed (Allen et al., 1976; Billiau, 1975, 1977; Billiau, et al., 1973, 1974, 1975, 1976a, b; Chang et al., 1977a; Friedman, 1977; Friedman and Ramsaur, 1974; Friedman et al., 1975, 1976, 1977; O'Shaughnessy et al., 1974; Peries et al., 1968; Ramsaur and Friedman, 1976; Salzberg et al., 1978; Shapiro et al., 1977; Van Griensven et al., 1971). It was suggested by Van Griensven that the C-type particles were defective in RNA content. Billiau, however, was unable to detect any physical deficiencies.

In the case of Moloney leukemia virus, interferon treatment of infected cells causes production of virions with high particle/infectivity ratios and an accumulation of a large 85,000 dalton glycoprotein which was suspected to be an uncleaved precursor of viral protein gp67–71 (Chang and Friedman, 1977; Chang et al., 1977b; Wong et al., 1977).

Thus it appears that the inhibitory action of interferon on tumor virus replication is at the later stages of replication, either during assembly, maturation or release. These effects could be achieved by inhibition of cleavage of a viral component, inhibition of translation of viral genome, or alteration of cell membrane, such as the thickening of the mucopolysaccharide layer of interferon-treated cells as proposed by Billiau et al. (1977). Even in the case of an incomplete inhibition of virus replication, a partial reduction in synthesis of viral components may lead to an increased yield of defective virus particles, in which case interferon would have successfully limited subsequent virus cycles.

2.3. Antiviral Actions of Interferon—A Simple Model

Virus infection of cells and the subsequent production of progeny viruses involve many stages, each of which could be subjected to some inhibitory action of interferon, although the bulk of information available on interferon mechanism of action seems to point to translation inhibition.

We will briefly review the virus infection process and propose a simple model of all the possible inhibitory actions of interferon on the infection process. Attachment, penetration (pinocytosis) and uncoating of virus in cells does not normally seem to be inhibited by interferon treatment of these cells. After uncoating, the infection process depends upon the type of genetic material carried by the virus, e.g. single-stranded RNA or DNA (positive or negative strand) and double-stranded RNA or DNA. With
negative-stranded RNA virus, progeny viral proteins can be directly translated from this template; however, if the virus contains either positive-stranded RNA, or DNA (single or double), at least one round of transcription is required before any progeny viral proteins can be translated. This extra step in the replicative process can be subjected to interferon inhibition in the following ways: template degraded; transcriptase inactivated; initiation of transcription arrested; elongation of transcript inhibited; and finally errors in transcript processing by inhibition of polyadenylation and capping of transcript. Splicing errors in transcription could also occur. If an infecting virus (except minus-strand RNA viruses) survives all these inhibitory actions, it is now ready to translate progeny viral protein. A multifaceted inhibition of translation by interferon could occur. They are as follows: template degradation; binding of mRNA to ribosomes inhibited; initiation of translation inhibited, either via a deficiency of initiation factors or inactivation of initiation factors; elongation arrest, by either alteration, or a deficiency of elongation factors and/or transfer RNA; and finally defects in termination either by premature release or inhibited release. Accumulation of double-stranded RNA (replicative forms) could signal initial successful virus infection events. The presence of dsRNA structures within the cell could then trigger 'second-line' mechanisms induced by interferon within the cell to try harder to inhibit the viral replicative process. These mechanisms involve the expenditure of ATP for activation of a kinase and another enzyme to synthesize the low molecular weight inhibitor of translation (LMWIT), inactivation of initiation factors and activation of endonuclease. This endonuclease can then inhibit translation by degrading viral (and cellular?) mRNAs. Further accumulation of dsRNA in the cell, if the interferon-induced first- and second-line defenses fail, could cause the cell to undergo suicide via toxicity enhancement of dsRNA by interferon treatment, thus preventing further virus multiplication. Should a viral infection progress beyond translation inhibition, the replicative process could still be inhibited by preventing cleavage of translated precursor proteins and, finally, interferon-induced membrane alterations may inhibit the release of mature virus. Interferon treatment may also cause the increased assembly of defective virions and their release, which will interfere in subsequent cycles of virus infection and replication.

It seems that interferon treatment triggers a myriad of actions in the host cell, in a way 'arming' the treated cell with many alternate means of defense against many types of virus infection and replicative processes, and should all else fail, the cell is set to self destruct (lysis by toxicity enhancement of dsRNA) to prevent further virus replication, thereby altering pathogenesis of virus infection.

3. NON-ANTIVIRAL ACTIONS OF INTERFERONS

The term non-antiviral activity (NAVA) of interferon was coined by Stewart II et al. (1971a). There are prior reports which described activities of interferon other than antiviral, but were mostly disregarded as due to impurities found in interferon preparations or being mediated by the antiviral activity of interferon. With improved purification techniques, it is now certain that interferon can cause a number of alterations in cells, and the list of NAVAs is growing steadily. Some of these NAVAs are obviously related, and some may prove not to be caused by interferon after all. We will examine each of these NAVAs in the following section with emphasis on determining whether they are actually induced by interferons or by contaminants. The literature published on this aspect of 'interferonology' is tremendous, hence only representative references will be cited.

3.1. ANTIMICROBIAL ACTIONS (OTHER THAN ANTIVIRAL)

Interferons have been shown to inhibit several microbial agents: Chlamydia sp. (Sueltenfuss and Pollard, 1963; Hanna et al., 1966, 1967); protozoa including Plasmodium sp. (Sutharasarai and Rytel, 1973; Jahiel et al., 1970; Remington and
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Merigan, 1968, 1969); Rickettsia sp. (Kazar et al., 1971); and even bacteria Shigella flexneri (Gober et al., 1972). The sensitivities of these microbes to interferon were found to be generally less than that of virus (vesicular stomatitis virus), but mechanistically this is unrevealing as viruses can exhibit a broad spectrum of sensitivity. Interferon inducers have also been reported to inhibit the multiplication of: Klebsiella pneumoniae (Weinstein et al., 1970); Pasteurella tularensis; Diplococcus pneumoniae (Giron et al., 1972) and Mycobacterium leprae (Levy and Merigan, 1977) and the enhancement of fungal infection (Worthington and Hasenclever, 1972); Trypansoma cruzi (Kumar et al., 1971) and Listeria monocytogenes (Gruenewald and Levine, 1976). Since interferon itself does not exhibit these activities, these observations can at best be classified as having cursory relationship to interferon action.

There are other observations which involve interferon more directly. Rabbit interferon was found to be inhibitory for Toxoplasma gondii in rabbit cells (Schmunis et al., 1973), and Herman demonstrated interferon interference of Plasmodium gallinaceum malaria in chickens (Herman, 1972; Herman et al., 1973).

3.2. PRIMING AND BLOCKING

Priming is defined as the increased production of interferon by cells which are treated with interferon prior to exposure to inducer. Blocking is defined as the decreased production of interferon by cells which are treated with high concentrations of interferon prior to induction. The two phenomenon differ in the amount of interferon used for pretreatment, with dramatically different end results.

We now compare and contrast these two non-antiviral actions of interferon in an attempt to resolve the reason for the diametrical results.

Repeated exposure to inducers of interferon has been found also to cause priming (Burke and Isaacs, 1958; Ho and Breining, 1962; Mahdy and Ho, 1964; Billiau, 1970; Goorha and Gifford, 1970a, b). Interferon-primed cells produce more interferon than normal cells when they are induced with poly(rI).poly(rC) (Rosztoczy and Mecs, 1970; Stewart II et al., 1971b) and primed cells have the same size requirement for poly(rI).poly(rC) molecules to trigger interferon production (Stewart II and DeClercq, 1975). Interferon-blocked cells are also blocked in interferon production when induced with poly(rI).poly(rC) (Youngner and Hallum, 1969; Stewart II et al., 1971b; Golgher and Paucker, 1973; Roussel, 1974; Barmak and Vilcek, 1973). Development of priming differs from the development of blocking in temporal aspects. Cells become primed in less than 1 hr when treated with 100–1000 units of interferon per ml (Giron et al., 1971; Stewart II et al., 1971a) whereas several hours of exposure to 1000 units of interferon per ml is required for blocking to develop (Paucker and Boxaca, 1967; Stewart II et al., 1971b; Barmak and Vilcek, 1973; Roussel, 1974; Lobodzinska et al., 1975). Protein synthesis in host cells is not required for the development of priming since cells treated with interferon in the presence of cycloheximide, puromycin or p-fluorophenylalanine became fully primed (Stewart II et al., 1971a; Knight, 1974b; Rosztoczy, 1974; Barmak and Vilcek, 1973). Protein synthesis, however, is required during exposure to interferon for blocking to develop; if protein synthesis is arrested, the cells do not become blocked even after prolonged exposure to high concentrations of interferon but, instead, become primed. Thus, the time period of exposure and the requirement for protein synthesis appear to be the major distinctions between priming and blocking development. After the development of priming or blocking, subsequent production of interferon at the altered level (enhanced or depressed) occurs more quickly than in normal cells (Paucker and Boxaca, 1967; Stewart II et al., 1971a, b; Rosztoczy and Mecs, 1970; Rosztoczy, 1971; Stewart II et al., 1972d; Ustacelibi and Williams, 1973; Friedman, 1966; Levy et al., 1966; Stewart II and DeClercq, 1973; Levy–Kowmig et al., 1970a). The production of interferon in the interferon–treated cultures requires RNA and protein synthesis, but the lag period required for interferon messenger RNA synthesis is shorter in primed cells (demonstrated by actinomycin D treatment). This finding suggests that interferon
mRNA synthesis in primed cells is much faster probably, through a shortened induction process. In cell cultures that normally have a short induction-lag phase, there is no observable quicker response time when these cells were pretreated with interferon (Stewart II et al., 1971b; Tovell and Cantell, 1971; Barmak and Vilcek, 1973). These data suggest that interferon priming removes some restriction on the induction process that normal cells with long induction-lags must perform before they can initiate interferon mRNA synthesis (Stewart II et al., 1972d). Recent experiments in our laboratory have directly demonstrated that interferon mRNA is made more quickly in primed cells than in normal cells, but there is no increase in the amount of interferon mRNA in primed cells as compared to unprimed cells and the half-life of the interferon mRNA is the same in both primed and unprimed cells. Thus, the increased interferon yields must result from more efficient translation of this interferon mRNA (S. Abreu and W. Stewart II, unpublished data).

Interferon priming also removes the requirement of mouse cells for DEAE dextran to be induced by poly(rI)·poly(rC) (Rosztoczy, 1971; Stewart II et al., 1972a), suggesting a cell surface alteration by interferon treatment. Priming activity in human cells is, in spite of claims to the contrary (DeClercq et al., 1975a), apparently determined by chromosome 21 (Frankfort et al., 1978).

Finally, the question of whether priming and/or blocking activities of interferon preparations are really due to interferon and not some co-purifying contaminant. Priming activity has been found in every species that has been tested, with each interferon preparation assayed. Priming activity exhibits the same defined host-range of activity as the antiviral activity (Levy–Koenig et al., 1970b; Stewart II et al., 1971a; Ito and Kobayashi, 1974; Rousset, 1974). Interferon was found to maintain a constant ratio of antiviral unit/priming (and blocking) unit through more than a 1000-fold purification (Stewart II et al., 1971a), and a 1,000,000-fold purification (Stewart II, 1975b); and we have recently found that mouse interferon purified to 10⁶ units/mg of protein is able to prime cells in the same ratio/antiviral unit as ‘crude’ (10⁶ units/mg protein), ‘semi-crude’ (10⁵ units/mg), ‘partially purified’ (10⁴ units/mg), ‘purified’ (10³ units/mg) and ‘highly purified’ (10² units/mg) preparations. The low molecular weight modified form of mouse interferon, the ‘interferoid’, is also identical in this respect to native mouse interferon (Stewart II, Lin and Wiranowska-Stewart, unpublished data). The priming (and blocking) factor fulfills the criterion for acceptance as interferon.

3.3. CELL-MULTIPLICATION-INHIBITION (CMI)

3.3.1. Evidence that CMI Is Due to Interferon

The ability of interferon preparations to inhibit normal cell replicative events and cell multiplication was first reported by Paucker et al. in 1962. Since then this observation has been the subject of many disagreements with one side claiming this inhibition is due to interferon itself (Fontaine–Brouty–Boyé et al., 1969; Gresser et al., 1970a, b, 1973, 1974; Lindahl–Magnusson et al., 1971; Tovey et al., 1975; Knight, 1973; Hilfenhaus and Karges, 1974; Adams et al., 1975; Tan, 1975; Gaffney et al., 1973; Hilfenhaus et al., 1976; Lee et al., 1972; O’Shaughnessy et al., 1972; McNeill and Gresser, 1973; Kishida et al., 1971, 1973; Ohwaki and Kawade, 1972), while others either failed to observe any inhibition or observed fluctuation in ratios of antiviral to cell-multiplication-inhibitory activity in interferon preparations, thus assigning this activity to factors in the preparation other than interferon (Cocito et al., 1965; Baron et al., 1966c; Levy and Merigan, 1966; Baron and Isaacs, 1962; Marcus and Salb, 1966; Moehring and Stinebring, 1971; Kishida et al., 1971; Borecky et al., 1972; Fuchsberger et al., 1975; Matsuizawa and Kawade, 1974). One of the reasons for this controversy regarding cell-multiplication-inhibitory activity of interferon was due to the different assays used to demonstrate this effect. The conditions delineated by Lindahl–Magnusson et al. (1971) help to alleviate this problem, viz. to demonstrate cell-multiplication-inhibition (CMI), cultures must be initiated at sufficiently low density to allow several days of observations before control cell cultures reach saturation.
Despite all disclaimers, the evidence now available is vastly in favor of the interpretation that interferon inhibits cell multiplication:

(a) Interferon preparations, regardless of source, inducing agents and degree of purity, exhibit constant ratios of antiviral and CMI activity with identical defined host-range in both activities (Gresser et al., 1970a, b; 1971, 1973; Stewart II et al., 1976; Babiuk and Rouse, 1976).

(b) Mouse L_{1210} cells resistant to the antiviral action of interferon (Gresser et al., 1970a, b), unable to bind interferon (Gresser et al., 1974), are also resistant to the CMI action of interferon preparations (Gresser et al., 1970a, b; Lindahl–Magnusson et al., 1971; Gresser et al., 1974). Human cells trisomic for chromosome 21 are more sensitive to the antiviral activity of human interferon (Tan et al., 1973), bind more interferon (Wiranowska-Stewart and Stewart II, 1977) and are also more sensitive to the CMI actions of interferon preparations (Tan, 1976, 1977; Cupples and Tan, 1977).

(c) The individual species of interferons from both human and mouse sources isolated by SDS-polyacrylamide gel electrophoresis are identical with respect to antiviral and CMI activities (Stewart II et al., 1976; Knight, 1976a).

(d) Highly purified preparations of interferons have been shown to induce CMI equally as well as crude preparations. The highly purified interferons tested include: mouse interferon with a specific activity of up to $10^9$ units/mg protein (Gresser, 1977; Stewart II et al., 1978b); human fibroblast interferon at $2 \times 10^8$ units/mg (Knight, 1976); human leukocyte interferon purified to a single spot in two-dimensional gel electrophoresis (Lin et al., 1978); and mouse interferoid purified to about $10^9$ units/mg of protein (Stewart II et al., 1978a).

3.3.2. **Cellular Systems Susceptible to CMI Action of Interferon**

Interferon-induced cell inhibition is a reversible event (Gresser et al., 1970a, b; Paucker et al., 1962; Gaffney et al., 1973; O'Shaughnessy et al., 1974). Upon removal of interferon, cells return to their normal growth rates. As with other biological systems, different types of cells respond to CMI activities of interferon to different degrees. Multiplication of mouse L_{1210} cells can be inhibited almost completely by 100 units/ml of interferon and shows 90% inhibition with about 10 units/ml (Stewart II et al., 1976; Gresser et al., 1970a, b). Human lymphoblastoid cell lines showed vast differences in their response to CMI activities of interferon: Daudi cells are inhibited by about one unit or less (Stewart II et al., 1976) while others are resistant to several thousand units (Adams et al., 1975; Hilfenhaus et al., 1977a; Hilfenhaus and Karges, 1974). Primary cell cultures are usually less sensitive than established cell lines (Lindahl–Magnusson et al., 1971, 1972; Knight, 1973; Lee et al., 1972). Strander and Einhorn (1977) reported that several lines of osteosarcoma cells were all inhibited by human leukocyte interferon, and were more sensitive than non-tumor-derived lines.

Cell-multiplication-inhibitory effects of interferon are not due to toxicity of interferon, as ratios of viable cell counts to total cell counts remain about the same during inhibition, but interferon-treated cells often plateau at a lower saturation density than normal cells (Gresser et al., 1970a, b; Knight, 1973). Collyn d'Hooghe et al. (1977) have reported that the intermitotic time, as followed by time-lapse photomicrography was markedly and progressively increased at all phases rather than arrested at any given phase. Sokawa et al. (1977) reported that interferon suppressed the transition of 3T3 cells from a quiescent to a growing state.

3.3.3. **Cell Effects In Vivo**

Interferon also was found to inhibit the growth of normal and tumor cells *in vivo*. The inhibition of tumor cells *in vivo* is discussed in Section 6; here we describe only activities of interferon on normal cells *in vivo*.

Inducers of interferon and interferon itself inhibit the multiplication of allogenic and syngeneic bone marrow cells in irradiated mice (Cerottini et al., 1973). Inoculation of hamsters with poly(rI)-poly(rC) resulted in the discovery of a hemopoietic cell-
colony formation inhibitor in the serum of these animals by McNeill and his colleagues (McNeill and Fleming, 1971; Fleming et al., 1972; McNeill et al., 1972). Interferon inducers [poly(rI)-poly(rC), Newcastle disease virus and statolon] were reported to inhibit the mitotic response of liver cells to partial hepatectomy (Jahiel et al., 1971); later interferon itself was shown to have the same effect (Frayssinet et al., 1973).

Repeated injections of 32,000–64,000 units per day of interferon into newborn mice do not affect growth or development in these animals (Gresser and Bourali, 1970a). However, when the dosage was increased to 800,000 units per day, the newborn mice died with extensive liver damage after about one week (Gresser et al., 1975b). If injection was halted between days 6 and 9, liver damage appears to be reversible, and the animal recovers, but several of the apparently recovered animals died a few months later of progressive glomerulonephritis (Gresser et al., 1976b).

Riviere et al. (1977) inoculated newborn mice with lymphocytic choriomeningitis virus and found the following pathology: decreased weight gain, liver necrosis and death. With inoculation of anti-interferon antiserum into these animals, virus levels increased more than 100-fold, but disease manifestations were inhibited, suggesting that chronic virus-induced interferon led to decreased weight gain, liver disease and eventually death. Bekesi et al. (1976) also reported that repeated injection of high doses of interferon into AKR mice caused early death with marked signs of ‘wasting’ (organ atrophy, small spleens, athymic).

3.3.4. Metabolic Alterations in Interferon-treated Cells

The exact mechanisms of the suppression of cell multiplication by interferon are far from approachable at present. Since the antiviral mechanism of interferon does inhibit viral mRNA translation, it is easy to assume that some of the cellular mRNAs are also inhibited in their translation. There are early reports that interferon exerts no effect on cell metabolism (Joklik and Merigan, 1966; Levy and Merigan, 1966; Merigan et al., 1965; Wagner, 1963; Cocito et al., 1962; Sonnabend, 1964; Friedman and Sonnabend, 1970); however, refinements and sophistication in molecular biological techniques and experimental designs resulted in reports that demonstrate clearly that interferon does alter metabolism of cells.

In 1968, Johnson et al. reported that mouse interferon (at 800 units/ml) inhibited amino acid incorporation in L cells, but had no effect on heterologous cells. Falcoff et al. (1975) reported that mouse interferon (1000 units/ml) consistently inhibited endogenous protein synthesis in L cells by 20–40 per cent, and that this inhibition parallels kinetics of virus resistance. Brouty-Boyé et al. (1973) reported that mouse L1210 cells (sensitive to interferon) showed a significant decrease in total cellular RNA and protein synthesis when treated with interferon, whereas L1210r cells (resistant to interferon) did not show any such effects. O'Shaughnessy et al. (1972) reported a delay of thymidine uptake in interferon-treated synchronized L cells. Fuse and Kuwata (1976) also found reduced synthesis of DNA and protein in interferon-treated human RSa cells. Synchronized RSa cells stopped DNA synthesis if interferon was added at the G1 phase but showed no such effect if added at the G1/s boundary phase. Chemostat culture systems for animal cells were developed by Tovey and co-workers (Tovey et al., 1975; Tovey and Brouty-Boyé, 1976; Brouty-Boyé and Tovey, 1977); mouse interferon was maintained in this system at a final concentration of 24,000 units/ml by continuous addition, and its effect on mouse L1210 cells cultured at steady state was investigated. The following results were reported: rapid inhibition of thymidine incorporation (within 2 hr of interferon addition) but not of deoxyadenosine or deoxy-D-glucose; no inhibition of amino acid or uridine uptake was observed.

3.3.5. Restraints Imposed by Interferon

Interferon-treated cells are slowed from normal growth, and are also restrained from stimulated proliferation. Lindahl–Magnusson et al. (1972) showed that interferon
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preparations inhibited DNA synthesis induced in mouse splenic lymphocytes by phytohemagglutinin or allogeneic lymphocytes. Blomgren et al. (1974) reported that human leukocyte interferon (10 units/ml) suppressed human lymphocyte proliferative stimulation by phytohemagglutinin, concanavalin A and PPD and the mixed lymphocyte reactions.

Interferon is also able to suppress cells in vivo. Pacheco et al. (1976) reported that spleen cells from mice inoculated with interferon (10 units) at 18 hr before excision do not incorporate thymidine, even when stimulated with lectin, phytohemagglutinin, concanavalin A or lipopolysaccharide. Cupples and Tan (1977) noted that cells from Down's syndrome patients exhibited inhibition of DNA synthesis to a greater degree than normal cells by interferon treatment prior to antigenic or mitogenic stimulation.

In addition to decreased DNA synthesis by interferon treatment, specific cellular constituents (enzymes) were also reported to be inhibited. These include: decreased tyrosine amino transferase production in rat HTC cells exposed to dexamethasone (Beck et al., 1974; Vassef et al., 1974); inhibited production of glycerol-3-phosphate dehydrogenase in rat glial cells induced with hydrocortisone hemisuccinate (Illinger et al., 1976); suppressed induction of glutamine synthetase in chick embryonic neural retina by hydrocortisone (Matsuno et al., 1976).

The above data all indicate a general restraint induced in cells by interferon. Recent reports that interferon can stimulate release of prostaglandin E (Yaron et al., 1977; Karmazyn et al., 1977) and that inhibitors of prostaglandin E production (cortisol and indomethacin) prevented the inhibitory effect of interferon on synovial fibroblast growth suggest that the restraint interferon imposes may be a secondary effect, since prostaglandin E is capable of regulating cell replication.

3.4. TOXICITY ENHANCEMENT

It has often been shown that there is a direct correlation between the ability of polynucleotides to induce interferons and their toxicity (Niblack and McCreary, 1971; DeClercq et al., 1972; DeClercq and Stewart II, 1972; Stewart II and DeClercq, 1974); in fact, these two properties of dsRNAs have not been separable, although such claims have been made (O'Malley et al., 1975; Ts'o et al., 1976). Poly(rI)-Poly(rC) at concentrations too low to induce interferon synthesis in normal cells were capable of stimulating production of interferon in primed cells (Rosztoczy, 1971) which were also found to be markedly more sensitive than normal cells to toxicity by the dsRNA, poly(rI)-poly(rC) and are lysed within 3-6 hr (Stewart II et al., 1972a). This enhanced sensitivity to toxicity was also found with several natural and synthetic dsRNAs and correlated with the relative abilities of these polynucleotides to induce interferon and with the minimum required polynucleotide size for induction of both effects (Stewart II et al., 1973a; Stewart II and DeClercq, 1974). The fact that toxicity enhancement was not seen with single-stranded RNA, DNA, tilorone, endotoxin, CoAM, cycloheximide, actinomycin D, DEAE-dextran, rattlesnake venom, diphtheria toxin, or cholera toxin suggests that the enhancement process was specific for dsRNAs.

Toxicity enhancement was also observed when primed cells were infected with vaccinia virus. This system was studied by many investigators and their respective observations were compiled as follows: interferon-treated L cells began to convert to 'ghost' at about 3 hr after vaccinia virus infection; at about 6 hr practically all the cells are lysed; a viral gene product must be synthesized before cell lysis occurs; and treatment of the primed cells with cycloheximide or actinomycin D at the time of infection prevents cell lysis (Joklik and Merigan, 1966; Horak et al., 1971; Jungwirth et al., 1972a, b; Bodo et al., 1972; Stewart II et al., 1972a, 1973a). These data suggest that a viral gene product, not the virus itself is responsible for the lysis of interferon-treated cells. This along with the observation that dsRNA was found in vaccinia-infected cells (Colby and Duesberg, 1969) adds to the speculation that toxicity enhancement is specific for dsRNAs.

Similar cell lysis phenomena were observed in interferon-primed cells infected with
vesicular stomatitis virus (Katz et al., 1974), primed human conjunctival cells infected with influenza virus (Green and Mowshowitz, 1978) and repeated exposure of cells to poly(rI)-poly(rC) (Billiau et al., 1972; Martelly and Jullien, 1974), possibly due to induced interferon priming the cells for enhanced toxicity by the dsRNA.

The amount of interferon required to induce this effect is similar to that required for inducing resistance to virus. The extent of cell destruction is dependent on both the amount of interferon used to prime cells and the amount of dsRNA applied (Stewart II et al., 1972b; Lackovic and Borecky, 1976). Several hours of treatment with interferon are required for cells to develop toxicity enhancement, during which time protein synthesis is required (Stewart II, unpublished data). This indicates that toxicity enhancement differs from priming in that cellular metabolic activity is required for this phenomenon to occur. Addition of dsRNA to interferon-treated cells leads to cell lysis within 3 hr after addition of dsRNA; no damage to the cell is visible before that time, and lysis is complete in 6 hr. Just prior to lysis, internal destruction within these cells can be detected by cytochemical staining. Loss of succinic dehydrogenase indicates injury to mitochondria; diffuse acid phosphatase activities suggest lysosomal damage and nuclear swelling concomitant with a decrease in protein synthesis (Stewart II et al., 1975a). Heremans et al. (1976) demonstrated by electron microscopy the same mitochondrial and nuclear damage in these cells just prior to lysis.

Cells treated with interferon were reported to be more sensitive to the toxicity of a variety of compounds, e.g. DEAE-dextran, protamine sulfate, methylated albumin and concanavalin A (Lee and Rozee, 1975; Katz et al., 1974; Stewart II et al., 1973a, 1975a). However, this increased sensitivity does not seem to involve the same mechanism as that for dsRNA. At least the increased toxicity of concanavalin A may be related to the increased binding of this lectin to interferon-treated cells (Huet et al., 1974).

Toxicity enhancement by interferon likely plays a role in vivo as well as in cell culture. The presence of interferon in virus-infected patients could preclude using dsRNAs as a therapeutic (Stewart II et al., 1972a). Virus-infected mice were found to be more susceptible to dsRNA than were normal, uninfected mice (DeClercq et al., 1973). Injection of rabbits with human leukocyte interferon (a few million units per rabbit) and Newcastle disease virus in combination caused death in most rabbits whereas neither virus nor interferon singly was lethal (Cantell et al., 1974b). Following the observation that intramuscularly inoculated interferon binds locally (Harmon and Janis, 1975), Stewart and his co-workers used combination injections of interferon followed by poly(rI)-poly(rC) into the palpable autochthonous tumor induced by Moloney sarcoma virus in mice (Stewart II et al., 1975b; DeClercq and Stewart II, 1974). Interferon alone was ineffective, poly(rI)-poly(rC) was marginally effective: sequential injection of interferon and poly(rI)-poly(rC) was effective in regressing tumor growth and prolonging life. This encouraging preliminary observation definitely warrants further investigation.

The toxicity-enhancement factor in interferon preparations has been shown to be interferon: it is purified with interferon through more than 1000-fold (Stewart II et al., 1972a) and one million-fold (Stewart II et al., 1973b) increases of interferon specific activity; identical ratios of antiviral and toxicity-enhancing activity in mouse interferon were found in mouse interferon purified to 10^9 units/mg of protein and in pure mouse interferoid (Stewart II et al., 1978).

The above described non-antiviral activities (priming, blocking, cell-multiplication-inhibition and toxicity-enhancement) are now all clearly ascribed to interferons. The following non-antiviral activities are not so well characterized as clearly due to interferon. Studies using pure interferon should soon clarify its involvement in these activities.

### 3.5. Enhanced Synthetic Activities

In addition to the priming activity of interferon on interferon production, it can apparently also increase abilities of cells to produce other products.
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Yaron et al. (1976, 1977) reported that either poly(rI)-poly(rC) or human interferon could enhance production of hyaluronic acid and prostaglandin E by human rheumatoid and nonrheumatoid synovial fibroblasts. The production of hyaluronic acid led these workers to suggest that there is a relationship between interferon production and pathogenesis of accumulated joint fluid during virus infections. Since prostaglan-
din E is a mediator of inflammatory processes, it is tempting to speculate that the 'interferon fever' following inoculation with human fibroblast interferon (DeSomer et al., 1977), and the fibrile response often observed with systemic administration of human leukocyte interferon, may be related to this activity.

Interferon has also been found to enhance the amount of certain induced cell products. Pretreatment with mouse interferon (100 units/ml) enhanced the amount of aryl hydrocarbon hydroxylase produced when these cultures were induced with benzoanthracene (Nebert and Friedman, 1973). Ida et al. (1977) found that either virus, poly(rI)-poly(rC) or human leukocyte interferon enhanced the ability of human leukocytes to release histamine when exposed to ragweed antigen E or anti-IgE; they suggested that interferon may play a role in precipitating (or potentiating) attacks of bronchial asthma during viral infections. Skurkovich and Eremkina (1975) further suggested the role of interferon in allergy and have proposed use of anti-interferon immunoglobulin in the treatment of certain autoimmune diseases.

3.6. INDUCED SURFACE ALTERATIONS

Interferon treatment has been reported to increase the resistance of cultured cells to diphtheria toxin (Yabrov, 1966, 1967; T. J. Moehring et al., 1971; Boquet, 1975; Marchenko et al., 1976), but this effect was not observed in other laboratories (Stewart II et al., 1973a). Kohn et al. (1976) reported that interferon and cholera toxin interfere with receptor interaction of each other; it seems likely that interferon might interfere with diphtheria toxin in the same manner, though Yabrov (1966, 1967, 1975, 1976) suggests that interferon acts by stabilizing cells against perturbation of protein synthesis.

By demonstrating that interferon-treated cells have greater net negative charge on the cell surface, and migrate faster than normal cells in an electric field, Knight and Korant (1977) provided direct evidence for interferon-induced cell surface alteration. Huet et al. (1974) reported an increased binding of 65Ni-labeled concanavalin A to interferon-treated L-1210 cells; the increase was slight at 24 hr, but reaches a maximum after 48 hr. L-1210 cells (resistant to interferon) did not show this phenomenon.

Upon treatment of mouse cells with interferon, the following observations on surface antigen expressions were reported: increased cell-antibody absorbing capacity in L-1210 cells (interferon sensitive) (Lindahl et al., 1973); enhanced expression of histocompatibility antigens of thymocytes and splenic lymphocytes from young mice (Lindahl et al., 1974); enhanced expression of histocompatibility antigens on L-1210 cells similar in all stages of the cell cycle, suggesting that the enhancement was not due to a concentration of cells in a particular phase of the cycle (Killander et al., 1976). Skurkovich et al. (1976a) reported that interferon-treated L-1210 cells exerted an enhanced cell-mediated immune response in mice. Lindahl et al. (1976a, b) also found that injection of interferon into young or mature mice enhanced the histocompatibility displays on the surfaces of their thymocytes and splenic lymphocytes.

The availability of restricted antisera against specific determinants of H-2 complex on mouse lymphocytes allowed investigators to study the surface changes on lymphocytes after interferon treatment with the following results: splenic lymphocytes displayed an increase of four- to eight-fold of H-2K and H-2D antigen but no increase in Ia antigens (Vignaux and Gresser, 1977); an increase in H-2 antigens exposed on mouse T cells with no increase in Ia antigens was also reported by Lonai and Steinman (1977). Injection of mice with interferon also enhances the display of H-2K, H-2K4 and H-2D on splenic lymphocytes and thymocytes (Vignaux and Gresser, 1977). It is of interest to note that interferon is released by immunocytes in response
to antigens or target cells (Svet-Moldavsky et al., 1974), and interferon so induced can, in turn, alter the reactivity of the producing cells to these stimuli.

3.7. ENHANCED IMMUNOLYSIS

Svet-Moldavsky and Chernyakovskaya (1967) demonstrated that, in the presence of crude mouse interferon, normal mouse lymphocytes acquired a killer activity on target mouse L cells; syngeneic lymphoid cells also acquired the ability to exert an antitumor effect against sarcoma in mice inoculated with benzantracene (Chernyakovskaya and Slavin, 1972). Skurkovich and Aleksandrovskaya (1973) also reported stimulation of cytotoxic activity of lymphocytes of mice toward target cells following administration of interferon in vivo. Svet-Moldavsky and his colleagues (1974) also demonstrated that lymphoid cells removed from mice at the peak of interferon production (induced by injection of allogeneic cells) exhibited a strong cytotoxic effect on non-specific target L cells. This suggests that interferon may play a role as a mediator molecule in initiation of various immune reactions.

Lindahl et al. (1972) demonstrated that, when lymphocytes sensitized for leukemia L\textsubscript{1210} cells were treated with interferon, the enhanced cytotoxicity observed was a result of an effect of interferon on lymphocytes and not on the target L\textsubscript{1210} cells. Slavina and Svet-Moldavsky (1973) reported that interferon induced the sensitivity of L cells to the cytotoxic effect of lymphocytes. Thus it seems that in the non-specific system the alteration may be in the target cells, whereas in a specific system the alteration may be in the effector cells.

Recently, Heron et al. (1976) reported an enhancement of the killer activity of human lymphocytes by human leukocyte interferon treatment; Skurkovich et al. (1976b) reported similar findings of enhanced cytotoxicity of human lymphocytes (after interferon exposure) toward cells of lymphoblastoid lines; they also reported that interferon-treated L\textsubscript{1210} cells were more sensitive to the action of cytotoxic antibodies (Skurkovich et al., 1976a, c).

3.8. ENHANCEMENT OF PHAGOCYTOSIS

Phagocytic activities of macrophages, monocytes, peritoneal cells and reticuloendothelial systems could be stimulated by interferon or its inducers to a significantly higher level. Huang et al. (1971) demonstrated an increase of 200–300 per cent in phagocytic activity when mouse peritoneal macrophages were exposed to 50 units/ml of mouse interferon. They showed that this increase of activity could be achieved with several different preparations of mouse interferon and that the enhancing effect on macrophages could be eliminated by treatment with anti-mouse interferon antiserum (Donahoe and Huang, 1973). They further demonstrated that this effect could be accomplished with the interferon inducer, Newcastle disease virus, in vivo (Donahoe and Huang, 1976); the enhancement effect began after several hours and lasted for 60 hr. Imanishi et al. (1975) did not observe this lag in enhancement effect when they treated human peripheral monocytes with human leukocyte interferon. They observed an instantaneous enhancement of phagocytic activity, with an increase in number of phagocytic cells, also. All of the above studies involved enhanced phagocytosis in inanimate particles—latex beads and colloidal particles. Other studies have demonstrated the enhancement with bacteria (Remington and Merigan, 1970), protozoa (Herman and Baron, 1970), and RC\textsubscript{19} leukemia cells (Gresser and Bourali, 1970b). Although there are no studies demonstrating increased phagocytosis of virus, it is tempting to speculate that interferon could enhance the uptake of some virions by cells, thus providing enhanced viremic clearance in infected animals.

3.9. MACROPHAGE ACTIVATION

Khesin et al. (1973) studied the peritoneal exudate macrophages of mice which were injected with interferon. Using criteria of comparative morphology, cytochemistry
and biochemistry, they determined that these macrophages were 'activated' and ascribed the activation effect to interferon. Interferon inducers such as pyran copolymers, poly(rI)-poly(rC) and dextran sulfate, when injected into mice, were found to have the same effect; an enhanced cytotoxicity for tumor cells (Schultz et al., 1977) enhanced spreading on glass and plastic and prominent cytoplasmic granulations (Rabinovitch et al., 1977). This effect was induced by as little as 100 units/ml of interferon and was maximal at 1000 units/ml. Human interferon was only about 1 percent effective in mouse cells. These findings further implicate the interferon system as the determinant in yet another mechanism of 'immune'-mediated antitumor and antiviral activity.

3.10. Delayed-type Hypersensitivity Inhibition

Delayed-type hypersensitivity (DTH) inhibition effect of interferon was first demonstrated by DeMaeyer et al. (1975) who reported that mice inoculated with interferon inducers (Newcastle disease virus, Sendai virus, or statolon) 8 hr before challenge for DTH reaction with picryl chloride painted on the ears showed decreased swelling. Four doses of about $10^6$ units of mouse interferon administered either the day before, or on the same day as, challenge inhibited the DTH reaction. These investigators (DeMaeyer-Guignard et al., 1975) also showed that the afferent arc of the DTH response (primary sensitization), as well as the efferent arc, was inhibited by interferon. Mice treated with interferon 1 or 2 days before sensitization had decreased response to sheep red blood cell (the sensitizing agent). Similar results were obtained using a viral immunogen, Newcastle disease virus (DeMaeyer, 1976). Thus interferon can inhibit sensitization and expression of the DTH reactions to either a hapten, a T-cell-dependent antigen, or a virus.

These studies point up a paradox of interferon activities: interferon, an antiviral agent important in recovery from virus diseases and tumors, can inhibit cell-mediated immune reactions which are essential to defense against certain virus diseases and tumor cell destruction. It may be that different doses and different schedules of interferon administration mediate the immune response to the overall benefit of the animal.

3.11. Interferon Effect on Transplantation Graft-vs-Host Reaction

The effects of interferon on graft survival are quite conflicting with one group reporting an enhanced rejection of transplanted graft, while another group reported a suppression of allograft rejection.

Chernyakhovskaya and Slavina (1972) and Skurkovich et al. (1973a, b) both reported that injections of interferon preparations into mice accelerated the rejection of allografts. Repeated transplantations to mice which were treated with interferon during the first grafting accelerated rejection of the second-set grafts. These workers concluded that interferon given after transplantation enhanced cell-mediated rejections Cerottini et al. (1973) also found that interferon-inducers or interferon preparations exerted inhibitory effects on the multiplication of transplanted allogeneic spleen cells and syngeneic bone marrow cells in irradiated mice. O'Reilly et al. (1976) reported the lack of suppression of marrow engraftment in two bone marrow transplant patients given daily doses of $10^6$ units of crude human leukocyte interferon.

Hirsch et al. (1973) reported that interferon could inhibit the proliferative response of the graft-vs-host reaction in mice and could inhibit the activation of leukemia virus concomitant with this reaction. Injection with daily dosage of $10^6$ units interferon one day before injection of spleen cells led to suppression of the graft-vs-host response. Mobraaten et al. (1973) also found that injection of mice with Newcastle disease virus or statolon, sufficient to give serum interferon levels of $10^6$ units/ml on the day of, or after, grafting significantly prolonged allograft survival; however, if the inducer was given prior to grafting, there was no suppression effect. The inducer tilorone was effective in prolonging allograft survival if given orally; it was also effective in
prolonging skin and heart allografts in rats (Wildstein et al., 1976b) and kidney transplants in dogs (Wildstein et al., 1976a). DeMaeyer et al. (1973) reported that interferon injected intraperitoneally was able to delay allograft rejections across the H-2 barrier. They also found that the better interferon producer mouse strain IF-1b exhibited longer allograft survival than the IF-1 mouse strain when induced with Newcastle disease virus (1975). Hirsh et al. (1977) showed that about 10^5 units of mouse interferon given daily reduced virus activation and the incidence of lymphomas after graft-vs-host reaction in mice and reduced the severity of the rejection reaction itself.

A report that may reconcile the contrasting results on the effects of interferon in graft-vs-host reactions is that of Imanishi et al. (1977). They reported that, in rabbits receiving corneal xenograft, rejection was suppressed if 2 × 10^6 units/ml of interferon were given one drop per eye and administered twice daily. However, a dosage of 2 × 10^5 units/ml with the same regimen of administration enhanced the rejection reaction of the xenograft. It appears that the rejection reaction enhancement or suppression may depend completely upon the dosage, with a high dosage of interferon suppressing the graft-vs-host rejection reaction and a low dosage enhancing the rejection reaction.

3.12. EFFECTS ON ANTIBODY PRODUCTION

3.12.1. In Vivo Antibody Production

The earliest reports regarding this aspect of interferon action claimed that there was no effect in mice (Anderson, 1965; DeSomer et al., 1967; Mazzur and Paucker, 1967; Mazzur et al., 1967). Later investigators were able to demonstrate that interferon and its inducers do have an effect on antibody production with a similar phenomenon to that demonstrated in the graft-vs-host rejection reaction, i.e. high doses of interferon suppress the production of antibody, whereas low doses enhance antibody production (Braun and Levy, 1972).

Merigan and his co-workers have demonstrated that intravenous injections of interferon were able to inhibit both the primary and secondary hemolysin and agglutinin antibody response, depress the synthesis of both IgM and IgG and exert a direct action on B-cell lymphocytes (Chester et al., 1973; Merigan et al., 1975; Brodeur and Merigan, 1974, 1975). Others have been unable to demonstrate some of these effects (Thorbecke et al., 1974). Ngan et al. (1976) reported that, in addition to IgM and IgG, IgE production was completely inhibited with a relatively low dose of interferon (600 units/ml). Humoral response in mice was also found to be modified when the animals are infected with the corona virus, murine hepatitis virus-3, and these modifications correlated with the levels of circulating interferon (Virelizier et al., 1976); primary and anamnestic responses in hamsters were also reported to be suppressed by interferon (Berencsi and Beladi, 1977).

3.12.2. In Vitro Antibody Production

It is gratifying to find that the seemingly contradictory reports about the effect of interferon on in vitro antibody production follow the same pattern as with other immune responses. In this case, the 'bifunctional' reaction is again seen with interferon action, with a high dosage resulting in suppression and a low dose in enhancement (Gisler et al., 1974; Johnson et al., 1974, 1975b; Booth et al., 1976a, b). Inhibition of the antibody responses of spleen cells was found, with no concomitant inhibition of the growth of spleen cell cultures. It was also shown that poly(rI)-poly(rC) was able to inhibit primary antibody response to sheep red blood cells and E. coli lipopolysaccharide in mouse spleen cells (Johnson et al., 1975a), and concanavalin A and staphylococcal enterotoxin were also able to inhibit the plaque-forming cell response (Johnson and Baron, 1976a, b). It is interesting that the effect of poly(rI)-poly(rC) could be neutralized by antiserum against type I interferon, whereas the effects due to
concanavalin A and staphylococcal enterotoxin were not neutralized by the same antiserum. These observations suggest that the effect may be due either to type II interferon or some other as yet unidentified factor.

The action of interferon as an immunomodulator is certainly a new and exciting branch of interferonology.

4. PHARMACOKINETICS OF INTERFERONS

We have described many actions of interferon, from its ability to induce resistance to virus to some potentially useful modifications of immune mechanisms. There are obvious desirable characteristics of actions of interferon that could be exploited for therapeutic use in patients, but how do we need to administer it to attain and maintain maximal effectiveness? In view of the different effects observed with high or low doses, more attention should be paid to this problem than the current philosophy of as much as possible, based on either limited availability or restriction imposed by side effects.

4.1. DISTRIBUTION OF INTERFERON

4.1.1. Circulating Interferon Levels

Interferons, whether induced by viruses, endotoxins, or synthetic inducers, disappear rapidly from both the blood and tissue of animals. Exogenously administered interferon also disappears quite rapidly. Early works included injection dosage from 300 units to $10^4$ units per animal; the injection route was intravenous and the test animals were either mice or rabbits; the average time for circulating interferon to drop to trace amounts ranges from 5 min to 15 min (Baron et al., 1966b; Finter, 1966; Subrahmanyan and Mims, 1966; Gresser et al., 1967a; Ho and Postic, 1967; Ho et al., 1967; Ho, 1967, Bocci et al., 1967).

At one time it was assumed that the cleared interferon was stored to be released rapidly as 'preformed' material (Baron and Levy, 1966). DeClercq and co-workers reported that repeated injections of a low dose of interferon into mice every 2 hr saturated this clearance mechanism, increasing the early half-life of circulating interferon from 1 to 1/2 min (DeClercq et al., 1970; Nuwer et al., 1972). They claimed that the interferon receptor sites in the body became saturated after three injections, and concluded that treatment of virus infection by passive interferon might be feasible, and that subsequently the previously cleared interferon could be released as preformed interferon by injection of cycloheximide (Chester et al., 1972).

Interferon given intravenously exhibits a different clearance profile than that given intramuscularly. The amount of interferon given does not alter the clearance rate, but higher dosage does lengthen the duration when it can be found in the serum. When interferon is given intravenously, the profile of serum interferon exhibits a biphasic curve, a sharp initial drop from the time of injection to about 2 hr, then a gradual drop lasting up to more than 48 hr. The average half-life of the initial serum interferon drop is about 10–20 min, and the average half-life for serum interferon in the latter part of the curve is about 2–4 hr.

Intramuscularly injected interferon exhibits a different profile of serum interferon. When injected intramuscularly, it is likely that interferon sets up a local pool and is gradually absorbed into the circulatory system. The serum interferon profile suggests this possibility: the level gradually rises after intramuscular injection, reaches a peak at about 4 hr, then gradually trails off at a rate similar to that exhibited by the i.v. route. Intramuscular injections apparently maintain serum interferon at a higher level and for a longer period than the i.v. route (Cantell and Pyhala, 1973, 1976; Pyhala and Cantell, 1974; Cantell et al., 1974a; Mogensen et al., 1974; Edy et al., 1975, 1976; Skreko et al., 1973; Cantell et al., 1974b; Habif et al., 1975; Emodi et al., 1975a, b; Finter, 1973; Arvin et al., 1976).

Harmon and Janis (1975) found that poly(rI)-poly(rC) was protective against rabies.
in mice if injected into the same leg that was inoculated with the virus, but was ineffective if injected into the opposite leg. The injected leg muscle contained significantly higher levels of interferon than the other leg. Strander et al. (1973) reported adverse side-effects in a patient about 90 min after intravenous injection of interferon (7000 unit/kg body weight). These side-effects included nausea, fever, increased blood pressure and pulse rate, vomiting and severe shivering. The symptoms decreased with hydrocortisone injection and the patient was normal 10 hr later. Subsequent to this study, all patients received interferon via intramuscular injections, and the only side-effect after injection was fever (Ahstrom et al., 1974; Jordan et al., 1974; Desmyter et al., 1976).

4.1.2. Clearance from the Cerebrospinal Fluid: the Blood–Brain Barrier for Interferon

A few studies have been performed to test the effectiveness of the blood–brain barrier for interferon, by analysis of serum for circulating interferon in test animals after injections of interferon and/or interferon inducers into various parts of the central nervous system, and the reverse experiment, i.e. inject interferon either intramuscularly or intravenously, and then analyze for interferon in cerebrospinal fluid. The animals tested include mice, hamsters, rabbits, monkeys and humans; the sites of injections include cerebrum, theca vertebralis, cisterna magna, lateral ventricle, directly into the cerebrospinal fluid, and lumbar-spinal; inducers include poly(rI).poly(rC), blue tongue virus, rabies virus, and Sendai virus (Kono and Ho, 1965; Ho and Ke, 1970; Cathala and Baron, 1970; Jameson et al., 1977; Stewart II and Sulkin, 1966; Allen and Cochran, 1972; Ho et al., 1974; Habif et al., 1975; Hilfenhaus et al., 1977b). The overwhelming agreement among all the studies reported was encouraging. Interferon remains localized (except intravenous injections) in the injection site area, and the blood–brain barrier was very effective, allowing passage of only a small per cent of the blood interferon into the cerebrospinal fluid. The clearance from the cerebrospinal fluid was found to be at the same rate as labeled albumin, indicating a non-specific clearance. In addition to the blood–brain barrier, Luby et al. (1969, 1971) found what appears to be compartmentalization of interferon at different levels in different areas of the brain in at least two viral encephalitis—St. Louis encephalitis and Western equine encephalitis.

4.1.3. Placental and Other Barriers

A few studies have pointed to other compartment barriers restricting general distribution of interferon within the body. The placenta proved to be an effective barrier for interferon, even when inducers were inoculated into the uterus (Ho et al., 1967; Overall and Glasgow, 1970; Korsantiya and Smorodintsev, 1971; Schafer et al., 1972). In view of the cell-multiplication-inhibitory effect of interferon, the placental barrier for interferon should be extremely important for the welfare of the rapidly developing fetus.

Some studies indicated that interferon is restricted in migrating between the blood stream and the aqueous and vitreous humor of the eye in either direction (Oh and Gill, 1966; Pollikoff et al., 1970; Weissenbacher et al., 1970). Others reported the contrary: interferon injected subconjunctivally was detected in the conjunctiva and serum. A moderate level of interferon was also found in the collateral eyes, with equal levels in the aqueous and vitreous humor. Intramuscular injections of interferon seemed to be beneficial for a patient suffering from herpes keratitis (Kobza et al., 1975). These results suggest a free passage of interferon from the circulatory system to these tissues.

4.2. Metabolism of Interferons

Distribution seems to account for only slight drops of interferon activities after its local production or injection. The possible roles of renal clearance and tissue degradations have been suggested.
4.2.1. Renal Clearance

Ho and Postic (1967) reported that interferon injected into rabbits was partially passed in urine, but this only accounted for about 1 per cent of the injected interferon. Ho (1967) calculated that the renal clearance of virus-induced and endotoxin-induced interferon occurs at different rates, probably due to the differences in molecular weights (Ke and Ho, 1967, 1968; Ho, 1973). A number of reports describe the fate of injected interferons (Gresser et al., 1967a; Bocci et al., 1967, 1968a, b, 1977a, b; Emodi et al., 1975a, b). Cesario and Tilles (1973) reported that human interferon can be inactivated by urine, which probably makes it difficult to have an accurate account of amount of interferon loss via this route. Patients with mumps (Waddell et al., 1968) and other virus infections (Bucknall et al., 1968) were found to have high levels of serum interferon but no detectable urine interferon. This may seem to contradict the other results, but could be reconciled in this manner: in some studies, normal animals were injected with interferon, which does not have any beneficial function in healthy animals, hence is subject to removal by normal body waste elimination mechanisms, while in the latter reports, the patients were suffering from virus infections where interferon was induced to serve a function. Given intricate balances and controls within the body, it is unlikely that during active virus infection there will be superfluous interferon produced that necessitates its removal via renal clearance.

4.2.2. Catabolism of Interferon: Role of Carbohydrates

Several investigators have attempted to modify the clearance of interferon by altering the carbohydrate moiety. Treatment of interferons by most investigators with glycolytic enzymes resulted in an altered rate of clearance (Bose and Hickman, 1977; Bocci et al., 1977a; Bridgen et al., 1977; Mogensen et al., 1974). The majority of the data suggest that a modified carbohydrate moiety on interferon leads to rapid clearance in the liver. Further studies with different forms of native interferons and interferoids are needed to ascertain the fate of interferon in vivo.

4.3. EFFECTIVE INTERFERON LEVELS

Are prolonged circulating interferons desirable? We cannot safely guess; we do not even know what circulating interferons means, or what they are doing there. Are they being 'transported' to diseased (infected) loci or are they being 'deported' via eliminating organs (liver, kidney, etc.)? Does the same level of circulating interferon in a healthy animal and in a diseased animal mean the same thing? The current trend in interferon therapeutics is based on the pharmacology of antibiotics administration, i.e. as much as the body will tolerate, for as long as the body will tolerate it. This approach calls for improvement; even if this philosophy of administering interferon does not have harmful effects to the patient, the cost of interferon production necessitates more efficient use. Given the multifaceted actions of interferon, it is hard to imagine that prolonged high dosage will not have any undesirable effects on the patient.

5. ANTIVIRAL ACTIONS OF INTERFERONS IN ANIMALS

5.1. INTERFERON MECHANISMS AND PATHOGENESIS

The entry of virus into the body initiates the protective reaction mechanisms of interferon, cell-mediated immune response, antibodies and non-specific reactions. Interferon is probably not produced in sufficient amounts to prevent infections at the primary portal of entry, as the first cycle of virus replication will likely be nearly

*Current cost of production of human leukocyte interferon is approximately $40.00 per 10^6 units; most patients require doses of several million units per day. On the other hand, for penicillin, the average daily patient dose costs only about 10¢.
complete before interferon is produced, which usually requires several hours. The interferon produced in response to the initial invader must then induce antiviral resistance in cells it contacts, which also requires several hours, and this may not have become developed before the second or third generation virions can partially arrest its progression by destroying these cells. Thus the antiviral action of interferon is not likely to be effective in arresting viral infections at the primary portal of entry; consequently, most primary virus infections are able to become established at the portal of entry.

Local inflammatory reaction consisting of leukocyte accumulation, acidity, fever, and hypoxia has been attributed to tissue damage caused by virus replication, but may result from immune-mediated interactions of cells (Snyderman et al., 1972), which may in turn be related to the release of interferon in the area, indirectly through its enhancing of histamine release (Ida et al., 1977) or induction of prostaglandin E (Yaron et al., 1977). Elevated hormone levels increase the susceptibilities of animals to virus infections, and have been related partly to the interferon inhibitory influences of hormone (Kilbourne et al., 1961; DeMaeyer and DeMaeyer, 1963; Smart and Kilbourne, 1966; Rytel and Kilbourne, 1966; Talas and Stoger, 1972).

The true involvement of interferon can be determined only if specific blocks of interferon actions can be achieved. This involvement of endogenous interferon in the natural resistance to virus diseases can be demonstrated by the use of antibodies prepared against interferon. Fauconnier (1970, 1971) demonstrated that inoculation of mice with anti-interferon antibodies after infection with Semliki Forest virus leads to both earlier onset of disease and increased mortality. Gresser et al. (1976a, b) demonstrated the same involvement of interferon in mice infected with encephalomyocarditis virus by using a very potent antiserum against mouse interferon. The pathogenesis of antiserum-treated mice was entirely different from the disease developing in normal mice. In infections of mice with herpes simplex, the anti-interferon antibody accelerated disease development and increased the infectivity of the virus stock by several hundred-fold in lethal dose/ml of the virus stock. The antibodies also caused earlier appearance of Moloney sarcoma virus tumors, which became larger, and were present longer, than in control mice. The tumor-inducing efficiency of the virus stock was also increased. The antiserum shortened the incubation period in mice inoculated with vesicular stomatitis virus but did not alter influenza virus infection. These data clearly demonstrate the early role of endogenous interferon responses in virus resistance to primary virus disease. Apparently, interferon is able to offer some protection for the animal against primary virus infection, without the involvement of antibodies; it would be interesting to determine the role of interferon in immunized animals; by use of anti-interferon serum it might be possible to observe the role of antibodies alone without interferon involvement.

The role of interferon in viral pathogenesis is not necessarily only through its antiviral mechanisms. Through its interaction with the immune system it can influence other defense mechanisms of the animal. Interferon production did not correlate with infectious outcome in virus infections of immunodeficient animals (Subrahmanyan, 1968; Vilcek, 1964; Craighead, 1966). It should be considered in these cases that infection outcome could be determined by interferon not only acting alone, but also as an adjunct to immune mechanisms. The obvious involvement of interferon with the immune system has been discussed earlier, including increased cytotoxicity of both antibodies and lymphocytes, enhanced phagocytosis, macrophage activation and the enhanced antibody response. These involvements could also explain the findings that in vitro sensitivities of a virus to interferon (antiviral) actions does not necessarily correlate with the in vivo sensitivities of the virus to interferon actions. Vaccinia virus, which is quite resistant to interferon action in rabbit cell cultures (Stewart II et al., 1969; Youngner et al., 1972), was found to be affected by rabbit interferon in rabbit skin (Isaacs and Westwood, 1959b) and rabbit eyes (Cantell and Tommila, 1960; Oh and Yoneda, 1969). Herpesvirus is quite insensitive to interferon in many in vitro systems, but appears to be very sensitive in the eye. Meyer and Kruger (1970) found a
reversed order of sensitivities of viruses to interferon inducers statolon and poly(rI)-poly(rC) in vivo as compared to their sensitivities in vitro. These observations support the interpretation that interferon actions in vivo are not restricted to the antiviral action alone, but include a myriad of multiple interactions with other host defense mechanisms.

5.2. ANTIVIRAL STUDIES IN ANIMALS WITH INTERFERON AND INTERFERON INDUCERS

After the first report that interferon was active against a variety of viruses in vitro and was not overtly toxic in animals, numerous studies were undertaken to investigate the effectiveness of interferon both for prophylactic and therapeutic uses in animals. It is often difficult to interpolate between results from different sources as there are too many variables in these studies: interferon dosages have ranged from a few to a few million units; doses of challenging virus vary enormously; time of interferon administration ranged from before virus infection to late stages of disease; both route of virus and interferon administration have varied; and each of these variables has been reported in several animal species. The general conclusion from a survey of such literature is that interferons are effective against a variety of virus infections in all animals tested, usually being more effective if administered early, and the higher the dosage, the better the protection. Induction of endogenous interferons in animals has usually been found to be more effective than exogenous interferon. In Tables 2, 3 and 4 the in vivo actions of exogenous interferon and endogenous inducers are listed in relation to several different types of viral diseases.

All interferon inducers have basically the same common drawbacks: toxicity and hyporesponsiveness of interferon to repeated inductions. Principal among the spectrum of toxic effects in animals is pyrogenicity. It has been suggested that

| Virus | Reference |
|-------|-----------|
| Monkey | Desmyer et al. (1976) |
| | Neumann-Haeffelin et al. (1975, 1976); Sugar et al. (1973) |
| | Neumann-Haeffelin et al. (1976, 1977) |
| | Hilfenhaus et al. (1975a, 1977b); Majer et al. (1977) |
| | Neumann-Haeffelin et al. (1975) |
| | Neumann-Haeffelin et al. (1976) |
| | Pinto et al. (1970) |
| | Scientific Committee on Interferon (1970) |
| | Hitchcock and Isaacs (1960) |
| | Olsen et al. (1976); Baron et al. (1966a, b); Finter (1964a); Gresser et al. (1968b) |
| | DeClercq (1975) |
| | Link et al. (1963); Pollikoff et al. (1961); Takano et al. (1963) |
| | Berman (1970); DeClercq and DeSomer (1971a); Rhim and Huebner (1971) |
| | Baer et al. (1977); Karakuyumchan and Bektemirova (1968) |
| | Lieberman et al. (1971) |
| | Gresser et al. (1968b) |
| | Finter (1964a, b, 1966, 1967); Worthington et al. (1973) |
| | Baron et al. (1966b) |
| | Baron et al. (1966b); DeClercq and DeSomer (1968, 1971b); Glasgow (1970); Glasgow and Habel (1963); Gresser et al. (1975a) |
| | Ermoljeva and Purer (1968); Finter (1970) |
| | Oh and Gill (1966) |
| | Ho et al. (1974); Postic and Fenje (1971); Vieuchange (1967a, b) |
| | Cantell and Tammila (1960); Oh and Yoneda (1969) |
| | Arakawa et al. (1965) |
| | Isaacs and Westwood (1959b); Lindenmann et al. (1957); Pinto et al. (1970) |
| Virus | Inducer | Reference |
|-------|---------|-----------|
| Rabbit | Herpes simplex | influenza virus | Tommila and Penttinen (1962) |
| | Herpes simplex keratitis | poly(rI)-poly(rC) | Kaufman et al. (1969); Pollikoff et al. (1970); Park and Baron (1968); Park et al. (1969) |
| | Newcastle disease | endotoxin, typhoid vaccine | Pollikoff et al. (1968) |
| | Vaccinia | endotoxin, typhoid vaccine | Oh and Yoneda (1969) |
| | Mice | poly(rI)-poly(rC) | Haahr (1971); Kunz and Hofmann (1969); Worthington and Baron (1971) |
| | Arbovirus encephalitis | | |
| | Buyamwera | avirulent influenza virus | Hitchcock and Isaacs (1960) |
| | Encephalomyocarditis | blue tongue (American BT8) | Jameson et al. (1977) |
| | Newcastle disease virus | | Baron et al. (1966b) |
| | Tilorone, poly(rI)-poly(rC) | | Stringfellow et al. (1974a, b) |
| | poly(rI)-poly(rC)-poly L-lysine | | Olsen et al. (1976) |
| | Enteroviral encephalitis | | Catalano and Baron (1970); Gresser et al. (1969b); Lindh et al. (1969); Nemes et al. (1969) |
| | Herpes encephalitis | poly(rI)-poly(rC) | Catalano and Baron (1970); Catalano et al. (1972); Lindh et al. (1969) |
| Influenza | Inactivated Influenza virus | | Denys et al. (1961); Schulman and Kilbourne (1963) |
| | Statolot | poly(rI)-poly(rC) | Kleinschmidt (1970) |
| | Meningitis | Listeria monocytogenes, Toxoplasma gondii | Hill et al. (1969); Lindh et al. (1969); Nemes et al. (1969) Remington and Merigan (1969) |
| | Pneumonia | Endotoxin | Nemes and Hilleman (1962) |
| | Rabies | poly(rI)-poly(rC) | Fenje and Postic (1970); Harmon and Janis (1975); Janis and Habel (1972); Levy et al. (1973) |
| | Vaccinia | Brucella abortus | DeSomer et al. (1970); Feingold et al. (1976) |
| | | Proteus rettgeri, E. coli | DeClercq and DeSomer (1969) |
| | | poly(rI)-poly(rC) | Lindh et al. (1969) |
| | Venezeula equine encephalitis | poly(rI)-poly(rC) | Tazulakhova et al. (1973) |
| | Vesicular stomatitis | Pyran | Kleinschmidt (1970) |
poly(rI)-poly(rC), endotoxin, pyran and other inducers damage cell membranes and release pyrogens along with interferons and other lymphokines (Braun, 1969). It is tempting to speculate that many of the toxic manifestations and side-effects attributed to inducers may be mediated by the interferons they induce. It is not presently possible to prove this, but many adverse effects seen with administration of interferons to date closely resemble those seen with the inducers. To date it has not been possible to administer exogenous interferon in amounts sufficient to match that maintained for several hours by inducers, and exogenous interferon is rapidly cleared from circulation. When high levels of interferon have been administered for prolonged periods, it has been toxic, or lethal or caused wasting. It seems likely that there are reasons for interferons being inducible rather than constitutive.

6. ANTITUMOR ACTIVITIES OF INTERFERON

6.1. MECHANISMS OF ANTITUMOR ACTIVITIES

The mechanism of antitumor activities of interferons apparently depends on the type of tumor involved, the time of administration and, possibly, the amount of interferon used. Mechanisms of inhibition against two types of tumor will be discussed separately.

6.1.1. Virus-induced Tumors

The tumorigenic potentials of virally-induced neoplasms correlate directly with the virus inoculum dose, and the proliferating potential of the virus in the host. In some cases of reported success in antitumor treatment with interferon (Table 5) or its inducers (Table 6), pretreatment of the animal with interferon prior to viral infection was necessary to effect protection. This seems likely in the case of inhibition of the oncogenicity of polyoma virus and Rous sarcoma virus (Atanasiu and Chany, 1960; Strandstrom et al., 1962). In other cases, interferon was administered after infection to achieve inhibition (i.e. Friend virus, Rauscher virus leukemias), where continued virus suppression would account for the effect. Some investigators have suggested that the activity of interferon against Rauscher leukemia is mediated by immunologic enhancement (Toth et al., 1971a, b), and others have discounted completely the role of interferon in these activities (Furmanski et al., 1975). However, in view of the complexity of interferon involvement in defense mechanisms, a composite of each of the actions ascribed to interferon is most likely its action against virus-induced tumors.

6.1.2. Transplantable Tumors

In the case of tumors developing from transplanted cells, it appears that tumor progression may not lead to continued transformation of host cells by tumor viruses. In these cases, the antitumor action of interferon (Table 7) or its inducers (Table 8) cannot be satisfactorily explained in terms of antiviral activities. Rather, the resistance mechanisms would appear to involve a direct cell-multiplication-inhibitory effect or enhancement of immune-mediated defense mechanisms involved in tumor limitation and elimination. A number of other interferon actions, including enhanced lymphocyte cytotoxicity (Svet–Moldavsky and Chernyakovskaya, 1967) and im-

**Table 4. Antiviral Activities of Exogenous Interferon in Combination with Other Agents in Animals (Mice)**

| Virus                      | Other agent                  | Reference                           |
|----------------------------|------------------------------|-------------------------------------|
| Encephalomyocarditis       | ammonium 5-tungsto-2-antimoniate | Werner et al. (1976)               |
| (HPA 23)                  | isoprinosine                 | Chany and Cerutti (1977a, b)       |
| Herpes                    | adenoarabinoside             | Lerner and Bailey (1975)           |
| Animal | Tumor                        | Dosage | Effects                        | Reference                                      |
|--------|------------------------------|--------|--------------------------------|------------------------------------------------|
| Chicken | Rous sarcoma                 | —      | inhibits appearance of tumor   | Strandstrom et al. (1962)                      |
| Hamster| Polyoma                      | ‘low titer’ (crude) | inhibits appearance of tumor   | Atanasu and Chany (1960)                       |
| Mouse  | Friend leukemia              | —      | inhibits splenomegaly          | Gresser et al. (1966, 1967a, b, c, d)          |
|        | Graft-induced malignant lymphoma | $10^7$ | prevents development of malignant lymphomas | Hirsch et al. (1973) |
|        | Moloney sarcoma              | —      | inhibits tumor development     | DeClercq and DeSomer (1971a)                  |
|        | Murine sarcoma (Harvey)      | —      | prolongs survival              | Berman (1970)                                 |
|        | Rauscher leukemia            | ‘low titer’ | prolongs survival             | Gresser et al. (1968a); Glasgow and Friedman (1969); Toth et al. (1971a, b) |
|        | Spontaneous AKR leukemia     | $5 \times 10^4$ | prolongs survival             | Graft et al. (1970); Bekesi et al. (1976); Gresser et al. (1968a, 1969a, 1970c) |
|         | Spontaneous mammary carcinoma | $10^7$ | inhibits tumor development     | Came and Moore (1971, 1972)                   |
| Monkey | Herpesvirus                  | —      | lymphocyte count returns to normal | Rabin et al. (1976) |
| Animal         | Tumor          | Inducer          | Effect                 | Reference                      |
|---------------|----------------|------------------|------------------------|--------------------------------|
| Mouse         | Friend leukemia| coxal virus      | inhibits splenomegaly  | Stim (1970)                    |
|               |                | Statolon         | inhibits splenomegaly  | Regelson and Foltyn (1966)     |
|               |                | pyran copolymer  | inhibits splenomegaly  | Regelson and Foltyn (1966);    |
|               |                |                  |                        | Regelson (1967, 1968);         |
|               |                |                  |                        | Schuller et al. (1975)         |
|               |                | tilorone         | inhibits splenomegaly  | Barker et al. (1971)           |
|               |                |                  |                        | Rana et al. (1975)             |
| Rauscher leukemia | pyran copolymer | inhibits disease  |                        | Chirigos et al. (1969)         |
|                | poly(r1)-poly(rC) | inhibits disease |                        | Youn et al. (1968)             |
|                | lymphocytic     | inhibits disease  |                        | Barski and Youn (1964);        |
|                | choriomeningitis virus | prolongs survival |                        | Youn and Barski (1966)         |
| Murine sarcoma | Statolon        | inhibits splenomegaly |                    | Rhim and Huebner (1969)        |
| Moloney sarcoma| COAM            | inhibits development |                    | Claes et al. (1970); DeClercq |
|                |                |                  |                        | and DeSomer (1972)             |
| Chicken       | Polyoma         | pyran copolymer  | inhibits tumor         | Hirsch et al. (1972)           |
|                | Rous sarcoma    | West Nile virus  | inhibits tumor         | Shirodkar (1965)               |
|                |                | rabies virus vaccine | inhibits tumor    | Kravchenko et al. (1967)       |
|                |                | poly(r1)-poly(rC) | protects animal       | Nemes et al. (1969)            |
|                | Polyoma         | herpes virus     | inhibits tumor         | Barski (1963)                  |
| Hamster       | Adenovirus-induced | poly(r1)-poly(rC) | protects animal       | Larson et al. (1969)           |
|                | SV40-induced    | poly(r1)-poly(rC) | protects animal       | Larson et al. (1970)           |
| Rat           | Polyoma         | poly(r1)-poly(rC) | protects animal       | Vandeputte et al. (1970)       |
| Guinea pig    | Kirsten-murine erythroblastosis | poly(r1)-poly(rC) | circumvents erythroblastosis | Slamon (1973, 1975)          |
|               | Leukemia        | lymphocytic      | prolonged survival    | Jungeblut and Kodza (1962)     |
| Tumor                  | Dosage(units/animal) | Effect                     | Reference                        |
|-----------------------|---------------------|----------------------------|----------------------------------|
| Ehrlich ascites       | —                   | inhibits tumor growth      | Ferris et al. (1971)             |
| Friend leukemia       | —                   | prolongs survival          | Rossi et al. (1975)              |
| HeLa                  | —                   | inhibits tumor growth      | Yokota et al. (1976)             |
| Lewis Lung carcinoma  | —                   | prevents tumor development |                                  |
| LSTRA leukemia        | (with BCNU)         | inhibits metastases        | Gresser and Bouri-Maury (1972)   |
| Polyoma tumor cells   | —                   | prolones survival          | Chirigos and Pearson (1973)      |
| RC19 ascites          | $4 \times 10^4$     | increases survival         | Corraggio et al. (1965)          |
| Sarcoma 180           | $2.5 \times 10^4$   | inhibits tumor growth      | Gresser and Bouri (1969)          |
| Sarcoma MC-36         | 300(TYPE II)        | inhibits tumor growth      | Yokota et al. (1976)             |
| Brown-Pearce Carcinoma| —                   | inhibits metastases        | Salvin et al. (1975)             |
| Walker carcinosarcoma | 600                 | blocks tumor formation     | Baddar et al. (1973)             |
### Table 8. Antitumor Activities of Endogenous Interferon in Animals (Transplanted Tumors)

| Tumor                  | Inducer                  | Effect                  | Reference                      |
|------------------------|--------------------------|-------------------------|--------------------------------|
| Mouse                  |                          |                         |                                |
| AKR-leukemia           | M-P virus                | inhibits tumor growth   | Molomut and Padnos (1965)      |
| mammary carcinoma      | pyran copolymer          | inhibits tumor growth   | Morahan and Kaplan (1976)      |
| B-16 melanoma          | poly(rI)-poly(rC)        | tumor necrosis          | Levy et al. (1969, 1970)       |
| Ehrlich ascites        | Newcastle disease virus  | inhibits tumor growth   | Rhim and Huebner (1971)        |
| Friend leukemia        | Newcastle disease virus  | inhibits tumor growth   | Rossi et al. (1975)            |
| L-1216                 | poly(rI)-poly(rC)        | inhibits tumor growth   | Snodgrass et al. (1975)        |
| RC-19 ascites          | Newcastle disease virus  | inhibits tumor growth   | Gresser and Bourali (1969)      |
| reticulum cell sarcoma | poly(rI)-poly(rC)        | inhibits tumor growth   | Levy et al. (1969, 1970)       |
| Sarcoma 180            | BRU-PEL                  | tumor necrosis          | Keleti et al. (1977)           |
| Walker carcinoma 256   | pyran copolymer          | inhibits tumor development | Regelson (1967, 1968)       |
|                        | tilorone                 | inhibits tumor development | Adamson (1971)               |

### Table 9. Combined Antitumor Activities of Endogenous or Exogenous Interferons and Other Agents

| Tumor          | Endogenous Inducers | Effect                  | Reference                      |
|----------------|---------------------|-------------------------|--------------------------------|
| Friend leukemia| poly(rI)-poly(rC),  | increased survival time | Barker et al. (1971)           |
| Lymphoma       | Sendai virus in sequence | increased survival time | Gresser et al. (1978)          |
| Moloney sarcoma| cyclophosphamide + interferon | reduced tumor | Stewart II et al. (1975a)      |
| Murine leukemia | 1,3-bis(2-chloroethyl)-1-nitrosourea + interferon | reduced tumor | Chirigos and Pearson (1973)    |
# Table 10. Antiviral Activities of Exogenous Interferons in Man

| Virus                      | Dosage (units/dose) | Interferon type* | Route of Administration* | Effects* | Reference                                |
|----------------------------|---------------------|------------------|---------------------------|----------|------------------------------------------|
| **Local Infection**        |                     |                  |                           |          |                                          |
| A. Prophylactic            |                     |                  |                           |          |                                          |
| Vaccinia                   | ~ 1200              | Monkey           | i.d.                      | +        | Scientific Committee on Interferon (1962) |
| Rhinovirus, Parainfluenza-1| ~ 10^4              | Monkey           | i.n.                      | -        | Scientific Committee on Interferon (1965) |
| Coxsackie A-21             | 10^5                | HuLeIF           | i.n.                      | +        | Tyrell and Reed (1973)                   |
| Rhinovirus                 | 10^6                | HuLeIF           | i.n.                      | ±        | Merigan et al. (1973)                    |
| Influenza                  | 10^4–10^5           | HuLeIF           | i.n.                      | +        | Soloviev (1967, 1969)                    |
| B. Therapeutic             |                     |                  |                           |          |                                          |
| Vaccinia                   | ?                   | Monkey           | s.c.                      | -        | Connolly et al. (1962)                   |
| gangrenose Postvaccinal skin lesion | 4000/g ointment | HuLeIF          | Ointment                  | +^       | Soos et al. (1972)                       |
| Vaccinal keratitis         | ?                   | Monkey           | Eyedrops                  | +        | Jones et al. (1962)                      |
| Herpes keratitis           | 10^5 (5/day)        | HuLeIF           | Eyedrops                  | ±        | Tommila (1963)                           |
|                            | 10^5                | HuLeIF           | Eyedrops                  | +^       | Kobza et al. (1975)                      |
|                            | 2–6×10^5 (3/day)    | HuLeIF           | Eyedrops                  | -        | Kaufman et al. (1976)                    |
|                            | 6×10^5 (3/day)      | HuLeIF           | Eyedrops                  | ±        | Sundmacher et al. (1976c)                |
|                            | 3×10^6 (2/day)      | HuLeIF           | Eyedrops                  | +        | Pullin et al. (1976)                     |
|                            |                     |                  |                           |          |                                          |
| Genital herpes virus lesions| 4×10^7/g ointment  | HuLeIF           | Ointment                  | +        | Ikic et al. (1974, 1975a)                |
| Genital warts              |                     |                  |                           |          |                                          |
| (Condylomata acuminata)    | 4×10^7/g ointment   | HuLeIF           | Ointment                  | +        | Ikic et al. (1975b, c)                   |
| Systemic Infections                     | Dose          | Interferon | Route      | Effect | Reference  |
|-----------------------------------------|---------------|------------|------------|--------|------------|
| Herpesvirus zoster                      | 1-3 x 10^6 (3/week) | HuLeIF | i.m. | + | Strander et al. (1973) |
|                                         | 3 x 10^6      | HuLeIF | i.m. | + | Jordan et al. (1974); Merigan et al. (1977) |
|                                         | 10^6          | HuLeIF | i.m. | + | Emodi et al. (1975a, b) |
| Disseminated herpes simplex             | 5 x 10^6      | HuLeIF | i.m. | + | Kobza et al. (1975)  |
|                                         | 12 x 10^6     | HuLeIF | i.m. | + | DeClercq et al. (1975b) |
| Cytomegalovirus inclusion disease       | 5 x 10^6      | Human Amnion, HuLeIF | i.v. | ± | Falcoff et al. (1966) |
|                                         | 10^5-10^6     | HuLeIF | i.m. | + | Emodi et al. (1976) |
|                                         | 2-4 x 10^7/kg | HuLeIF | i.m. | ± | Arvin et al. (1976) |
|                                         | 3 x 10^7/kg   | HuLeIF | i.m. | + | Merigan et al. (1977) |
| Cytomegalovirus complicating bone      | 10^6          | HuLeIF | i.m. | ± | O'Reilly et al. (1976) |
| marrow-transplantation                  |               |           |           |      |            |
| Chronic Hepatitis-B                     | 6 x 10^7-2 x 10^9/kg | HuLeIF | i.m. | + | Greenberg et al. (1976); Merigan et al. (1977) |
|                                         | 1.5-2.0 x 10^7/kg | HuLeIF | i.m. | + | Desmyter et al. (1976) |
|                                         | 10^7          | HuLeIF | i.m. | + | Kingham et al. (1977) |
| Congenital Rubella syndrome             | 3 x 10^6      | HuLeIF | i.m. | + | Larson et al. (1976) |
| Marburg virus                           | 3 x 10^6      | HuLeIF | i.m. | + | Anonymous (1977) |

*Interferon type: HuFilF, human fibroblast interferon; HuLeIF, human leukocyte interferon.

*b Route of administration: i.m., intramuscular; i.v., intravenous; i.d., intradermal; s.c., subcutaneous.

*c Effects: -, no effect; ±, suggestive effects; +, effective.

*d Uncontrolled trial with only one or two patients.
| Disease                  | Dosage (units/dose) | Route of administration | Effects | References                  |
|-------------------------|---------------------|-------------------------|---------|-----------------------------|
| Acute leukemia          | $\sim 10^3$         | i.v.                    | $\pm$   | Falcoff et al. (1966)       |
|                         | $2 \times 10^6$     | i.m.                    | antiviral | Ahstrom et al. (1974)       |
| Hodgkin's Disease (stage IVB) | $5 \times 10^6$ | i.m.                    | $+^c$   | Blomgren et al. (1976)      |
| Multiple myeloma        | $6 \times 10^6$     | i.m.                    | $+^c$   | Strander (1977a, c)         |
| Juvenile larynx papilloma | $3 \times 10^6$     | i.m.                    | $+$     | Strander (1977a, c)         |
| Osteosarcoma            | $3 \times 10^6$     | i.m.                    | $+$     | Strander et al. (1974, 1975, 1976, 1977); Strander (1977a, b, c); Adamson et al. (1977) |

* Route of administration: i.v., intravenous; i.m., intramuscular.
* Effects demonstrated: $\pm$, suggestive effect; $+$, effective.
* Uncontrolled trial with only one or two patients.
mune responses (Yakota et al., 1976), have been implicated in the antitumor activities of interferon. It would seem likely that a composite of interferon actions is again a key figure behind the death or survival of the tumor-laden animals. In some cases it may be that the actions of interferon alone, or other antitumor agents (i.e. chemotherapeutics) alone, may be insufficient to erradicate tumors; in limited attempts made, combined therapy has proven more effective (Table 9).

7. INTERFERON IN MAN

Twenty years have gone into work on interferons. During this time speculations of all sorts have been raised as to the possible clinical use of interferon. Only in recent years have sufficient amounts of human interferon become available for even small preliminary clinical trials. Yet even these limited trials of interferon have evidenced its potential in the treatment of a variety of diseases in man. A list of reported trials demonstrating the antiviral and antitumor efficacies of interferon is presented in Tables 10 and 11. The scarcity of interferon for clinical use has led to a search for effective inducers of endogenous interferon. The inducers shown to have antiviral activities in man include: inactivated viruses; poly(rI)-poly(rC); poly(rI)-poly(rC)-poly l-lysine; and propanediamine. However, clinical applications have been prohibited by problems of inducer toxicities and hyporesponsiveness.

The suggestive success of limited trials with exogenous interferon in the clinic have encouraged a number of other ventures in the area of interferon therapy. Trials in patients with osteosarcoma and neuroblastoma were recently reported to be underway using human fibroblast interferon (DeSomer, 1977), and human lymphoblastoid interferon is being tested in osteosarcoma (Bodo, G., personal communication). A study of non-Hodgkin's lymphoma patients who failed standard therapy is presently underway (Merigan et al., 1977). A trial of human leukocyte interferon to prevent metastases in patients who have lung-removal for adenocarcinoma will soon begin (Oettgen, H., personal communication), and a study is presently underway to evaluate interferon in therapy of breast cancer (Gutterman, J., personal communication). Initial successes were reported by Merigan et al. (1978) in the treatment of herpes zoster in patients with cancer; and encouraging results have been observed in the therapy of breast cancer (Gutterman, J., personal communication).

In closing, it seems that after 20 years of dark ages of interferonology, the initial hope of clinical application is slowly being realized. A worldwide increase in interferon production is anticipated to meet the increasing demand as encouraging results from clinical trials begin to appear in print. With increased availability of interferons, it should soon be possible to more clearly define the potential of interferon as an antiviral agent in the clinic.

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REFERENCES

ADAMS, A., STRANDER, H. and CANTELL, K. (1975) Sensitivity of Epstein-Barr virus transformed human lymphoid cell lines to interferon. J. gen. Virol. 28: 207-214.

ADAMSON, R. H. (1971) Antitumor activity of tilorone hydrochloride against some rodent tumors: Preliminary report. J. natn. Cancer Inst. 46: 431-433.

ADAMSON, U., APARISI, T., BROSTROM, L. A., CANTELL, K., EINHORN, S., HALL, K., INGIMARSSON, S., NILSONNE, U., STRANDER, H., SODERBERG, G. (1977) The role of non-specific immunity in treatment of cancer. Study Week of the Pontifical Acad. Sci. Vatican City, 17-21 Oct. 1977. Interferon treatment of human osteosarcoma.

AHL, R. and RUMP, A. (1976) Assay of bovine interferons in cultures of the porcine cell line IB-RS-2. Infect. Immun. 14: 603-610.

AHSTROM, L., DORNWITZ, A., STRANDER, M., CARLSTROM, G. and CANTELL, K. (1974) Interferon in acute leukemia in children. Lancet 1(849): 166-167.

ALLEN, L. B. and COCHRAN, K. W. (1972) Target-organ treatment of neurotropic virus disease with interferon inducers. Infect. Immun. 6: 819-823.
BARON, S. and ISAACS, A. (1962) Absence of interferon in lungs from fatal cases of influenza.

BECK, G., POINDRON, P., ILLINGER, D., BECK, J. P., ESEL, J. P. and FALCO~a~, R. (1974) Inhibition of steroid...

BARON, S., BUCKLER, C. E., McCLOSKEY, R. V. and KIRSCHSTEIN, R. L. (1966b) Role of interferon during...

BARON, S. and LEVY, H. B. (1966) Interferon.

BARMAK, S. L. and VILCEK, J. (1973) Altered cellular responses to interferon induction by polyI.polyC:

BAER, G. M., SHADDOCK, J. H., MOORE, V. A., YAGER, P. A., BARON, S. S. and LEVY, H. B. (1977)...

BADER, J. P. (1962) Production of interferon by chick embryo cells exposed to Rous sarcoma virus.

BASBER, O. P., SINGH, D. P. and BAJPA1, S. K. (1973) Effect of interferon on tumor forming ability of...

ATANASIU, P. and CHANY, C. (1960) Action d'un interferon provenant de cellules malignes sur rinfection...

ARAKAWA, J., SAWA, I. and FUJIWARA, K. (1965) Influence du facteur inhibiteur du virus sur la multiplication...

ANKEL, H., CHANY, C., GALLIOT, B., CHEVALIER, M. J. and ROBERT, M. (1973) Antiviral effect of interferon...

ALLEN, L. B., EAGLE, N. C., HUFFMAN, J. M., SHUMAN, D. A., MAYER, R. B., JR, and SIDWELL, R. A. (1974) Enhancement of interferon antiviral action in L-cells by cyclic nucleotides. Proc. Soc. exp. Biol. Med. 146: 580–584.

ALLEN, P. T., SCHELLEKENS, H., VAN GRIENSVEN, L. J. L. D., and BILLIAU, A. (1976) Differential sensitivity of Rauscher Murine Leukemia Virus (MuLV-4) to interferons in two interferon-responsive cell lines. J. gen. Virol. 31: 429–435.

ANDERSON, S. G. (1965) The production of antibody in the presence of interferon. Aust. J. exp. Biol. Med. Sci. 43: 345–350.

ANKEL, H., CHANY, C., GALLIOT, B., CHEVALIER, M. J. and ROBERT, M. (1973) Antiviral effect of interferon covalently bound to sepharose. Proc. natn. Acad. Sci. U.S.A. 70(8): 2360–2363.

ANONYMOUS (1977) Interferon options.

ANDERSON, S. G. (1965) The production of antibody in the presence of interferon. Proc. Natl. Acad. Sci. USA. 51: 791–798.

BARSKI, G. (1963) Interference entre les virus d'herpes et de polyome chez le Hamster adulte

BARSKI, G. (1963) Interference entre les virus d'herpes et de polyome chez le Hamster adulte

BARSKI, G. and YOUN, J. K. (1964) Interference entre la choriomeningite lymphocytaire et la leucemie de soucis de Rauscher. C. r. hebdom. Séanc. Acad. Sci. Paris 259: 419–4193.

BAK, B., BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.

BARKER, A. D., RHEINS, M. S. and WILSON, H. E. (1971) Amelioration of Friend virus leukemia by sequential administration of viral and non-viral interferon inducers. Proc. Soc. exp. Biol. Med. 137: 981–983.
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**BESANCON, F. and ANKEL, H. (1974b)** Inhibition of interferon action by plant lectins. *Nature, Lond.* 250: 784-786.

**BESANCON, F. and ANKEL, H. (1976)** Inhibition of interferon action by glycoprotein hormones. *C. r. hebod. Séanc. Acad. Sci., Paris D.* 283: 1807-1809.

**BESANCON, F., ANKEL, H. and BASU, S. (1976a)** Specificity and reversibility of interferon ganglioside interaction. *Nature, Lond.* 259: 576-578.

**BESANCON, F., BASU, S. and ANKEL, H. (1976b)** Interaction of interferon with gangliosides. *Hoppe-Seyler's Z. physiol. Chem.* 357: 251-255.

**BIAŁY, H. S. and COLBY, C. (1972)** Inhibition of early vaccinia virus ribonucleic acid synthesis in interferon treated chicken embryo fibroblasts. *J. Virol.* 9: 286-289.

**BILLIAU, A. (1970)** The refractory state after induction of interferon with double-stranded RNA. *J. gen. Virol.* 7: 225-232.

**BILLIAU, A. (1975)** Sensitivity of oncornavirus-carrier lines to the antiviral and growth-inhibitory properties of interferon. *Proc. Symp. Clin. Use of Interferon.* Zagreb: Yugoslavia, p. 105.

**BILLIAU, A. (1977)** Effect of interferon on RNA tumor viruses. *Tex. Rep. Biol. Med.* 35: 406-419.

**BILLIAU, A. and BUCKLER, C. E. (1970)** Production and assay of rat interferon.

**BILLIAU, A., EDY, V. G., DECLERCQ, E., HEREMANS, H. and DESOMER, P. (1974)** Influence of interferon on the synthesis of virus-particle in oncornavirus carrier cell lines. *Int. J. Cancer* 12: 646-653.

**BILLIAU, A., EDY, V. G., DECLERCQ, E., HEREMANS, H. and DESOMER, P. (1975)** Influence of interferon on oncornavirus-carrier lines. *IV. Relevance to the potential application of interferon in natural infectious diseases.* *J. infect. Dis.* 133: A51-A57.

**BILLIAU, A., EDY, V. G., HEREMANS, H., VAN DAMMS, J., DESMYTER, J., GEORGIADES, J. A., and DESOMER, P. (1977)** Human interferon: Mass production in a newly established cell line. *MCG63. Antimicrob. Ag. Chemother.* 12: 11-14.

**BILLIAU, A., EDY, V. G., HEREMANS, H., VAN DAMMS, J., DESMYTER, J., GEORGIADES, J. A., and DESOMER, P. (1977)** Human interferon: Mass production in a newly established cell line. *MCG63. Antimicrob. Ag. Chemother.* 12: 11-14.

**BILLIAU, A., EDY, V. G., HEREMANS, H., VAN DAMMS, J., DESMYTER, J., GEORGIADES, J. A., and DESOMER, P. (1977)** Human interferon: Mass production in a newly established cell line. *MCG63. Antimicrob. Ag. Chemother.* 12: 11-14.

**BLOMGREN, H., CANTELL, K., JOHANSSON, B., LAGERGREN, C., RINGBORG, U. STRANDER, H. (1976)** Effect of human leukocyte interferon on the control of virus particle formation in different oncornavirus carrier cell lines. *Int. J. Cancer* 12: 646-653.

**BLALOCK, J. E. and GIFFORD, G. E. (1975)** Suppression of interferon production by vitamin A. *J. gen. Virol.* 29: 315-319.

**BLALOCK, J. E. and GIFFORD, G. E. (1976a)** Suppression of interferon production by vitamin A. *J. gen. Virol.* 32: 143-146.

**BLALOCK, J. E. and GIFFORD, G. E. (1976b)** Comparison of the suppression of IF production and inhibition of its action by vitamin A and related compounds. *Proc. Soc. exp. Biol. Med.* 153: 298-301.

**BLALOCK, J. E. and GIFFORD, G. E. (1977)** Retinoic acid (vitamin A) induced transcriptional control of interferon production. *Proc. nat. Acad. Sci. U.S.A.* 74: 5382-5386.

**BLALOCK, J. E. and GIFFORD, G. E. (1977)** Inhibition of interferon action by vitamin A. *J. gen. Virol.* 29: 315-319.

**BLALOCK, J. E. and GIFFORD, G. E. (1977a)** Inhibition of interferon action by vitamin A. *J. gen. Virol.* 29: 315-319.

**BLALOCK, J. E. and GIFFORD, G. E. (1977b)** Inhibition of interferon action by vitamin A. *J. gen. Virol.* 32: 143-146.

**BLALOCK, J. E. and GIFFORD, G. E. (1978)** Effect of interferon on the synthesis of virus-particle in oncornavirus carrier cell lines. III. Survey of effects on A-, B- and C-type oncornaviruses. *Int. J. Cancer* 15: 947-950.

**BILLIAU, A., EDY, V. G., DECLERCQ, E., HEREMANS, H., ALLEN, P. T., DEMAEYER-GUIGNARD, J. and DESOMER, P. (1976)** Trapping of oncornavirus particles at the surface of interferon treated cells. *Virology* 73: 537.

**BILLIAU, A., EDY, V. G., DECLERCQ, E., HEREMANS, H. and DESOMER, P. (1974)** Influence of interferon on oncornavirus-carrier lines. *II. Evidence for a direct effect on particle release.* *Int. J. Cancer* 14: 335-340.

**BILLIAU, A., EDY, V. G., DECLERCQ, E., HEREMANS, H. and DESOMER, P. (1977)** Influence of interferon on the synthesis of virus-particle in oncornavirus carrier cell lines. III. Survey of effects on A-, B- and C-type oncornaviruses. *Int. J. Cancer* 15: 947-950.
CERUTI, J. C., BRUNNER, K. T., LINHARD, P. and GRESSER, I. (1973) Inhibitory effect of interferon on viral RNA. *Biochem. Biophys. Acta* 155: 437-443.

CARVER, D. H. and MARCUS, P. I. (1967) Enhanced interferon production from chick embryo cells aged in *in vitro*. *Virology* 32: 247-257.

CASSINGENA, R., CHANY, C., VIGNAL, M., SUAREZ, H., ESTRADA, S. and LAZAR, P. (1971) Use of monkey-mouse hybrid cells for the study of the cellular regulation of interferon production and action. *Proc. natn. Acad. Sci. U.S.A.* 68: 580-584.

CATALANO, L. W., Jr and BARON, S. (1970) Protection against herpes virus and encephalomyocarditis virus encephalitis with a double-stranded RNA inducer of interferon. *Proc. Soc. exp. Biol. Med.* 133: 684-688.

CATHALA, F. and BARON, S. (1970) Interferon in rabbit brain, cerebrospinal fluid and serum following administration of polyinosinic-polycytidylic acid. *J. Virol.* 160: 1355-1358.

CEMBRZYNSKA-NOWAK, M. (1977) Inhibitor of interferon activity from mouse embryo tissues: its physicochemical characteristics. *Arch. Immun. ther. exp.* 25: 663-668.

CERROTTO, J. C., BONOMO, L. T., LINDALI, P. and GRESSER, I. (1973) Inhibitory effect of interferon preparations and inducers on the multiplication of transplanted allogeneic spleen cells and syngeneic bone marrow cells. *Nature, New Biol.* 242(118): 152-153.

CESARIO, T. C. and TILLES, J. G. (1973) Inactivation of human interferon by urine. *J. infect. Dis.* 127: 331-341.

CHANG, E. H. and FRIEDMAN, R. M. (1977) A large glycoprotein of Moloney leukemia virus derived from infected cells. *Biochem. Biophys. Res. Commun.* 77: 392-398.

CHANG, E. H., MYERS, M. W., WONG, P. K. Y. and FRIEDMAN, R. M. (1977a) The inhibitory effect of interferon on a temperature-sensitive mutant of Moloney murine leukemia virus. *Virology* 77: 625-636.

CHANG, E. H., MIMS, S. J., TRICHE, T. J. and FRIEDMAN, R. M. (1977b) Interferon inhibits mouse leukemia virus release: an electron microscope study. *J. gen. Virol.* 34: 363-371.

CHANY, C. (1976) Membrane-bound interferon specific cell receptor system: role in the establishment and amplification of the antiviral state. *Biomedicine* 24: 148-160.

CHANY, C. and BRAILOVSKY, C. (1965) Les stimulons facteurs antagonistes de l'interferon favorisant la multiplication intracellulaire des virus. *C. r. hebd. Séanc. Acad. Sci., Paris* 261: 4282-4285.

CHANY, C. and BRAILOVSKY, C. (1967) Stimulating interaction between viruses (stimulons). *Proc. natn. Acad. Sci. U.S.A.* 57: 87-94.

CHANY, C. and CERUTI, I. (1977a) Effet stimulant de l'isoprinosine sur l'action antivirale de l'interferon. *C. r. hebd. Séanc. Acad. Sci., Paris, Ser. D.* 284: 499-501.

CHANY, C. and CERUTI, I. (1977b) Enhancement of antiviral protection against encephalomyocarditis virus by a combination of isoprinosine and interferon. *Arbs Virology* 55: 225-232.

CHANY, C. and VIGNAL, M. (1968) Etude du mécanisme de l'état réfractoire des cellules à la production d'interferon après inductions répétées. *C. r. hebd. Séanc. Acad. Sci., Paris, ser. D.*, 267: 1798-1800.

CHANY, C., LEMAITRE, J. and GREGOIRE, A. (1969) Facteurs antagonistes de l'action antivirale dans des extraits d'interferon provenant de différents sarcomes humains. *C. r. hebd. Séanc. Acad. Sci., Paris* 269: 2628-2631.

CHANY, C. and BRAILOVSKY, C. (1967) Potentiation of the antiviral activity of interferon by Actinomycin D. *Nature, New Biol.* 230: 113-114.

CHANY, C., GREGOIRE, A., VIGNAL, M., LEMAITRE-MONCUI, J., BROWN, P., BESANCON, F., SUAREZ, H. and CASSINGENA, R. (1973) Mechanism of interferon uptake in parental and syngeneic mouse-monkey hybrid cells. *Proc. natn. Acad. Sci. U.S.A.* 70(2): 557-561.

CHANY, C., ANKEL, H., GALLLOT, B., CHEVALIER, M. J. and GREGOIRE, A. (1974) Mode of action and biological properties of insoluble interferon. *Proc. Soc. exp. Biol. Med.* 147: 293-299.

CHANY, C., VIGNAL, M., COVILLIN, P., VAN CONG, N., BOVE, J. and BOYE, A. (1975) Chromosomal localization of human genes governing the interferon-induced antiviral state. *Proc. natn. Acad. Sci. U.S.A.* 72: 3129-3134.

CHANY-Fournier, F., PAULIN, A., and CHANY, C. (1977) Tissue antagonist of interferon (TAI): isolation and chemical characteristics. *Biochem. Biophys. Res. Commun.* 55: 225-232.

CHERRY, M. J. and WILLIAMS, B. R. G. (1978) Inhibition of cell-free protein synthesis by pppA'TpA-A: A novel oligonucleotide synthesized by extracts from interferon treated L cells. *Cell* 13: 565-572.

CHIRS, M. A., TURNER, W., PEARSON, J. and GRIFFIN, W. (1969) Effective antiviral therapy of two murine leukemias with an interferon-inducing synthetic carboxylate polymer. *Int. J. Cancer* 4: 267-269.

CLAES, P., BILLAUI, A., DECLERCQ, E., DESMYTER, J., SCHONNE, E., VANDERHAEGHE, H. and DE SOMER, P. (1970) Polyacetyl carboxylic acids: a new group of antiviral polyanions. *J. Virol.* 5: 313-320.

CLERMEN, M. J. and WILLIAMS, B. R. G. (1978) Inhibition of cell-free protein synthesis by pppA'TpA-A: A novel oligonucleotide synthesized by extracts from interferon treated L cells. *Cell* 13: 565-572.

COCTIO, D., DEMAETER, E. and DE SOMER, P. (1962) Synthesis of mRNA in neoplastic cells treated with interferon. *Life Sci.* 12: 759-764.
COSITO, C., SCHONNE, E. and DE SOMER, P. (1965) Metabolism of nucleic acids in uninfected fibroblasts incubated in vitro with rat interferon. Life Sci. 4: 1253-1262.

COLBY, C. and DUESBERG, P. M. (1969) Double-stranded RNA in vaccinia virus infected cells. Nature, Lond. 222: 940-944.

COLBY, C. and MORGAN, M. J. (1971) Interferon induction and action. Ann. Rev. Microbiol. 25: 333-360.

COLBY, C., PENHOET, E. E. and SAMUEL, C. E. (1976) A comparison of transfer RNA from untreated and interferon-treated murine cells. Virology 74: 262-264.

CONNOLLY, J., DICK, G. W. A. and FIELD, C. M. B. (1962) A fatal case of progressive vaccinia. Br. Med. J.: 1315-1317.

CONTENT, J., LEBLEU, B., NUDEL, V., ZILBERSTEIN, A., BERISSI, H. and REVÉL, M. (1975) Blocks in elongation and initiation of protein synthesis induced by interferon treatment in mouse L cells. Eur. J. Biochem. 54: 1-5.

COOPER, J. A. and FARRELL, P. J. (1977) Extracts of interferon-treated cells can inhibit reticulocyte lysate protein synthesis. Biochem. Biophys. Res. Commun. 77: 124-131.

CORAGGIO, F., COTO, V., FANTONI, V., GALEOTA, C. A. and LAVEGAS, E. (1965) Azione di un interferon, proveniente da culture in vitro di cellule embrionali di topo infettate col virus del polioma, su un tumore trapiantabile nel topo (ceppo C57). Boll. Ist. sieroter. milan. 44: 64-68.

CRAIGHEAD, J. E. (1966) Growth of parainfluenza type 3 virus and interferon production in infant and adult mice. Br. J. exp. Path. XXII: 235-241.

CREGAN, R. P., TAN, Y. H., CHEN, S. and RUDDLE, F. H. (1975) Somatic cell genetic analysis of the interferon system. Proc. Soc. exp. Biol. Med. 132: 699-703.

CUPPLES, G. C. and TAN, Y. H. (1977) Effect of human interferon preparations on lymphoblastogenesis in Down's syndrome. Nature, Lond. 267: 165-167.

DE CLEIR, E. (1975) Encephalitis induced upon intranasal challenge of mice with herpes simplex virus. Proc. Symp. Clin. Use of Interferon, Zagreb, Yugoslavia, pp. 129-139.

DE CLEIR, E. (1977) Effect of mouse interferon and poly[rI]-poly[rC] on L-cell tumor growth in nude mice. Cancer Res. 37: 1502-1508.

DE CLEIR, E. and DE SOMER, P. (1968) Protective effect of interferon and polyacrylic acid in newborn mice infected with a lethal dose of vesicular stomatitis virus. Life Sci. 7: 925-930.

DE CLEIR, E. and DE SOMER, P. (1969) Prolonged antiviral protection by interferon inducers. Proc. Soc. exp. Biol. Med. 132: 699-703.

DE CLEIR, E. and DE SOMER, P. (1971a) Role of interferon in the protective effect of the double-stranded polyribonucleotide against murine tumors induced by moloney sarcoma virus. J. natn. Cancer Inst. 47: 1345-1355.

DE CLEIR, E. and DE SOMER, P. (1971b) Comparative study of the efficacy of different forms of interferon therapy in the treatment of mice challenged intraanally with VSV. Proc. Soc. exp. Biol. Med. 138: 301-307.

DE CLEIR, E. and DE SOMER, P. (1972) Effect of chlorite-oxidized oxalamylase on moloney sarcoma virus-induced tumor formation in mice. Eur. J. Cancer 8: 535-538.

DE CLEIR, E. and STEWART II, W. E. (1972) Utilization of poly[rI]-poly[rC] for controlling virus diseases and tumors still in abeyance. Medikon 1: 331-345.

DE CLEIR, E. and STEWART II, W. E. (1974) Regression of autochthonous Moloney sarcoma virus-induced tumors in mice treated with polyriboinosinic acid polyribocytidylic acid. J. natn. Cancer Inst. 52: 591-595.

DE CLEIR, E., NUWER, M. R. and MERIGAN, T. C. (1970) Potentiating effects of Freund's adjuvant on interferon production by endotoxin or poly[rI]-poly[rC]. Infect. Immun. 2: 69-76.

DE CLEIR, E., STEWART II, W. E. and DE SOMER, P. (1972) Interferon production linked to toxicity of polyriboinosinic acid-polyribocytidylic acid. Infect. Immun. 6(3): 344-347.

DE CLEIR, E., STEWART II, W. E. and DE SOMER, P. (1973) Increased toxicity of double-stranded ribonucleic acid in virus-infected animals. Infect. Immun. 7: 167-172.

DE CLEIR, E., EDY, V. G. and CASSIMAN, J. J. (1975a) Non-antiviral activities of interferon are not controlled by chromosome 21. Nature, Lond. 256: 132-134.

DE CLEIR, E., EDY, V. G., DEVILLEGER, H., ECKELS, R. and DESMYTER, J. (1975b) Intrathecal administration of interferon in neonatal herps. J. Pediat. 86: 736-739.

DE CLEIR, E., EDY, V. G. and CASSIMAN, J. J. (1976) Chromosome 21 does not code for an interferon receptor. Nature, Lond. 264: 249-251.

DEMAEYER, E. (1976) Interferon and delayed-type hypersensitivity to a viral antigen. J. Infect. Dis. 133: A63-A66.

DEMAEYER, E. and DEMAEYER, J. (1963) Two-sided effect of steroids on interferon in tissue culture. Nature, Lond. 197: 724-725.

DEMAEYER, E. and DE MAEYER, P. (1962) Influence of pH on interferon production and activity. Nature, Lond. 194: 1252-1254.

DEMAEYER, E., MORRAanten, L. and DE MAEYER-GUIGNARD, J. (1973) Prolongation by interferon of the survival of skin grafts in the mouse. C. r. hebld. Séanc. Acad. Sci., Paris, set. D. 277: 2101-2103.

DEMAEYER, E., DE MAEYER-GUIGNARD, J. and VAN DEPUTTE, M. (1975) Inhibition by interferon of delayed-type hypersensitivity in the mouse. Proc. natn. Acad. Sci. U.S.A. 72: 1753-1758.

DE MAEYER-GUIGNARD, J., CACHARD, A. and DE MAEYER, E. (1975) Delayed-type hypersensitivity to sheep red blood cells: inhibition of sensitization by interferon. Science, N.Y. 190: 574-578.
DEMAEVR-GUIGNARD, J., THANG, M. N. and DEMAEVER, E. (1977) Binding of mouse interferon to polynucleotides. Proc. natn. Acad. Sci. U.S.A. 74: 3787-3790.

DENYS, P., DESOMER, P. and PRINZIE, A. (1961) Protective effect of interferon in influenza-infected mice. *Antonie van Leeuwenhoek J. Microbiol. Serol.* 27: 261-263.

DESMYTER, J., RAY, M. B., DEGROOTE, J., BRADBURNE, A. F., DESMET, V. J., EDY, V. G., BILLIAU, A., DESOMER, P. and MORTELMANS, J. (1976) Administration of human fibroblast interferon in chronic hepatitis B infection. *Lancet,* No. 7987 ii: 645-648.

DESOMER, P. (1977) Clinical trials with human fibroblast interferon. *Fifth Aharon Katzir-Katchalsky Conference,* Rehovot, Israel.

DESOMER, P., PRINZIE, A., DENYS, P. and SCHONNE, E. (1962) Mechanism of action of interferon. I. Relationship with viral RNA. *Virology* 16: 63-70.

DESOMER, P., BILLIAU, A. and DECLERCQ, E. (1970) The interferon inducer from Brucella.

DESOMER, P., PRINZIE, A., DENYS, P. and SCHONNE, E. (1962) Mechanism of action of interferon. I. Relationship with viral RNA. *Virology* 16: 63-70.

DESOMER, P., BILLIAU, A. and DECLERCQ, E. (1967) Inhibition of antibody production in rats and mice by intravenous injection of interferon inducing amounts of Sindbis virus or E. coll. *Arch. ges. Virolog.* 20: 205-214.

DESOMER, P., DELECRQ, E., COCITO, C. and BILLIAU, A. (1970) The interferon inducer from Brucella. *Ann. N.Y. Acad. Sci.* 173: 274-278.

DESOMER, P., EDY, V. G. and BILLIAU, A. (1977) Interferon-induced skin reactivity in man. *Lancet,* 8027 ii: 47-50.

DIANZANI, F. and BARON, S. (1975) Unexpectedly rapid action of human interferon in physiological conditions. *Nature, Lond.* 257: 682-684.

DIANZANI, F. and BARON, S. (1977) The continued presence of interferon is not required for activation of cells by interferon. *Proc. Soc. exp. Biol. Med.* 155: 562-566.

DIANZANI, F., CANTAGALLI, P., GAGNONI, S. and RITA, G. (1968) Effects of DEAE-dextran on production of interferon induced by synthetic double-stranded RNA in L cell cultures. *Proc. Soc. exp. Biol. Med.* 128: 708-710.

DIANZANI, F., BARON, S., LEVY, H. B., GULLINO, P., VIANO, I. and ZUCCA, M. (1975) Studies on the action of human interferon under physiologic conditions. *Proc. Symp. Clin. Use of Interferon,* Yugoslav Acad. Sci. and Arts, Zagreb, pp. 93-104.

DIANZANI, F., LEVY, H. B., BERG, S. and BARON, S. (1976) Kinetics of the rapid action of interferon. *Proc. Soc. exp. Biol. Med.* 152: 593-596.

DIANZANI, F., VIANO, I., SANTIANO, M., ZUCCA, M. and BARON, S. (1977) Effect of cell density on development of the antiviral state of interferon-producing cells: A possible model of in vivo conditions. *Proc. Soc. exp. Biol. Med.* 153: 460-463.

DIDERI4OLM, H. and DINTER, Z. (1966) Interference between strains of bovine virus diarrhea virus and their capacity to suppress interferon of a heterologous virus. *J. natn. Cancer Inst.* 54: 1054-1058.

DOBSON, R. M. and HUANG, K.-Y. (1973) Neutralization of the phagocytosis-enhancing activity of interferon preparations by anti-interferon serum. *Infect. Immun.* 7(3): 501-503.

DONAHOE, R. M. and HUANG, K.-Y. (1976) Interferon preparations enhance phagocytosis in vivo. *Infect. Immun.* 13: 1250-1253.

DUBUY, H., BARON, S., UHLENDORF, C. and JOHNSON, M. L. (1973) Role of interferon in murine lactic dehydrogenase virus infection in vivo and in vitro. *Infect. Immun.* 8: 977-984.

EDY, V. G., BILLIAU, A. and DESOMER, P. (1975) Pharmacokinetics of human fibroblast interferon. *Symp. Antivirals with Clinical Potential,* Stanford, Calif.

EDY, V. G., BILLIAU, A., DESOMER, P. (1976) Comparison of rates of clearance of human fibroblast and leukocyte interferon from the circulatory system of rabbits. *J. infect. Dis.* 133: A18-A20.

EMODI, G., RUFFI, T., JUST, M. and HERNANDEZ, R. (1975a) Circulating interferon in man after intravenous injection of interferon inducing amounts of Sindbis virus or E. coll. *Proc. Soc. exp. Biol. Med.* 128: 708-710.

EMODI, G., RUFFI, T., JUST, M. and HERNANDEZ, R. (1975b) Human interferon therapy for herpes zoster in adults. *Scand. J. infect. Dis.* 7: 1-5.

EMODI, G., O'REILLY, R., MULLER, A., EYERSON, L. K., BINSWANGER, U. and JUST, M. (1976) Effect of human exogenous leukocyte interferon in cytomegalovirus infections. *J. infect. Dis.* 133: A199-A204.

EPSTEIN, D. B. and SAMUEL, C. E. (1977) Mechanism of interferon action. Partial purification and characterization of low-molecular weight interferon-mediator of translation with nucleolytic activity. *Biochem. Biophys. Res. Comm.* 79: 145-153.

EPSTEIN, J. B. and EPSTEIN, Ch. J. (1976) Localization of the gene AVG for the antiviral expression of immune and classical interferon to the distal portion of the long arm of chromosome 21. *J. infect. Dis.* 133: A53-A56.

ERMOIJEVA, Z. V. and FURER, N. M. (1968) Experimental and clinical studies on interferon and interferon inducers. *Proc. Microbiol. Res. Grp hung. Acad. Sci.* 2: 49.

ERSHOF, F. I., TAZULAKHOVA, E. B. and ZHBAOV, V. M. (1976) Messenger RNA for antiviral protein. *Dokl. Akad. Nauk. USSR* 231-233, 1001.

ERSHOF, F. I., SOKOLOVA, T. M., TAZULAKHOVA, E. B., NOVOKHATSKY, A. S. and VERKHADSKAYA, A. A. (1977) Isolation and characterization of mRNA for antiviral protein. *Prob. Virol.* 4: 441-447.

ESTEBAN, M. and METZ, D. H. (1973) Inhibition of early vaccinia virus protein synthesis in interferon-treated chicken embryo fibroblasts. *J. gen. Virol.* 20: 111-115.

FALCOFF, E., FALCOFF, R., FOURNIER, F. and CHANT, C. (1966) Production en masse, purification partielle et caractérisation d'un interferon destiné à des essais thérapeutiques humains. *Annls Inst. Pasteur, Paris* 47-50.

FALCOFF, E., FALCOFF, R., LE BLEU, B. and REVELL, M. (1972) Interferon treatment inhibits Mengo RNA and haemoglobin mRNA translation in cell-free extracts of L cells. *Nature, New Biol.* 240: 145-147.

FALCOFF, E., FALCOFF, R., LE BLEU, B. and REVELL, M. (1973) Correlation between the antiviral effect of...
interferon treatment and the inhibition of in vitro mRNA translation in noninfected L cells. J. Virol. 12: 421-424.

FALCOFF, R., SCHEPS, R., SANCEAU, J., CATINOT, L. and FALCOFF, E. (1975) Protein synthesis in interferon-treated cells. Biochimie 57: 1109-1111.

FALCOFF, R., LEBLÉU, B., SANCEAU, J., WEISSENJACHT, J., DIRHEIMER, G., EBEL, J. P. and FALCOFF, E. (1976) The inhibition of translation of synthetic polyribonucleotides and Mengo RNA translations in extracts from interferon-treated L cells and its reversion by yeast tRNAs. Biochem. biophys. Res. Commun. 68: 1323-1328.

FAUCONNIER, B. (1970) Viral auto-inhibition studied by the effect of anti-interferon serum on plaque formation. Arch. ges. Virusforsch. 31: 266-272.

FAUCONNIER, B. (1971) Effect of anti-interferon serum on experimental viral pathogenicity in vivo. Path. Biol. 19: 575-578.

FEINGOLD, D. S., KELETTI, G. and YOUNGNER, J. S. (1976) Antiviral activity of Brucella abortus preparations: separation of active components. Infect. Immun. 13: 763-768.

FENIE, P. and POSTIC, B. (1970) Protection of rabbits against experimental rabies by poly I-poly C. Nature, Lond. 226: 171-172.

FERREIS, P., PADNOS, M. and MALDUMUT, N. (1971) Tumor inhibition in mice by M-P virus-induced interferon. Fedn Proc. 30: 341.

FINTER, N. B. (1964a) Interferon production and sensitivity of Semliki Forest virus variants. J. Hyg. 62: 337-342.

FINTER, N. B. (1964b) Protection of mice by interferon against systemic virus infections. Br. Med. J. 2: 981-985.

FINTER, N. B. (1966) Interferon as an antiviral agent in vivo: Qualitative and temporal aspects of the protection of mice against Semliki Forest virus. Br. J. exp. Path. 47: 361-371.

FINTER, N. B. (1967) Interferon in mice: protection against small doses of virus. J. gen. Virol. 1: 395-397.

FINTER, N. B. (1970) Exogenous interferon in animals and its clinical implications. Archs intern. Med. 126: 147-157.

FINTER, N. B. (1973) Interferons and inducers in vivo. I. Antiviral effects in experimental animals. In: Interferons and Interferon Inducers. pp. 295-362, FINTER, N. B., (ed.). North Holland, Amsterdam.

FITZGERALD, G. R. (1969) The effect of interferon on focus formation and yield of murine sarcoma virus in vivo. Proc. Soc. exp. Biol. Med. 130: 960-964.

FLEMING, W. A., MCNEILL, T. A. and KILLEN, M. (1972) The effects of an inhibiting factor (interferon) on the in vitro growth of granulocyte-macrophage colonies. Immunology 23: 429-437.

FONTAINE-BROUTY-BOYI~, D., GRESSER, I., MACIERA-COELHO, A., ROSENFELD, C. and THOMAS, M. T. (1969) Inhibition in vitro de la multiplication des cellules leucémiques murines L1210 par des préparations d'interferon. C. r. hebld. Séanc. Acad. Sci., Paris, ser. D, 269: 406-410.

FOURNIER, F., ROUSSET, S. and CHANY, C. (1968) Un facteur tissulaire antagoniste de l'action de l'interferon. C. r. hebld. Séanc. Acad. Sci., Paris, ser. D 266: 2306-2308.

FOURNIER, F., ROUSSET, S. and CHANY, C. (1969) Investigations on a tissue antagonist of interferon. Proc. Soc. exp. Biol. Med. 132: 943-950.

FOURNIER, F., CHANY, C. and SARRAGNE, M. (1972) Origin and possible mode of action of a tissue antagonist of interferon. Nature, New Biol. 235: 47-48.

FOURNIER, F., SARRAGNE, M., ROUFFET, A., LEAUTE, J. B. and CHANY, C. (1974) Mechanism of action of tissue factors inhibiting the antiviral state established by interferon. C. r. hebld. Séanc. Acad. Sci., Paris, ser. D 278: 1915-1918.

FRASSINET, C., GRESSER, I., TOVEY, M. and LINDAHL, P. (1973) Inhibitory effects of potent interferon preparations on the regeneration of mouse liver after partial hepatectomy. Nature, Lond. 245: 146-147.

FRIEDMAN, R. M. (1964) Role of interferon in viral interference. Nature, Lond. 201: 848-849.

FRIEDMAN, R. M. (1966) Effect of interferon treatment on interferon production. J. Immun. 96: 872-877.

FRIEDMAN, R. M. (1967) Interferon binding: the first step in establishment of antiviral activity. Science, N.Y. 156: 1760-1761.

FRIEDMAN, R. M. (1968) Inhibition of arbovirus protein synthesis by interferon. J. Virol. 2: 1081-1088.

FRIEDMAN, R. M. (1977) Antiviral activity of interferon. Bact. Rev. 41: 543-567.

FRIEDMAN, R. M. and PASTAN, T. (1969) Interferon and the cyclic-3'5'-adenosine monophosphate: Potentiation of antiviral action. Biochem. biophys. Res. Commun. 70: 1078-1081.

FRIEDMAN, R. M. and KNOB, L. D. (1976) Cholera toxin inhibits interferon action. Biochim. biophys. Res. Commun. 70: 1078-1081.

FRIEDMAN, R. M. and PASTAN, J. (1978) Interferon and the cyclic-3'5'-adenosine monophosphate: Potentiation of antiviral activity. Biochem. biophys. Res. Commun. 70: 735-739.

FRIEDMAN, R. M. and RAMSEUR, J. M. (1974) Inhibition of murine leukemia virus production in chronically infected AKR cells: a novel effect of interferon. Proc. natn. Acad. Sci. U.S.A. 71: 3542-3544.

FRIEDMAN, R. M. and SONNABEND, J. A. (1964) Inhibition of interferon action by puromycin. J. Immun. 95: 696-703.

FRIEDMAN, R. M. and SONNABEND, J. A. (1965b) Inhibition by interferon or production of double-stranded Semliki Forest virus ribonucleic acid. Nature, Lond. 206: 532-535.

FRIEDMAN, R. M. and SONNABEND, J. A. (1970) Mechanism of interferon action. Archs intern. Med. 126: 51-63.
FRIEDMAN, R. M. and SREEVALSAN, T. (1970) Membrane binding of input arbovirus ribonucleic acid: effect of interferon or cyclohexamide. J. Virol. 6: 169-175.

FRIEDMAN, R. M., METZ, D. H., ESTEBAN, R. M., TOVELL, D. R., BALL, L. A. and KERR, I. M. (1972) Mechanism of interferon action: inhibition of viral messenger RNA translation in L-cell extracts. J. Virol. 10: 1184-1196.

FRIEDMAN, R. M., CHANG, E. H., RAMSEUR, J. M. and MYERS, M. W. (1975) Interferon-directed inhibition of chronic marine leukemia virus production in cell cultures: lack of effect on intracellular viral markers. J. Virol. 16: 569-574.

FRIEDMAN, R. M., COSTA, J. C., RAMSEUR, J. M., MEYERS, M. W., JAY, F. T. and CHANG, E. M. (1976) Persistence of the viral genome in interferon-treated cells infected with oncogenic or nononcogenic viruses. J. Infect. Dis. 133 suppl.: A43-A47.

FRIEDMAN, R. M., JAY, F. T., CHANG, E. H., MYERS, M. W., RAMSEUR, J. M., MIMS, S. J., TRICHE, T. J. and WONG, P. K. Y. (1977) Interferon-directed inhibition of chronic marine leukemia virus production in cell cultures. In: Prog. Cancer Res. Ther. Vol. 2, p. 347. CHIRigos, M. A. (ed.). Raven Press, N.Y.

FROTHINGHAM, T. E. (1965) Further observations on cell cultures infected concurrently with mumps and Sindbis viruses. J. Immun. 94: 521-524.

FUCHSBERGER, N., HAJNICKA, V. and BORECKY, L. (1975) Antiviral and cell-growth inhibitory activities of highly-purified L cell interferon. An analysis of quantitative disproportions. Acta Virol. 19: 59-61.

FURMANSKI, P., JUNI, S., HALL, L. and RICH, M. A. (1975) The role of interferon in the spontaneous regression of Friend virus induced leukemia. Proc. Soc. exp. Biol. Med. 150: 11-13.

GAFFNEY, E. V., PICOANO, P. T. and GRANT, C. A. (1973) Inhibition of growth and transformation of human cells by interferon. J. natn. Cancer. Inst. 50(4): 871-878.

GAFFNEY, E. V. (1974) Relative insensitivity of spleen cells to interferon. J. Immun. 113: 1947-1953.

GALLAGHER, J. G. and LANGELEY, P. (1976) Formation and characteristics of reovirus subviral particles in interferon-treated mouse L-cells. Nucl. Acid. 3: 581-583.

GENDON, YU. Z. (1977) On the ability of certain viruses to block the effect of interferon. Acta Virol. 9: 186-187.

GENDON, YU. Z., BALADIN, I. G. and BABUSHKINA, N. (1966) On the mechanism of the ability of certain viruses to block the action of interferon. Acta Virol. 10: 268-270.

GLASGOW, L. A., HANSHAW, J. B., MERIGAN, T. C. and PETRALLI, J. K. (1967) Interferon and cytomegalovirus in vivo and in vitro. Proc. Soc. exp. Biol. Med. 125: 843-849.

GOBER, L. L., FRIEDMAN-KIEN, A. E., HAVELL, E. A. and VILCEK, J. (1972) Suppression of the intracellular growth of Shigella flexneri in cell cultures by interferon preparations and polyinosinic-polyctydylid acid. Infect. Immun. 5(3): 370-376.

GINSBERG, N. (1963) The role of interferon in the spontaneous regression of Friend virus induced leukemia. Proc. Soc. exp. Biol. Med. 150: 11-13.

GINSBERG, N. (1963b) Effect of environmental changes upon antiviral action of interferon. Proc. Soc. exp. Biol. Med. 136: 920-924.

GINSBERG, N. (1964a) Comparative studies on the production and essay of interferon. J. gen. Microbiol. 33: 437-443.

GINSBERG, N. (1964b) Effect of environmental changes upon antiviral action of interferon. Proc. Soc. exp. Biol. Med. 114: 644-649.

GINSBERG, N. (1974) Relative insensitivity of spleen cells to interferon. J. Immun. 113: 1947-1953.

GINSBERG, N. (1975) Sensitivity of adenosivirus types 1, 3, 4, 5, 8, 11 and 18 to human interferon. Proc. Soc. exp. Biol. Med. 136: 920-924.

GINSBERG, N. (1976) Adenosivirus susceptibility to human interferon during one-step replication. Infect. Immun. 5: 905-908.

GINSBERG, N. (1977) On the ability of certain viruses to block the effect of interferon. Acta Virol. 9: 186-187.

GINSBERG, N. (1965) The ability of certain viruses to block the action of interferon. Acta Virol. 9: 186-187.
HO, M. (1967) The induction of interferon and related problems. Jap. J. Exp. Med. 37: 169-182.

HO, M. (1973) Animal viruses and interferon formation. In: Interferons and Interferon Inducers. pp. 29-44, FINTER, N. B. (ed.) North-Holland, Amsterdam.

HO, M. and BREINIG, M. K. (1962) Conditions for the production of interferon appearing in chick cell cultures infected with Sindbis virus. J. Immun. 89: 177-185.

HO, M. and ENDERS, J. F. (1959) An inhibitor of viral activity appearing in infected cell cultures. Proc. natn. Acad. Sci. U.S.A. 45: 385-389.

HO, M. and KE, Y. H. (1970) The mechanism of stimulation of interferon production by a complexed polyrribonucleotide. Virology 40: 693-702.

HO, M. and POSTIC, B. (1967) Renal excretion of interferon. Nature, Lond. 214: 1230-1232.

HO, M., POSTIC, B. and KE, Y. H. (1967) The systemic induction of IF. In: Ciba Foundation Symp. on IF. pp. 19-35, WOLSTENHOLM, G. E. W. and O'CONNOR, M. (eds.) J. & A. Churchill, London.

HO, M., NASH, C., MORGAN, C. W., ARMSTRONG, J. A., CARROLL, R. G. and POSTIC, B. (1974) Interferon administered in the cerebrospinal space and its effect on rabies in rabbits. Infect. Immun. 9: 286-293.

HOUZAX, L., JUNGWIRTH, C. and BODO, G. (1971) FOXVIRUS specific cytopathic effect in interferon-treated L cells. Virology 45: 456-462.

HOVANESSIAN, A. G., BROWN, R. E. and KERR, I. (1977) Synthesis of low molecular weight inhibitor of protein synthesis with enzyme from interferon-treated cells. Nature, Lond. 268: 537-539.

HOVANESSIAN, A. G. and KERR, I. M. (1978) Synthesis of an oligonucleotide inhibitor of protein synthesis in rabbit reticulocytes lysates analogous to that formed in extracts from interferon-treated cells. Eur. J. Biochem. 84: 149-160.

HUANG, K. Y., DONAHOE, R. M., GORDON, F. B. and DRESSLER, H. R. (1971) Enhancement of phagocytosis by interferon-containing preparations. Infect. Immun. 4(5): 581-588.

HUET, C., GRESSER, I., BANDRU, M. T. and LINDAHL, P. (1974) Increased binding of Concanavalin A to interferon-treated murine leukemia L1210 cells. Proc. Soc. exp. Biol. Med. 147: 52-57.

IDA, S., HOOKS, J. J., SIRAGANIAN, R. P. and NOTKINS, A. L. (1977) Enhancement of IgE-mediated histamine release from rat basophilic cell line RBL-2H3 by interferon: role of interferon. J. exp. Med. 145: 892-899.

IKIC, D., SMERDEL, S., SOOS, E. and JUSIC, D. (1974) The use of interferon in herpes simplex infections and condylomata acuminatum. Rad. Immun. Zavod-S Zagreb 27: 69-75.

IKIC, D., BRNOBIC, A., JURKOVIC-VUKELIC, V., SMERDEL, S., JUSIC, D. and SOOS, E. (1975a) Therapeutic effect of human leukocyte interferon incorporated into ointment and cream on condylomata acuminata. Proc. Symp. Clin. Use of Interferons. Yugoslav Acad. Sci. Arts, pp. 235-238.

IKIC, D., ORESCANIN, N., KRUSIC, J., CESTAR, Z., ALAC, Z., SOOS, E., JUSIC, D. and SMERDEL, S. (1975b) Preliminary study of the effect of human leukocyte interferon on condylomata acuminata in women. Proc. Symp. Clin. Use of Interferons. Yugoslav Acad. Sci. Arts, pp. 223-225.

IKIC, D., SMERDEL, S., RAJNINGER-MIHOLIC, M., SOOS, E. and JUSIC, D. (1975c) Treatment of lalbal and genital herpes with human leukocytic interferon. Proc. Symp. Clin. Use of Interferons. Yugoslav Acad. Sci. Arts, pp. 195-202.

ILLINGER, D., COUPIN, G., RICHARDS, M. and POINDRON, P. (1976) Rat interferon inhibits steriod-inducible glycerol 3-phosphate dehydrogenase synthesis in a rat glial cell line. FEBS Lett. 64: 391-394.

IMANISHI, J., YOKOTA, Y., KISHIDA, T., MUKAINAKA, T. and MATSUO, A. (1975) Phagocytosis-enhancing effect of human leukocyte interferon prepared on human peripheral monocytes in vitro. Acta Virol. 19: 52-55.

IMANISHI, J., OISHI, K., KISHIDA, T., NEGORO, Y. and IZUKA, M. (1977) Effects of interferon preparations on rabbit corneal xenograft. Archs Virol. 53: 157-161.

ISSACS, A. and KORAMAN, R. S. (1960) Antiviral action of interferon in embryonic cells. The Lancet ii: 946-947.

ISSACS, A. and WESTWOOD, M. A. (1959a) Duration of protective action of interferon against infection with West Nile virus. Nature, Lond. 184: 1223-1223.

ISSACS, A. and WESTWOOD, M. A. (1959b) Inhibition by interferon of the growth of vaccinia virus in the rabbit skin. Lancet ii: 324-325.

ISSACS, A., PORTERFIELD, J. S. and BARON, S. (1961) The influence of oxygenation on virus growth. II. Effect on the antiviral action of interferon. Virology 14: 450-455.

ITO, T. and KOBAYASHI, S. (1974) Enhancing effect of interferon pretreatment on interferon production. Jap. J. Microbiol. 18(3): 223-228.

ITO, Y. and MONTAGNER, L. (1977) Heterogeneity of the sensitivity of vesicular stomatitis virus to interferons. Infect. Immun. 18: 13-27.

JAHIEL, R. I., TAYLOR, D., RAINFORD, N., HIRSCHBERG, S. E. and KROMAN, R. (1971) Inducers of interferon inhibit the mitotic response of liver cells to partial hepatectomy. Proc. natn. Acad. Sci. U.S.A. 68: 740-742.

JAHIEL, R. I., VLCEK, J. and NUSSENZWEBG, R. S. (1970) Exogenous interferon protects mice against Plasmodium berghei malaria. Nature, Lond. 227: 1350-1351.

JAMESON, P., SCHONHERR, C. K. and GROSSBERG, S. E. (1977) Bluetongue virus induction of interferon and resistance to viral infection. Interferon Workshop, Lake Placid, New York.

JANIS, B. and HABEL, K. (1972) Rabies in rabbits and mice: protective effect of polyriboinosinic-polyribocytidylic acid. J. infect. Dis. 125: 345-353.

JARVIS, A. and NUSSENZWEIG, R. S. (1970) Exogenous interferon protects mice against Plasmodium berghei malaria. Nature, Lond. 227: 1350-1351.

JANIS, B. and HABEL, K. (1972) Rabies in rabbits and mice: protective effect of polyriboinosinic-polyribocytidylic acid. J. infect. Dis. 125: 345-353.

Faraday 35: 355-364.

JOHNSON, H. M. and BARON, S. (1976a) The nature of the suppressive effect of interferon and interferon inducers on the in vitro immune response. Cell Immun. 28: 106-109.

JOHNSON, H. M. and BARON, S. (1976b) Regulatory role of interferons in the immune response. IRCS J. med. Sci. 4: 60.

JOHNSON, T. C., LERNER, M. P. and LANZC, G. J. (1968) Inhibition of protein synthesis in noninfected L cells by partially purified interferon preparations. J. cell. Biol. 36: 617-624.

JOHNSON, H. M., SMITH, B. G. and BARON, S. (1974) Inhibition of the primary in vitro antibody response of mouse spleen cells by interferon preparations. IRCS J. med. Sci. 2: 1616.
GROSSBERG, S. E. and HOLLAND, J. J. (1962) Interferon and viral RNA. Effect on virus-susceptible and insusceptible cells. J. Immun. 88: 708-714.

GROSSBERG, S. E. and MORAHAN, P. S. (1971) Repression of interferon action: induced dedifferentiation of embryonic cells. Science, N.Y. 171: 77-79.

GROSSBERG, S. E. and Scherer, W. (1964) Inapparent viral infection of cells in vitro. II. An interferon produced in chicken embryonic cell cultures inoculated with Japanese encephalitis virus. Am. J. Path. 45: 519-531.

GRIENWALD, R. and LEVINE, S. (1976) Effect of tilorone on susceptibility of mice to primary and secondary infection with Listeria monocytogenes. Infect. Immun. 13: 1613-1618.

GUPTA, S. L., GRAZIADEI, W. D. 3rd, WEIDELI, M., SOPORI, M. L. and LENGYEL, P. (1974) Selective inhibition of viral protein accumulation in interferon-treated cells; nondiscriminate inhibition of the translation of added viral and cellular messenger RNAs in their extracts. Virology 57: 49-63.

GUPTA, S. L., SOPORI, M. L. and LENGYEL, P. (1973) Inhibition of protein synthesis directed by virus and cellular messenger RNAs in extracts of interferon-treated Ehrlich ascites tumor cells. Location and dominance of the inhibitor(s). Biochem. biophys. Res. Commun. 54: 777-783.

HAAR, S. (1971) The influence of poly I:C on the course of infection in mice inoculated with West Nile virus. Arch. ges. Virusforsch. 35: 1-9.

HABIF, D. V., LIPTON, R. and CANTELL, K. (1975) Interferon crosses blood-brain barrier in monkeys. Proc. Soc. exp. Biol. Med. 149: 287-293.

HALLUM, J. V., YOUNGER, J. S. and ARNOLD, N. J. (1968) Effect of pH on the protective action of interferon in L cells. J. Virol. 2: 772-780.

HALLUM, J. V., THACORE, H. R. and YOUNGER, J. S. (1970) Factors affecting the sensitivity of different viruses to interferon. J. Virol. 6: 156-162.

HANNA, L., MERGIAN, T. C. and JAWETZ, E. (1966) Inhibition of TRIC agents by virus-induced interferon. Proc. Soc. exp. Biol. Med. 122: 417-421.

HANNA, L., MERGIAN, T. C. and JAWETZ, E. (1967) Effect of interferon on TRIC agents and induction of interferon by TRIC agents. Am. J. Ophthal. 63: 1115-1119.

HARMON, J. A., W. and JANIS, B. (1975) Therapy of murine rashes after exposure: efficacy of polynosinic-polycytidylic acid alone and in combination with three rabies vaccines. J. infect. Dis. 132: 241-247.

HARRIS, R. E., COLEMAN, P. H. and MORAHAN, P. S. (1974) Erythrocyte association and interferon production by minute virus of mice. Proc. Soc. exp. Biol. Med. 145: 1288-1292.

HEREMANS, H., STEWART II, W. E., BILLIAU, A. and DESOMER, P. (1976) Toxicity of poly(rI).poly(rC) for interferon-treated cells. An ultrastructural evaluation. J. gen. Virol. 30: 131-136.

HERMAN, R. (1972) The effects of interferon and its inducers on experimental protozoan parasitic infections. Trans. N.Y. Acad. Sci. 34: 178-180.

HERMAN, R. and BARON, S. (1970) Effects of interferon inducers on the intracellular growth of the protozoan parasite Leishmania donovani. Nature, Lond. 226: 168-170.

HERMAN, R., SHROIHI, T. and BUCKLER, C. E. (1973) Viral interference with exoerythrocytic forms of malaria (Plasmodium gallinaceum) in ovo. J. infect. Dis. 138: 148-153.

HERMODSSON, S. (1963) Inhibition of interferon by an infection with parainfluenza virus type 3 (PIV-3). Virology 20: 333-343.

HERMODSSON, S. (1964) Action of parainfluenza virus type 3 on synthesis of interferon and multiplication of heterologous virus. Acta Path. Microbiol. scand. 62: 224-238.

HERON, I., BERG, K. and CANTELL, K. (1976) Regulation effect of interferon on T-cells in vitro. J. Immun. 117: 1370-1377.

HILFENHAUS, J. and KARGES, H. E. (1974) Growth inhibition of human lymphoblastoid cells by interferon preparations, obtained from human leukocytes. Z. Naturf. C. 29: 618-622.

HILFENHAUS, J., KARGES, H. E., WEINMANN, E. and BARTH, K. (1975a) Effect of administered human leukocyte interferon on experimental rashes in monkeys. Infect. Immun. 11: 1156-1162.

HILFENHAUS, J., THIERFELDER, H. and BARTH, R. (1975b) Sensitivity of various primate cells and animal viruses to the antiviral activity of human leukocyte interferon. Archs Virol. 48: 203-208.

HILFENHAUS, J., DAMM, H., KARGES, H. E. and MANTHEY, K. F. (1976) Growth inhibition of human lymphoblastoid Daudi cells in vitro by interferon preparations. Archs Virol. 51: 87-97.

HILFENHAUS, J., DAMM, H. and JOHANNSEN, R. (1977a) Sensitivities of various human lymphoblastoid cells to the antiviral and antieucllular activity of human leukocyte interferon. Archs Virol. 54: 271-277.

HILFENHAUS, J., WEINMANN, E., MAIER, M., BARTH, R. and JAEGER, J. (1977b) Post-exposure administration of human interferon to rabbits infected monkeys. J. infect. Dis. 135: 846-851.

HILL, D. A., BARON, S., and CHANOCK, R. M. (1969) Sensitivity of common respiratory viruses to an interferon inducer in human cells. Lancet II: 187-188.

HILSER, G., WINKLER, I., VIENHAUSER, G., JUNGWIRTH, C., BODO, G., DUBE, S. and OSTERTAG, W. (1976) Failure of globin mRNA to stimulate globin synthesis in cell-free extracts of interferon-treated globin-synthesizing mouse erythroleukemic cells. Virology 69: 360-368.

HIRSCH, M. S., BLACK, P. H., WOOD, M. L. and MONACO, A. P. (1972) Effect of pyran copolymer on oncogenic virus infections in immunosuppressed hosts. J. Immun. 108: 1312-1318.

HISCOCK, G. and ISAACS, A. (1966) Protection of mice against the lethal action of an encephalitis virus. Br. Med. J.: i: 1268-1270.

HO, M. (1968) Inhibition of the infectivity of poliovirus ribonucleic acid by an interferon. Proc. Soc. exp. Biol. Med. 107: 639-644.

HO, M. (1962) Interferons. New Engl. J. Med. 266: 1258-1265; 1313-1318; 1367-1371.
Antiviral activities of interferons

JOHNSON, H. M., BUKOVIC, J. A., SMITH, B. G. (1975a) Inhibitory effect of synthetic polyribonucleotides on the primary in vitro immune response. Proc. Soc. exp. Biol. Med. 149: 599–605.

JOHNSON, H. M., SMITH, B. G. and BARON, S. (1975b) Inhibition of the primary in vitro antibody response by interferon preparations. J. Immun. 114: 403–409.

JOKLIE, W. K. (1977) The mechanism of action of interferon. Ann. N.Y. Acad. Sci. 284: 711–717.

JOKLIE, W. K. and MERIGAN, T. C. (1966) Concerning the mechanism of action of interferon. Proc. natn. Acad. Sci. U.S.A. 56: 558–565.

JONES, B. R., COSTER, D. J., FALLON, M. G. and CANTELL, K. (1976) Clinical trials of tropical interferon therapy of ulcerative viral keratitis. J. infect. Dis. 133: A169–A174.

JORDAN, G. W. (1972) Quantitative aspects of interferon-induced plaque reduction: kinetics of interferon action. Virology 48: 425–432.

JORDAN, G. W., FRIED, R. P. and MERIGAN, T. C. (1974) Administration of human leukocyte interferon in herpes zoster. I. safety, circulating, antiviral activity, and host responses to infection. J. infect. Dis. 130: 56–62.

JUNGBLUT, C. W. and KODZA, H. (1962) Interference between lymphocytic choriomeningitis virus and the leukemia-transmitting agent of leukemia L2C in guinea pigs. Arch. ges. Virusforsch. 12: 552–555.

JUNGWIRTH, C., HORAK, I., BODO, G., LINDNER, J. and SCHULTZE, B. (1972a) The synthesis of poxvirus-specific RNA in interferon treated cells. Virology 48: 59–70.

JUNGWIRTH, C., HILLER, G., POHL, D. and BODO, G. (1972b) Smallpox virus specific early function in interferon treated cells: transcription and processing of small pox virus specific early mRNA. Hoppe-Seyler's Z. physiol. Chem. 353: 1531–1534.

JUNGWIRTH, C., KROATH, H. and BODO, G. (1977) Effect of interferon on poxvirus replication. Tex. Rep. Biol. Med. 35: 247–259.

KARANKUYUMCHAN, M. K. and BEKTEMIROVA, M. S. (1968) Production and effect of interferon in experimental infection with fatal rabies virus. Vop. Virus. 13: 596–599.

KAZAR, J., KRAUTWURST, P. A. and GORDON, F. B. (1971) Effect of interferon and interferon inducers on infections with a nonviral intracellular microorganism Rickettsia akari. Infect. Immun. 3: 819–823.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATA, N., OKADA, A. and OKITA, F. (1965a) Production of a viral growth enhancing factor (Enhancer) in eggs infected with influenza virus (PR8). Arch. ges. Virusforsch. 17: 631–640.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATA, N., OKADA, A. and OKITA, F. (1965b) A factor capable of enhancing virus replication appearing parainfluenza type 1 (HVJ)-infected allantoic fluid. Virology 26: 630–637.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.

KATZ, L. J., LE, S. H. S. and ROZEE, K. R. (1974) Interferon-mediated increased lysis of L-cells by vesicular stomatitis virus. Can. J. Microbiol. 20(8): 1077–1083.
Kilbourne, E. D., Smart, K. M. and Pokorny, B. A. (1961) Inhibition by cortisone of the synthesis and action of interferon. Nature, Lond. 190: 650-651.

Kilander, D., Lindahl, P., Lundin, L., Leary, P. and Gresser, I. (1976) Relationship between the enhanced expression of histocompatibility antigens on interferon-treated L1210 cells and their position in the cell cycle. Eur. J. Immun. 6: 56-59.

Kingham, J. G., Ganguly, N. K., Shari, Z. D., Mendelson, R., Cartwright, T., Scott, G. M., Richards, B. M. and Wright, R. (1977) Treatment of HBsAg-positive chronic active hepatitis with human fibroblast interferon. Interferon Workshop, Zagreb, Yugoslavia.

Kishida, T., Toda, S., T. and Hattori, T. (1971) Effect of interferon on malignant mouse cells. C. r. Sêmc. Soc. Biol. 165(6): 1489-1492.

Kishida, T., Morikawa, K., Ito, M. and Yokota, Y. (1973) Influence of interferon on the inhibition by macrophages of the in vitro multiplication of murine malignant cells (FM3A). C. r. Sêmc. Soc. Biol. 167(1): 1503-1505.

Kleinschmidt, W. J. (1970) In vitro and in vivo studies with statolon against influenza virus. Ann. N.Y. Acad. Sci. 173: 547-550.

Kleinschmidt, W. J. (1972) Biochemistry of interferon and its inducers. Ann. Rev. Biochem. 41: 517-542.

Kleinschmidt, W. J. and Ellis, L. F. (1967) Statolon as an inducer of interferon. In: Interferon, pp. 39-46, Wolstenholme, G. E. W. and O'Connor, M. (eds.). CIBA Fnd Symp., J. and A. Churchill.

Klesel., N., Wolfe, W., Miller, G., Jungwirth, C. and Bodo, G. (1974) Synthesis of poly (A) sequences in poxvirus-infected cells treated with interferon or poly(I):poly(C). Virology 57: 570-573.

Knight, E., Jr (1973) Interferon: effect on the saturation density to which mouse cells will grow in vitro. J. cell Biol. 58(3): 846-849.

Knight, E., Jr (1974a) Interferon-sepharose: induction of the antiviral state. Biochem. biophys. Res. Commun. 56: 860-864.

Knight, E., Jr (1974b) Interferon-sepharose: priming of L cells for induction of interferon by MM virus. J. gen. Virol. 25(1): 143-145.

Knight, E., Jr (1976) Antiviral and cell growth inhibitory activities reside in the same glycoprotein of human fibroblast interferon. Nature, Lond. 262: 302-303.

Knight, E., Jr and Korant, B. D. (1977) A cell surface alteration in mouse L cells induced by interferon. Biochem. biophys. Res. Commun. 6: 707-713.

Kozba, K., Emodi, G., Just, M., Hilti, E., Leuenberger, A., Binswanger, U., Thiel, G. and Brunner, F. P. (1975) Treatment of herpes infection with human exogenous interferon. Lancet 1(7820): 1343-1344.

Kohn, L. D., Friedman, R. M., Holmes, J. M. and Lee, G. (1976) Use of thymopterin and cholera toxin to probe the mechanism by which interferon initiates its antiviral activity. Proc. natn. Acad. Sci. U.S.A. 73: 3695-3699.

Kohn, S., Buckler, C. E., Levy, H. B. and Baron, S. (1975a) Elution of cell-bound interferon as a cause of development of antiviral activity subsequent to washing of interferon-treated cell culture. IRCS J. med. Sci. 3: 57.

Kohn, S., Buckler, C. E., Levy, H. B. and Baron, S. (1975b) Studies on the role of cell-bound interferon in the induction of antiviral activity. In: Effects of Interferon on Cells, Viruses and the Immune System. pp. 123-133, Geraldes, A. (ed.).Academic Press, New York.

Kono, Y. and Ho, M. (1965) The role of the reticuloendothelial system in interferon formation in the rabbit. Virology 25: 162-166.

Korsantya, B. M. and Smorodintsev, A. A. (1971) Transplacental transmission of endogenous interferon in pregnant mice inoculated with influenza of Newcastle Disease viruses. Nature, Lond. 232(312): 560-561.

Korsantya, B. M., Smorodintsev, A. A. and Gvоздилова, Д. А. (1967) Some aspects of the interferon-cell interaction. Vop. Virolog. 9: 1304-1309.

Kravchenko, A. T., Voronen, E. S. and Kosmiada, N. (1967) Effects of anti-rabies vaccine and fixed rabies virus on the development of tumor caused by Rous sarcoma virus. Acta Virol. 11: 145-150.

Kumar, R., Worthington, M., Tilles, J. G. and Abelmann, W. H. (1971) Effect on the interferon stimulator polyinosinic-polycytidylic acid on experimental Trypanosoma cruzi infection. Proc. Soc. exp. Biol. Med. 137: 884-888.

Kunz, C. and Hofmann, H. (1969) The influence of the interferon-inducing compound poly I:C on the experimental infection with tick-borne encephalitis (TBE) virus. Zentbl. Bakter. ParasitKde, Abt. 1 Referat. 211: 270-273.

Kuwata, T., Fuse, A. and Morinaga, N. (1976a) Effects of interferon on cell and virus growth in transformed human cell lines. J. gen. Virol. 33: 7-11.

Kuwata, T., Oda, T., Sakiya, S., Morinaga, N. (1976b) Characteristics of a human cell line successively transformed by Rous sarcoma virus and Simian virus 40. J. natn. Cancer Inst. 56: 919-926.

Lab, M. and Koehren, F. (1972) POTENTIATION of the antiviral action of interferon by cycloheximide. Annls Inst. Pasteur, Paris 122: 567-573.

Lab, M. and Koehren, F. (1976) Maintenance and recovery of the interferon-induced antiviral state. Proc. Soc. exp. Biol. Med. 153: 112-118.

Lackovic, V. and Borecky, L. (1975) Increased resistance of an interferon-resistant cell subline to the action of double-stranded RNA. Acta Virol. 20: 347-362.

Lampson, G. P., Tytell, A. A., Nemes, M. M. and Hilleman, M. R. (1963) Purification and characterization of chick embryo interferon. Proc. Soc. exp. Biol. Med. 112: 468-481.

Larson, V. M., Clark, W. R. and Hilleman, M. R. (1969) Influence of synthetic (poly I-C) and viral double-stranded ribonucleic acids on adenovirus 12 oncogenesis in hamsters. Proc. Soc. exp. Biol. Med. 131: 1002-1008.

Larson, V. M., Panteleakis, P. N. and Hilleman, M. R. (1970) Influence of synthetic double stranded ribonucleic acid (poly IC) on SV40 viral oncogenesis and transplant tumor in hamsters. Proc. Soc. exp. Biol. Med. 133: 14-20.
Antiviral activities of interferons 501

LARSSON, A., FORSGREN, M., HARD, S., STRANDER, H. and CANTELL, K. (1976) Administration of interferon to an infant with congenital rubella syndrome involving persistent viremia and cutaneous vasculitis. *Acta Pediatr. Scand.* 65: 105–119.

LEBLEU, B., SEN, G. C., SHAILA, CABRER, B. and LENGYEL, P. (1976) Interferon, double-stranded RNA and protein phosphorylation. *Proc. natn. Acad. Sci. U.S.A.* 73: 3107–3111.

LEBON, P., MOREAU, M. C., COHEN, L. and CHANY, C. (1975) Different effect of ouabain on interferon production and action. *Proc. Soc. exp. Biol. Med.* 149: 108–112.

LEE, S. H. S., O'SHAUGHNESSY, M. V., ROZEE, K. R. and KIND, L. S. (1972) Interferone-induced growth depression in diploid and heteroploid human cells. *Proc. Soc. exp. Biol. Med.* 139: 1438–1440.

LEE, S. H. S. and ROZEE, K. R. (1975) Enhanced responsiveness of L929 cells treated with interferon to arginine starvation. *Exp. Cell Res.* 93: 143–158.

LEMAIR, A. and BAILEY, E. J. (1974) Synergy of a 9-beta-D-arabinofuranosyl-adenine and human interferon against herpes simplex virus type 1. *J. infect. Dis.* 130: 549–552.

LEVINE, S. (1966) Persistence of active interferon in cells washed after treatment with interferon. *Proc. Soc. exp. Biol. Med.* 121: 1041–1045.

LEVINE, S., MAGEE, W. E., HAMILTON, R. D. and MILLER, O. V. (1967) Effect of interferon on early enzyme and viral DNA synthesis in virus vaccine infection. *Virology* 32: 33–39.

LEVY, H. B. and MERIGAN, T. C. (1966) Interferon and uninfected cells. *Proc. Soc. exp. Biol. Med.* 121: 53–55.

LEVY, H. B. and RILEY, F. L. (1973) Effect of interferon treatment on cellular messenger RNA. *Proc. natn. Acad. Sci. U.S.A.* 70(12): 3815–3819.

LEVY, L. and MERIGAN, T. C. (1977) Inhibition of multiplication of *Mycobacterium leprae* by poly i-poly C. *Antimicrob. Ag. Chemother.* 11: 122–134.

LEVY, H. B., BUCKLER, C. E. and BARON, S. (1966) Effect of interferon on early interferon production. *Science, N.Y.* 152: 1274–1276.

LEVY, H. B. and CARTER, W. A. (1968) Molecular basis of the action of interferon. *J. molec. Biol.* 31: 561–576.

LEVY, H. B., LAW, L. W. and RABSON, A. S. (1969) Inhibition of tumor growth by polyinosinic-polycytidylic acid. *Proc. natn. Acad. Sci. U.S.A.* 62: 357–359.

LEVY, H. B., ASOFSKY, R., RILEY, F., GARAPIN, A., CANTOR, H. and ADAMSON, R. (1970) The mechanism of the antitumor action of poly i:poly C. *Ann. N.Y. Acad. Sci.* 173: 640–659.

LEVY, H. B., DUENWALD, J. and BUCKLER, C. E. (1973) Chorionate-oxidized amylase as an adjuvant for interferon production. *Infect. Immun.* 7(3): 457–460.

LEVY-KOENIG, R. E., GOLGHER, R. R. and PAUCKER, K. (1970a) Immunology of interferons. II. Heterospecific activities of human interferons and their neutralization by antibody. *J. Immun.* 104: 791–797.

LEVY-KOENIG, R. E., MUNDY, M. J. and PAUCKER, K. (1970b) Immunology of interferons I. Immune response to protective and nonprotective interferons. *J. Immun.* 104: 785–790.

LEWIS, J. A., FALCOFF, R. (1977) The molecular mechanism of interferon action. *Path. Biol.* 25: 9–13.

LIBIKOVA, H. (1965) Lowered susceptibility to exogenous interferon during the first stages of virus infection of cells. *Acta Virol.* 9: 279–281.

LIDIN, B. and ADAMS, A. (1975) Spontaneous interferon production and Epstein-Barr virus antigen expression in two human lymphoid cell lines and their somatic cell hybrids. *Intervirology* 5: 205–218.

LIEBERMAN, D., VOLOCH, Z., AVIV, H., NUDEL, V. and REVEL, M. (1974) Effect of interferon on hemoglobin synthesis and leukemia virus production in Friend cells. *Molec. Biol. Res.* 1: 447–454.

LIN, L. S., WIRANOWSKA-STEWART, M. and STEWART H. E. (1978) Purification of human leukocyte interferon to apparent homogeneity: Criteria for purity. *Abst. Ann. Meeting of Am. Soc. Microbiol.*

LINDAHL, P., LEARY, P. and GRESSER, I. (1976a) Increased expression of histocompatibility antigens on lymphoid cells. *Proc. natn. Acad. Sci. U.S.A.* 73: 3107–3111.

LINDAHL, P., LEARY, P. and GRESSER, I. (1974) Enhancement of the expression of histocompatibility antigens on murine leukemia L1210 cells. *Proc. natn. Acad. Sci. U.S.A.* 70: 2785–2788.

LINDAHL, P., LEARY, P. and GRESSER, I. (1973) Enhancement of the expression of histocompatibility antigens of mouse lymphoid cells by interferon in vitro. *Eur. J. Immun.* 4: 779–794.

LINDAHL, P., GRESSER, I., LEARY, P. and TOVEY, M. (1976a) Enhanced expression of histocompatibility antigens of lymphoid cells in mice treated with interferon. *J. infect. Dis.* 133: A66–A72.

LINDAHL, P., GRESSER, I., LEARY, P. and TOVEY, M. (1976b) Interferon treatment of mice-enhanced expression of histocompatibility antigens on lymphoid cells. *Proc. natn. Acad. Sci. U.S.A.* 73: 1284–1290.

LINDAHL-MAGNUSSON, P., LEARY, P. and GRESSER, I. (1971) Interferon and cell division. VI. Inhibitory effect of interferon on the multiplication of mouse embryo and mouse kidney cells in primary cultures. *Proc. Soc. exp. Biol. Med.* 138: 1044–1050.

LINDAHL-MAGNUSSON, P., LEARY, P. and GRESSER, I. (1972) Interferon inhibits DNA synthesis induced in mouse lymphocyte suspensions by phytohaemagglutinin or by allogenic cells. *Nature, New Biol.* 237: 120–121.

LINDEN, B. and ADAMS, A. (1975) Spontaneous interferon production and Epstein-Barr virus antigen expression in two human lymphoid cell lines and their somatic cell hybrids. *Intervirology* 5: 205–218.
LOCKART, R. Z., Jr (1963) Production of an interferon by L cells infected with WEE virus. J. Bact. 85: 556-566.

LOCKART, R. Z., Jr (1964) The necessity for cellular RNA and protein synthesis for viral inhibition from interferon. Biochem. biophys. Res. Commun. 15: 513-518.

LOCKART, R. Z., Jr (1966) Biological properties of interferons: criteria for acceptance of a viral inhibition as an interferon. In: Interferons, p. 1, FINTER, N. B. (ed.). North Holland, Amsterdam.

LOCKART, R. Z., Jr (1968) Viral interferon in aged cultures of chick embryo cells. In: Medical and Applied Virology, LERNER, E. H. (eds.). W. H. Green, St. Louis, Mo...

LOCKART, R. Z., Jr and HORN, B. (1963) Interaction of interferon with L cells. J. Bact. 85: 996-1002.

LOCKART, R. Z., Jr, STEWART, I1 and L. S. LIN 502

LOCKART, R. Z., Jr (1966) Production of an interferon by L cells infected with WEE virus. J. Bact. 85: 556-566.

LOCKART, R. Z., Jr (1964) The necessity for cellular RNA and protein synthesis for viral inhibition from interferon. Biochem. biophys. Res. Commun. 15: 513-518.

LOCKART, R. Z., Jr (1966) Biological properties of interferons: criteria for acceptance of a viral inhibition as an interferon. In: Interferons, p. 1, FINTER, N. B. (ed.). North Holland, Amsterdam.

LOCKART, R. Z., Jr (1968) Viral interferon in aged cultures of chick embryo cells. In: Medical and Applied Virology, LERNER, E. H. (eds.). W. H. Green, St. Louis, Mo...

LOCKART, R. Z., Jr and HORN, B. (1963) Interaction of interferon with L cells. J. Bact. 85: 996-1002.
Antiviral activities of interferons

McNeill, T. A., Fleming, W. A. and McCance, D. J. (1972) Interferon and haemopoietic colony inhibitor responses to poly I:poly C in rabbits and hamsters. *Immunology* 22: 711–721.

Mecs, I., Sonnabend, J. A., Martin, E. M. and Fantes, K. H. (1967) The effect of interferon on the synthesis of RNA in chick cells infected with Semliki Forest virus. *J. gen. Virol.* 1: 25–40.

Mecs, I., Kasler, M., Lozosa, A. and Kovacs, G. (1974) Metabolic effect of interferon preparations and some interferon inducers: Activation of adenylate cyclase system. *Acta microbiol. hung.* 21: 265–268.

Melldolfs, M. F., Friedman, R. M. and Kohn, L. D. (1977) An interferon-induced increase in cyclic AMP levels precedes the establishment of the antiviral state. *Biochem. biophys. Res. Commun.* 79: 239–246.

Mendelson, J. and Glasgow, L. (1960) The in vitro and in vivo effects of cortisol on interferon production and action. *J. Immun.* 96: 345–362.

Mergan, T. C. (1964) Purified interferons: physical properties and species specificity. *Science, N.Y.* 145: 811–813.

Mergan, T. C., Winget, C. A. and Dixon, C. B. (1965) Purification and characterization of vertebrate interferons. *J. molec. Biol.* 13: 679–691.

Mergan, T. C., Reed, S. E., Hall, T. S. and Tyrrell, D. A. J. (1973) Inhibition of respiratory virus infection by locally applied interferon. *Lancet* 1(803): 563–567.

Mergan, T. C., Chester, T. J. and Pauker, K. (1975) In: *Effects of Interferon on Cells, Viruses and the Immune System*, pp. 347–388, Geraldies, A. (ed.). Academic Press, London.

Mergan, T. C., Pollard, R. B., Robinson, W. S., Gregory, P., Greenberg, H., Smith, J., Neal, A., Rand, K., Arvin, A. and Breeden, J. (1977) Clinical experiences with human interferon application in human. *Fifth Aharon Katzir-Katchalsky Conference on the Human Interferon*, Behovot, Israel.

Mergan, T. C., Rand, K. H., Pollard, R. B., Abdelilah, P. S., Jordan, G. W. and Fried, R. P. (1978) Human leukocyte interferon for the treatment of herpes zoster in patients with cancer. *New Engl. J. Med.* 298: 981–987.

Metz, D. H. (1975a) Interferon and interferon inducers. In: *Advances in Drug Research*, Vol. 10, pp. 101–124, Simons, Alma B. (ed.). Academic Press.

Metz, D. H. (1975b) The mechanism of action of interferon. *Cell* 6: 429–457.

Metz, D. H. and Esteban, M. (1972) Interferon inhibits viral protein synthesis in L cells infected with vaccinia virus. *Nature, Lond.* 238: 385–388.

Metz, D. H., Esteban, M. and Danielecu, G. (1975) The effect of interferon on the formation of virus polyribosomes in L cells infected with vaccinia virus. *J. gen. Virol.* 27: 197–213.

Metz, D. H., Levin, M. Y. and Oxman, M. N. (1976) Mechanism of interferon action: Further evidence for transcription as the primary site of action in simian virus 40 infection. *J. gen. Virol.* 32: 227–241.

Metz, D. H., Oxman, M. N. and Levin, M. J. (1977) Interferon inhibits the in vitro accumulation of virus specific RNA in nuclei isolated from SV40 infected cells. *Biochem. biophys. Res. Commun.* 75: 172–188.

Miner, N., Ray, W. J., Jr and Simon, E. M. (1966) Effect of interferon on the production and action of viral RNA polymerase. *Biochem. biophys. Res. Commun.* 24: 264–268.

Mostraaten, L. E., DeMaeyer, E. and DeMaeyer-Guignard, J. (1973) Prolongation of allograft survival in mice by inducers of interferon. *Transplantation* 16: 415–431.

Moehring, T. J., Moehring, J. M. and Stinebring, W. R. (1971) Response of interferon-treated cells to diphtheria toxin. *Infect. Immun.* 4: 747–752.

Moehring, J. M. and Stinebring, W. R. (1971) Prolonged application of interferon and "aging" of human diploid fibroblast. *Proc. Soc. exp. Biol. Med.* 137: 191–193.

Moehring, J. M., Stinebring, W. R. and Merchant, D. J. (1971) Survey of interferon production and sensitivity of human cell lines. *Appl. Microbiol.* 22: 102–108.

Molenkamp, K. E., Pyhalo, L., Torma, E. and Cantelli, K. (1974) No evidence for carbohydrate moiety affecting the clearance of circulating human leukocyte interferon in rabbits. *Acta path. microbiol. scand.* B 82: 305–310.

Molomut, N. and Padnos, M. (1965) Inhibition by transplantable and spontaneous murine tumors by the M-P virus. *Nature, Lond.* 208: 948–950.

Morahan, P. S. and Kaplan, A. M. (1976) Macrophage activation and antitumor activity of biologic and synthetic agents. *Int. J. Cancer* 17: 82–89.

Morahan, P. S., Munson, J. A., Baird, L. G., Kaplan, A. M. and Regelson, W. (1974) Antitumor action of pyran copolymer and tilorone against Lewis lung carcinoma and B-16 melanoma. *Cancer Res.* 34: 506–511.

Morgan, M. J., Colby, C. Jr and Hulsey, J. L. N. (1973) Isolation and characterization of virus-resistant mouse embryo fibroblast. *J. gen. Virol.* 20: 377–388.

Morgan, M. J. and Fair, P. (1977) The expression of the interferon system in clones of Chinese hamster cells. *Br. J. Cancer* 36: 254.

Murphy, B. R., Richman, D. D., Chalhub, E. G., Uhlenendorf, C. P., Baron, S. and Chanock, R. M. (1975) Failure of attenuated temperature-sensitive influenza A virus (H3N2) to induce heterologous interference in human to Parainfluenza Type 1 virus. *Infect. Immun.* 12: 62–74.

Nebert, D. W. and Friedman, R. M. (1973) Stimulation of aryl hydrocarbon hydroxylase induction in cell cultures by interferon. *J. Virol.* 11: 193–197.

Nemes, M. M. and Hilelman, M. R. (1962) Effect of Westphal lipid A on viral activities in mice and hamsters. *Proc. Soc. exp. Biol. Med.* 110: 500–510.

Nemes, M. M., Tytell, A. A., Lampson, G. P., Field, A. K. and Hilelman, M. R. (1969) Inducers of interferon and host resistance. VI. Antiviral efficacy of poly I:C in animal models. *Proc. Soc. exp. Biol. Med.* 132: 776–783.

Neumann-Haefelin, D., Sundatcher, R., Sauter, B., Karges, H. E. and Manthey, K. F. (1975) Effect of human leukocyte interferon on vaccinia- and herpes virus-infected cell cultures and monkey corneas. *Infect. Immun.* 12: 148–154.

Neumann-Haefelin, D., Shrestha, B. and Manthey, K. F. (1976) Effective antiviral prophylaxis and therapy by systemic application of human interferon in immunosuppressed monkeys. *J. infect. Dis.* 133: A211–A215.
NEUMANN-HAEFELIN, D., DINDMACHER, R., SKODA, R. and CANTELL, K. (1977) Comparative evaluation of human leukocyte and fibroblast interferon in the prevention of herpes simplex virus keratitis in a monkey model. Infect. Immun. 17: 468-470.

NGAN, J., LEE, S. H. S. and KIND, L. S. (1976) Suppressive effect of interferon on ability of mouse spleen cells synthesizing IgE to sensitize rat skin for heterologous adaptive cutaneous anaphylaxis. J. Immun. 117: 1063-1075.

NIBLACK, J. F. and McCREADY, M. B. (1971) Relationship of biological activities of poly I-poly C to mononucleotides. Nature, New Biol. 233: 52-53.

NICHOLS, F. R. and TERSHAK, D. R. (1967) Effect of 5-fluorouracil and 6-azauridine on interferon action. J. Virol. 1: 450-462.

O'MALLEY, J. A., AL-BUSSAM, N., BEUTNER, K., WALLACE, H. J., GAILANI, S., HENDERSON, E. S. and CARTER, W. A. (1975) Cytomegalovirus infection with acute myelocytic leukemia; antiviral (interferon and antibody) responses. N.Y. St. J. Med. 75: 738.

O'REILLY, R. J., EVERSON, L. K., EMODI, G., ANSEN, J., SMITHWICK, E. M., GRIMES, E., PAHWA, S., OHWAKI, M. and KAWADE, Y. (1972) Inhibition of multiplication of mouse cells in culture by interferon. J. Neuroimmun. 32: 299-302.

OHNO, S. and NOZIMA, T. (1964) Inhibitory effect of interferon on the induction of thymidine kinase in vaccinia virus-infected chick embryo fibroblasts. Acta Virol. 8: 479-483.

OHWAKI, M. and KAWADE, Y. (1972) Inhibition of multiplication of mouse cells in culture by interferon preparations. Acta Virol. 16: 477-486.

OIE, H. K., BUCKLER, C. E., UHLENDORF, C. P., HILL, D. A. and BARON, S. (1972) Improved assays for a variety of interferons. Proc. Soc. exp. Biol. Med. 140: 1178-1181.

OSEN, G. A., KERN, E. R., GLASGOW, L. A. and OVERALL, J. C. Jr (1976) Effect of treatment with exogenous interferon poly I-poly C or poly I-poly C-poly-lysin complex on EMC virus infections in mice. Antimicrob. Ag. Chemother. 10: 668-679.

PACHECO, D., FALCOFE, R., CATINOT, L., FLOCH, F., WERNER, G. H. and FALCOFF, E. (1976) Inhibitory effect of interferon on SV40 T antigen production in SV40 transformed cells. J. natn. Cancer Inst. 58: 1687-1696.

PAHWA, R., SCHWARTZ, S., ARMSTRONG, D., SIEGAL, F. P., GUPTA, S., DU PONT, B. and GOOD, R. A. (1976) Effect of exogenous interferon in cytomegalovirus infection complicating bone marrow transplantation. Clin. Immun. Immunopath. 6: 51-58.

PAUCKER, K. and CANTELL, K. (1963) Quantitative studies on viral interference in suspended L cells. Virology 21: 22-29.

PAUCKER, K. and CANTELL, K. (1967) Inhibition of SV40 T antigen formation by interferon. J. Virol. 12: 191-194.

PAUCKER, K. and HENLE, W. (1958) Interference between inactivated and active influenza virus in the chick embryo. Proc. natn. Acad. Sci. U.S.A. 44: 112-127.

PAUCKER, K. and HENLE, W. (1962) Quantitative studies on viral interference in suspended L cells. III. Effect of interfering viruses and interferon on the growth rate of cells. Virology 17: 324-334.

PAUCKER, K., CANTELL, K. and HENLE, W. (1975) Cytomegalovirus infection with acute myelocytic leukemia; antiviral (interferon and antibody) responses. N.Y. St. J. Med. 75: 738.

PAUCKER, K., BOXACA, M. (1967) Cellular resistance to induction of interferon. Proc. natn. Acad. Sci. U.S.A. 54: 941-948.

PAUCKER, K. and CANTELL, K. (1963) Quantitative studies on viral interference in suspended L cells synthesizing IgE to sensitize rat skin for heterologous adaptive cutaneous anaphylaxis. J. Immun. 117: 1063-1075.

PAUCKER, K. and CANTELL, K. (1967) Quantitative studies on viral interference in suspended L cells. Proc. natn. Acad. Sci. U.S.A. 54: 941-948.

PAULLIN, O., LUNDMARK, K. and BREGE, K. G. (1976) Interferon in severe herpes simplex of cornea. Lancet ii: 1187-1188.

PARK, J. H. and BARON, S. (1968) Herpetic keratoconjunctivitis: therapy with synthetic double-stranded RNA. Science, N.Y. 162: 811-813.

PARK, J. H., GALIN, M., BILLIAU, A. and BARON, S. (1969) Prophylaxis of herpetic keratoconjunctivitis with interferon inducers. Archs Ophthal. 81: 840-845.

PAUCKER, K., CANTELL, K. (1964) Inhibition of SV40 T antigen formation by interferon. J. Virol. 12: 191-194.

PAUCKER, K. and HENLE, W. (1962) Quantitative studies on viral interference in suspended L cells. III. Effect of interfering viruses and interferon on the growth rate of cells. Virology 17: 324-334.

PAULLIN, A., CHANY-FOURNIER, F., EPSTEIN, L. and CHANY, C. (1977) Degradation par la Phyto-
SALZBURG, S., SCHULLER, G. B., MORAHAN, P. S. and SNODGRASS, M. (1975) Inhibition and enhancement of Friend leukemia virus infection in cell cultures. Nature, New Biol. 237: 270-271.

ROSSI, G. B., MARCHENGIANI, M., MATARESE, G. and GRESSER, I. (1975) Inhibitory effect of interferon on multiplication of Friend leukemia cells in vivo. J. natn. Cancer Inst. 54: 993-999.

ROSSI, G. B., DOLEI, A., CIOE, L., BENEDETTO, A., MATARESE, G. P. and BELARDELLI, F. (1977a) Inhibition of transcription and translation of globin messenger RNA in dimethyl sulfoxide-stimulated Friend erythroleukemia cells treated with interferon. Proc. natn. Acad. Sci. U.S.A. 74: 2036-2040.

ROSSI, G. B., DOLEI, A., CIOE, L., BENEDETTO, A., MATARESE, G. P., BELARDELLI, F. and RITA, G. (1977b) Interferon and Friend leukemia cells in culture. Tex. Rep. Biol. Med. 35: 420-429.

ROSSI, G. B., MATARESE, G. P., GRAPPELLI, C., BELARDELLI, F. and BENEDETTO, A. (1977c) Interferon inhibits dimethyl sulfoxide-induced erythroid differentiation of Friend leukemia cells. Nature, Lond. 267: 50-52.

ROSSMAN, T. G. and VINCEK, J. (1969) Influence of the rate of cell growth and cell density on interferon action in chick embryo cells. J. Virol. 4: 7-18.

ROATZECZY, I. (1971) Interferon induced by poly I.C in interferon pretreated L cells in absence of DEAE-dextran. Acta Virol. 15: 431-440.

ROATZECZY, I. (1974) Further enhancement of priming that is a non-antiviral function of interferon. Acta microbiol. hung. 21: 305-309.

ROATZECZY, I. AND MECS, I. (1970) Enhancement of interferon synthesis by polyinosinic-polyribosalic acid in L cells pretreated with interferon. Acta Virol. 14: 398-400.

ROUSSET, S. (1974) Refractory state of cells to interferon induction. J. gen. Virol. 22(1): 9-20.

RUIZ-GOMEZ, J. AND ISAACS, A. (1963) Optimal temperature for growth and sensitivity to interferon among different viruses. Virology 19: 1-7.

RYTEL, M. W. (1975) Antagonism of interferon action by mouse tissue extracts and serum. Archs Virol. 48: 103-110.

RYTEL, M. W. AND KILBOURNE, E. D. (1966) The influence of cortisone on experimental viral infection. VIII. Suppression by cortisone of interferon formation in mice injected with Newcastle disease virus. J. exp. Med. 123: 767-776.

SALVING, S. B., YOUNGNER, J. S., NISHIO, J. AND NETA, R. (1975) Tumor suppression by a lymphokine released into the circulation of mice with delayed hypersensitivity. J. natn. Cancer Inst. 55: 1233-1235.

SALZBERG, S., BAKHANASHVILI, M. AND ABOUD, M. (1978) Effect of interferon on mouse cells chronically infected with murine leukemia virus. J. gen. Virol. 40: 121-130.

SAMPSON, C. E. (1976) Mechanism of interferon action. Studies on the mechanism of interferon-mediated inhibition of reovirus messenger RNA translation in cell free protein synthesis systems from mouse ascites tumor cells. Virology 75: 166-173.

SAMPSON, C. E. AND FARRIS, D. A. (1977) Mechanism of interferon action: species specificity of interferon and of the interferon-mediated inhibitor of translation from mouse, monkey and human cells. Virology 77: 556-566.

SAMPSON, C. E. AND JOGLIK, W. K. (1974) A protein synthesizing system from interferon-treated cells that discriminates between cellular and viral messenger RNAs. Virology 58(2): 476-491.

SARMA, P. S., SHU, G., BARON, S. AND HUEBNER, R. J. (1969) Inhibitory effect of interferon in murine sarcoma and leukemia virus infection in vitro. Nature, Lond. 223: 845-846.

SCHAFFER, T. W., LIEBERMAN, M., COHEN, M. AND CAME, P. E. (1972) Interferon administered orally: protection of neonatal mice from lethal virus challenge. Science, N.Y. 176: 1326-1327.

SCHMUNIS, G., GUILLON, J. C. AND TOVEY, M. G. (1977) Inhibition by anti-interferon serum of inhibition of reovirus messenger RNA translation in cell free protein synthesis systems from mouse ascites tumor cells. Virology 76: 459-463.

SCIENTIFIC COMMITTEE ON INTERFERON. (1962) Effect of interferon on vaccination in volunteers. Lancet, 28 April, pp. 873-875.

SCIENTIFIC COMMITTEE ON INTERFERON. (1965) Experiments with interferon in man. Lancet i: 505-510.

SCIENTIFIC COMMITTEE ON INTERFERON. (1970) Progress towards trials of human interferon in man. Ann. N.Y. Acad. Sci. 173: 770-774.

SCOTT, G. M., CARTWRIGHT, T., LEDU, G. AND DICKER, D. (1977a) Effect of human fibroblast interferon on vaccination in volunteers. Symp. Prep. Stand. Clin. Use of Interferon, Zagreb, Yugoslavia.

SCOTT, G. M., CARTWRIGHT, T., TYRRELL, D. A. J., BUTLER, J. K., PORTEOUS, M. AND STEVENS, R. M.
(1977b) Preliminary experience with fibroblast interferon against vaccinia virus in human and monkey skin. Symp. Prev. Stand. Clin. Use of Interferon, Zagreb, Yugoslavia.

Sela, I., Grossberg, S. E., Sedmak, J. J. and Mehler, A. H. (1976) Discharge of aminoacyl-viral RNA by a factor from interferon-treated cells. Science, N.Y. 194: 193-195.

Sellers, R. F. and Fitzpatrick, M. (1962) An assay of interferon produced in Rhesus monkey and calf kidney tissue cultures using bovine enterovirus M as, a challenge. Br. J. exp. Path. 43: 674-683.

Sen, G. C., Lebleu, B., Brown, G. E., Rebecco, M. S., Furchi, M. Y., Morgan, M., Shatkin, A. and Lengyel, P. (1975) Inhibition of reovirus messenger RNA methylation in extracts of interferon-treated Ehrlich ascites tumor cells. Biochem. biophys. Res. Commun. 65: 427-439.

Sen, G. C., Lebleu, B., Brown, G. E., Kawakita, M., Slattery, E. and Lengyel, P. (1976) Interferon, double-stranded RNA and mRNA degradation. Nature, Lond. 264: 370-377.

Sen, G. C., Shaila, S., Lebleu, B., Browne, G. E., Desrosiers, R. E. and Lengyel, P. (1977) Impairment of reovirus mRNA methylation in extracts of interferon-treated Ehrlich ascites tumor cells: Further characteristics of the phenomenon. J. Virol. 21: 69-76.

Shaila, S., Lebleu, B., Brown, G. E., Sen, G. C. and Lengyel, P. (1977) Characteristics of extracts from interferon-treated HeLa cells: presence of a protein kinase and endoribonuclease activated by dsRNA and of an inhibitor of mRNA methylation. J. gen. Virol. 37: 535-546.

Shapiro, S. Z., Shapero, S. P. and Lillie, J. (1977) Synthesis and cleavage processing of oncornavirus proteins during interferon inhibition of virus particle release. Infect. Immun. 16: 742-752.

Sheaff, E. T. and Stewart, R. B. (1969) Interaction of interferon with cells: induction of antiviral activity. Can. J. Microbiol. 15: 941-954.

Sheaff, E. T. and Stewart, R. B. (1970a) Interaction of interferon with cells: characteristics of the induction of interferon uptake in relation to interferon antiviral activity. Can. J. Microbiol. 17: 1087-1093.

Sheaff, E. T. and Stewart, R. B. (1970b) Interaction of interferon with cells: the relationship of cell-associated interferon and antiviral activity. Can. J. Microbiol. 16: 1303-1310.

Sheaff, E. T. and Stewart, R. B. (1970c) Interaction of interferon with cells: the synthesis of an interferon-induced protein. Can. J. Microbiol. 16: 1311-1318.

Shirodkar, M. V. (1965) The blocking effect of West Nile virus on production of sarcoma by Rous virus. J. natn. Cancer Inst. 35: 851-867.

Siewers, C. M. F., John, C. E. and Medearis, D. N. (1970) Sensitivity of human cell strains to interferon. Proc. Soc. exp. Biol. Med. 133: 1178-1183.

Skegato, F., Zazic, B., Bahnson, H. P., Haff, R. F. and Cantell, K. (1973) The kinetics of human interferon clearance in gibbons. Proc. Soc. exp. Biol. Med. 142: 946-947.

Skurkovich, S. V. and Aleksandrovskaya, I. M. (1973) Effect of interferon on immunological reactivity. Problemi Genet. Perifer. Kroi. 18: 43-50.

Skurkovich, S. V. and Ereminina, E. I. (1975) The probable role of interferon in allergy. Ann. Allergy 35: 377-383.

Skurkovich, S. V., Klinova, E. G., Aleksandrovskaya, I. M., Levina, N. V. and Arkhipova, N. A. (1973a) Stimulation of transplantation immunity and the plasmacyte reaction in mice by interferon. Biul. eksp. Biol. Med. 75: 66-69.

Skurkovich, S. V., Klinova, E. G., Aleksandrovskaya, I. M., Levina, N. V., Arkhipova, N. A. and Bulicheva, T. I. (1973b) Stimulation of transplantation, immunity and plasma cell reaction by interferon in mice. Immunology 25: 317-322.

Skurkovich, S. V., Kalinina, I. A., Ereminina, E. I. and Bulicheva, T. I. (1976a) Enhancement of the immune response following immunization with L210 cells preliminarily incubated with interferon. Biul. eksp. Biol. Med. 81: 706-707.

Skurkovich, S. V., Kalinina, I. A., Ereminina, E. I. and Bulicheva, T. I. (1976b) Increased sensitivity of leukemia cells incubated in interferon to the action of immune serum. Biul. eksp. Biol. Med. 12: 1459-1461.

Skurkovich, S. V., Klinova, E. G. and Ereminina, E. I. (1976) Stimulation of humoral immunity to surface antigens of leukemic cells. Bull. exp. Biol. Med. 81: 429.

Slamon, D. J. (1973) Protective effect of the double-stranded polyribonucleotide, polyinosinic-poly-cytidylic acid, against rat erythroblastosis induced by murine erythroblastosis virus. J. natn. Cancer Inst. 51: 851-867.

Slamon, D. J. (1975) Hemolytic anemia induced by murine erythroblastosis virus—possible mechanisms of hemolysis and effects of an interferon inducer. J. natn. Cancer Inst. 55: 329-339.

Slade, D. L., Shulman, L., Lawrence, J. B., Revel, M. and Ruddle, F. H. (1978) Presence of human chromosome 21 in some melanoma cell lines: evidence for hybrid cell formation. J. Virol. 25: 319-325.

Slavin, E. G. and Svjet-Moldavsky, G. J. (1973) Introduction by interferon of sensitivity of target cells to the cytotoxic action of lymphocytes. Vop. Virus. 18: 366-368.

Smart, K. M. and Killbourne, E. D. (1966) The influence of cortisone on experimental infection. VI. Inhibition by hydrocortisone of interferon synthesis in the chick embryo. J. exp. Med. 123: 299-307.

Smorgostinsev, A. A., Beare, A. S., Bynoe, M. L., Head, B. and Tyrrell, D. A. J. (1971) The formation of interferon during acute respiratory virus infection of volunteers. Arch. ges. Virusforsch. 33: 9-16.

Snoggrass, M. J., Morahan, P. S. and Kaplan, A. M. (1975) Histopathology of the host response to Lewis lung carcinoma: modulation by pyran. J. natn. Cancer Inst. 55: 455-467.

Snyderman, R., Wohlenberg, C. and Notkins, A. L. (1972) Inflammation and viral infection: Chemostatic activity resulting from the interaction of antiviral antibody and complement with cells infected with Herpes Simplex virus. J. infect. Dis. 126: 207-221.

Sokawa, Y., Watanehe, Y. and Kawade, Y. (1977) Suppressive effect of interferon on the transition from a quiescent to a growing state in 3T3 cells. Nature, Lond. 268: 236-238.

Soloviev, V. D. (1968) Some results and prospects in the study of endogenous and exogenous interferon. In: The Interferons. p. 233, RITA, G. (ed.). Academic Press, New York.
SOLOVIEV, V. D. (1969) The results of controlled observation on the prophylaxis of influenza with interferon. Bull. Wld. Hlth. Org. 41: 683–690.

SOLOVIEV, V. D. and MENTKEVICH, L. M. (1965) The effect of colchicine on viral interference and interferon formation. Acta Virol. 9: 308–312.

SONNABEND, J. A. (1964) An effect of interferon on uninfected chick embryo fibroblasts. Nature, Lond. 203: 496–498.

SONNABEND, J. A. and FRIEDMAN, R. M. (1973) Mechanism of interferon action. In: Interferons and Interferon Inducers, pp. 201–238, PINTER, N. B. North-Holland, Amsterdam.

SONNABEND, J. A., MARTIN, E. M., MECK, E. and FANTES, K. H. (1967) The effect of interferon on the synthesis of an RNA polymerase isolated from chick cells infected with Semliki Forest virus. J. gen. Virol. 1: 41–48.

SOOS, E., IRIČ, D., JUSIĆ, D., SMERDEL, S., PETRIČEVIĆ, I., KUNSTEN, D. and SOLDO, I. (1972) Treatment of local complications provoked by vaccinia virus with leukocytic interferon. Proc. Symp. on Combined Vaccines, Yugoslav Acad. Sci. and Arts, Zagreb, pp. 179–182.

STANCEK, D. and MATISOVA, E. (1968) Potentiation of the antiviral activity of interferon by histones. Acta Virol. 12: 309–321.

STEWART, R. B. and SHEAFF, E. T. (1972) Interaction of interferon with cells: the relationship between interferon uptake and activity. Can. J. Microbiol. 18: 725–730.

STEWART, W. E. (1975a) Uptake of interferon: the fate of cell-bound interferon during induction of antiviral and non-antiviral activities. In: Effects of Interferon on Cells, Viruses and the Immune System, pp. 75–98, GERALDES, A. (ed.). Academic Press, New York.

STEWART, W. E. (1975b) Antiviral and non-antiviral activities of distinct molecular populations of interferons. Symp. Antivirals with Clinical Potential, Stanford, Calif.

STEWART, W. E., LIN, L. S. and WIRANOWSKA-STEWART, M. (1978b) Antiviral and other activities of pure interferons and interferoids. Proc. IVth Int. Cong. Virology, Der Haag, Netherlands.

STEWART, W. E. and DECLERCQ, E. (1973) Non-antiviral effects of interferons. Medikon 6: 279.

STEWART, W. E. and DECLERCQ, E. (1974) Relationship of cytotoxicity and interferon-inducing activity of polyribioinosinic acid·polyribocytidylic acid to the molecular weights of the homopolymers. J. gen. Virol. 23: 83–89.

STEWART, W. E. and LOCKART, R. Z., Jr (1970) Relative antiviral resistance induced in homologous and heterologous cells by cross-reacting interferons. J. Virol. 6: 795–799.

STEWART, W. E. and SULKIN, S. E. (1966) Interferon production in hamsters experimentally infected with rabies virus. Proc. Soc. exp. Biol. Med. 123: 650–653.

STEWART, W. E. and SULKIN, S. E. (1968) Evaluating the role of interferon in rabies infection. Bact. Proc. V23.

STEWART, W. E., SCOTT, W. D. and SULKIN, S. E. (1969) Relative sensitivities of viruses to different species of interferon. J. Virol. 4: 147–153.

STEWART, W. E., GOSSER, L. B. and LOCKART, R. Z., Jr (1971a) Priming: a non-antiviral function of interferon. J. Virol. 7: 792–801.

STEWART, W. E., GOSSER, L. B. and LOCKART, R. Z., Jr (1971b) Distinguishing characteristics of the interferon responses of primary and continuous mouse cell cultures. J. gen. Virol. 13: 35–50.

STEWART, W. E., DECLERCQ, E., BILLIAU, A., DESMYTER, J. and DESOMER, P. (1972a) Increased susceptibility of cells treated with interferon to the toxicity of polyribioinosinic-polyribocytidylic acid. Proc. natn. Acad. Sci. U.S.A. 69: 1851–1854.

STEWART, W. E., DECLERCQ, E. and DESOMER, P. (1972b) Cellular alteration by interferon; a virus-free system for assaying interferon. J. Virol. 10: 896–901.

STEWART, W. E., DECLERCQ, E. and DESOMER, P. (1972c) Recovery of cell-bound interferon. J. Virol. 10: 707–712.

STEWART, W. E., GOSSER, L. B. and LOCKART, R. Z., Jr (1972d) The effect of priming with interferon on interferon production by two lines of L cells. J. gen. Virol. 15: 85–87.

STEWART, W. E., DECLERCQ, E. and DESOMER, P. (1973a) Specificity of interferon-induced enhancement of toxicity for double-stranded ribonucleic acids. J. gen. Virol. 18: 237–246.

STEWART, W. E., DECLERCQ, E., DESEMER, P., BERG, K., OGUBN, C. A. and PAUCKER, K. (1973b) Antiviral and non-antiviral activity of highly purified interferon. Nature, New Biol. 246: 141–143.

STEWART, W. E., WIRANOWSKA, M., KOBUS, M., SZMIGIELSKI, S. and KORBECKI, M. (1975a) Increased sensitivities of interferon-treated cells to the toxicities of double-stranded RNAs and lectins. Abst. Ann. Meeting, Am. Soc. Microbiol.

STEWART, W. E., WIRANOWSKA, M., KOBUS, M., KORBECKI, M., LUCZAK, M. and SZMIGIELSKI, S. (1975b) Synergistic antitumor activity of interferon and polyri·polyr against murine sarcoma. Symp. Antitritals with Clinical Potential, Stanford, Calif.

STEWART, W. E., GRESSER, I., TOVEY, M. G., BANDU, M. T. and LEFFOSS, S. (1976) Identification of the cell-multiplication-inhibitory factors in interferon preparations as interferons. Nature, Lond. 262: 300–303.

STEWART, W. E., LIN, L. S., WIRANOWSKA-STEWART, M. and CANTELL, K. (1977) Elimination of size and charge heterogeneities of human leukocyte interferons by chemical cleavage. Proc. natn. Acad. Sci. U.S.A. 74: 4200–4204.

STEWART, W. E., CHUDZIO, T., LIN, L. S. and WIRANOWSKA-STEWART, M. (1978a) Interferoids: In vitro and in vivo conversion of native interferons to lower molecular weight forms. Proc. natn. Acad. Sci. U.S.A. 75: 4814–4818.

STIM, T. B. (1970) Interference of coccal virus with Friend leukemia virus-induced splenomegaly in DBA/2J mice. Proc. Soc. exp. Biol. Med. 134: 413–418.

STRANDER, H. (1977a) Interferons: Anti-neoplastic drugs? Blut 35: 277–288.

STRANDER, H. (1977b) Antitumor effects of interferon and its possible use as an antineoplastic agent in man. Tex. Rep. Biol. Med. 35: 429–435.
Ribonucleic acid and protein synthesis in cells infected with mutants isolated from persistently infected L cells. J. Virol. 6: 42-48.

Thacore, H. R. and Youngner, J. S. (1972) Viral RNA synthesis by NDV mutants isolated from persistently infected L cells: effect of interferon. J. Virol. 9: 503-509.

Thacore, H. R. and Youngner, J. S. (1973a) Rescue of VSV from interferon-induced resistance by super-infection with vaccinia virus. I. Rescue in cell cultures from different species. Virolgy 56: 505-511.

Thacore, H. R. and Youngner, J. S. (1973b) Rescue of vesicular stomatitis virus from interferon-induced resistance by super-infection with vaccinia virus. II. Effect of uv-inactivated vaccinia and metabolic inhibitors. Virolgy 56: 512-521.

Thacore, H. R. and Youngner, J. S. (1975) Persistence of vesicular stomatitis virus in interferon-treated cell cultures. Virolgy 63: 345-357.

Thorbecke, G. J., Friedman-Kien, A. E. and Vilcek, J. (1974) Effect of rabbit interferon on immune responses. Cell. Immun. 12(2): 290-295.

Tilles, J. G. (1967) Enhancement of interferon titers by poly-L-ornithine. Proc. Soc. exp. Biol. Med. 125: 996-999.

Tomilla, V. (1963) Treatment of dendritic keratitis with interferon. Acta Ophthal. 65: 478-491.

Tomilla, V. and Penttininen, K. (1962) Effect of ultraviolet irradiated influenza Lee viruses on experimental herpes simplex virus infection in rabbit's eye. Acta Ophthal. 40: 520-533.

Toth, F. D., Vaczi, L. and Berencsi, C. (1971a) Effect of interferon treatment on the tumor-specific antibody response of Balb-C mice infected with Rauscher virus. Acta microbioi. hung. 18: 109-112.

Toth, F. D., Vaczi, L. and Berencsi, C. (1971b) Interferon and antibody production in inbred mice infected with Rauscher virus. Acta microbiol. hung. 23: 22-27.

Tovell, D. and Cantell, K. (1971) Kinetics of interferon production in human leukocyte suspensions. J. gen. Virol. 13: 485-489.

Tovey, M. G. and Brouty-Boyé, D. (1976) Characteristics of the chemostat culture of animal cells. Exp. Cell Res. 101: 346-354.

Tovey, M. G., Brouty-Boyé, D. and Gresser, I. (1975) Interferon and cell division. 10. Early effect of interferon on mouse leukemia cells cultivated in a chemostat. Proc. natn. Acad. Sci. U.S.A. 72: 2265-2270.

Truden, J. L., Sigel, M. M. and Dietrich, L. S. (1967) An interferon antagonist: its effect on interferon action in mengo-infected Ehrlich ascites tumor cells. Virolgy 33: 95-103.

Ts'o, P., Alderfer, J. L., Levy, J., Marshall, L. W., O'Malley, J. M., Horoszewicz, J. S. and Carter, W. A. (1976) An integrated and comparative study of the antiviral and other biological properties of the polynucleoside-polyacylidylic acid and its mismatched analogous. Molec. Pharmac. 12: 299-310.

Tyrell, D. A. J. and Reed, S. E. (1973) In: Non-specific Factors Influencing Host Resistance. pp. 438-442, Brown, W. (ed.) Basel, Karger.

Umino, Y. and Kohno, S. (1976) Binding and interspecies specificity of two rodent interferons. IRCS Med. Sci. 4: 138-145.

Ustacelebi, S. and Williams, J. F. (1973) Induction of interferon in chick cells by polyoma virus. J. gen. Virol. 21: 163-168.

Vandeputte, M., Datta, S. K., Billiau, A. and Desomer, P. (1970) Inhibition of polyoma-virus oncogenesis in rats by polyribonucleic–ribonucleic acid. Eur. J. Cancer 6: 323-327.

Van Griesven, L. J., Baudejant, M. F., Peries, J., Emanoil-Ravikovitch, R. and Boiron, M. (1971) Studies on the biosynthesis of murine leukemia virus RNA. I. Some properties of Rauscher leukemia virus isolated from interferon-treated JLSV5 cells. In: Le petit Colloq. on Biol. and Med. Biol. of Oncogen. Viruses. Vol. 2, pp. 145-153, North-Holland, Amsterdam.

Vasf, A., Spencer, C., Gelehrter, T. D. and Lengyel, P. (1974) Selectivity of interferon action: Hormonal induction of tyrosine aminotransferase in rat hepatoma cells is much less sensitive to interferon than the replication of vesicular stomatitis virus or reovirus. Biochem. biophys. Acta 353(1): 115-120.

Vengris, V. E., Stallor, B. D. and Pitha, P. M. (1975) Interferon externalization by producing cell before induction of antiviral state. Virolgy 65: 410-421.

Vengris, V. E., Reynolds, F. H., Jr, Hellenberg, M. D. and Pitha, P. M. (1976) Interferon action: role of membrane glycolipides. Virolgy 72: 486-496.

Vieuchange, J. (1967a) Role d’un interferon dans le phenomene de l’interference entre le virus vaccinal et le virus rabique fixe. C. r. hebld. S&anc. Acad. Sci., Paris, ser. D, 264: 426-428.

Vieuchange, J. (1967b) Interference entre le virus vaccinal et le virus rabique role eventuel d’un interferon. Arch. ges. Virolog 32: 88-89.

Vignaux, F. and Gresser, I. (1977) Differential effects of interferon on the expression of H-2K, H-2D and la antigens on mouse lymphocytes. J. Immun. 118: 721-723.

Vilcek, J. (1962) Studies on an interferon from tick-borne encephalitis virus infected cells. IV. Comparison of IF with interferon from influenza virus-infected cells. Acta Virol. 6: 144-160.

Vilcek, J. (1964) Production of interferon by newborn and adult mice infected with Sindbis virus. Virolgy 22: 651-652.

Vilcek, J. (1969) Interferon. pp. 1-141. Springer—Verlag, Wien.

Vilcek, J., Havell, E. A. and Yamazaki, S. (1977) Antigenic, physiochemical and biologic characterization of human interferons. Ann. N.Y. Acad. Sci. 284: 703-710.

Vilcek, J. and Lowy, D. R. (1967) Interaction of interferon with chick embryo cells. Arch. Virusforsch. 21: 254-264.

Vilcek, J. and Ng M. H. (1967) Potentiation of the action of interferon by extracts of Escherichia coli. Virolgy 31: 552-555.

Vilcek, J. and Rada, B. (1962) Studies on an interferon from tick-borne encephalitis virus infected cells. III. Antiviral action of IF. Acta Virol. 6: 9-15.
Vilcek, J. and Stancek, D. (1963) Formation and properties of interferon in the brain of tick-borne encephalitis virus-infected mice. Acta Virol. 7: 331-345.

Virelizier, J. L., Virelizier, A. M. and Allison, A. C. (1976) Role of circulating interferon in modifications of immune responsiveness by mouse hepatitis virus (MHV-3). J. Immun. 117: 748-764.

Waddell, D. J., Wilber, J. R. and Mergian, T. C. (1968) Interferon production in human mumps infection. Proc. Soc. exp. Biol. Med. 127: 320-326.

Wagner, R. R. (1960) Viral interference. Some considerations of basic mechanisms and their potential relationship to host resistance. Bact. Rev. 24: 151-166.

Wagner, R. R. (1961) Biological studies of interferon. I. Suppression of cellular infection with eastern equine encephalomyelitis virus. Virology 13: 323-337.

Wagner, R. R. (1963) Biological studies of interferon. II. Temporal relationship of virus and interferon production by cells infected with eastern equine encephalomyelitis and influenza viruses. Virology 19: 215-224.

Weber, J. M. and Stewart, R. B. (1975) Cyclic AMP potentiation of interferon antiviral activity and effect of interferon on viral replicative AMP levels. J. gen. Virol. 28: 363-372.

Weinstein, M. J., Weitz, J. A. and Came, P. E. (1970) Induction of resistance to bacterial infections of mice with polyI·polyC. Nature, Lond. 226: 170-171.

Wissensbach, J., Dirheimer, G., Falcoff, R., Sanceau, J. and Falcoff, E. (1977) Yeast tRNA<sup>U-A-G</sup> (anticodon U-A-G) translates all six leucine codons in extracts from interferon-treated cells. FEBS Lett. 74: 71-76.

Wissensbacher, M., Schachter, N., Galin, M. A. and Baron, S. (1970) Intraocular production of interferon. Arch. Ophthal. 84: 495-509.

Werene, J. and Rousseau, G. (1976a) Studies of the leukemia L1210 cells in culture: a comparison of clones differing in sensitivity to interferon. Arch. Int. Physiol. Biochem. 84: 683-684.

Werene, J. and Rousseau, G. (1976b) Double-stranded RNA-dependent protein phosphorylation in interferon-treated cells. Arch. Int. Physiol. Biochem. 84: 1123-1124.

Weber, G. H., Hemmings, M., Caten, H. A. and Hashmi, G. (1976) Effect of ammonium S-tungsts-2-antimoniate on EMC and VSV infections in mice. J. gen. Virol. 31: 59-64.

Wheelock, E. F. and Larke, R. P. B. (1968) Efficacy of interferon in the treatment of mice with established murine leukemia. Proc. Soc. exp. Biol. Med. 127: 230-236.

Wiebe, M. E. and Jorlik, W. K. (1975) The mechanism of inhibition of reovirus replication by interferon. Virology 66: 229-234.

Wietzerbin, J., Stephans, S., Falcoff, R. and Falcoff, E. (1977) Some properties of interferons induced by stimulants of T and B lymphocytes. Tex. Rep. Biol. Med. 35: 205-211.

Wildstein, A., Stevens, L. E., Appelbaum, H., McCabe, R. E., Hashmi, G. A. and Fitzpatrick, H. (1976a) Prolonged survival of canine renal allografts by Tilorone. Transplantation 22: 205-207.

Wildstein, A., Stevens, L. E. and Hashmi, G. (1976b) Skin and heart allograft prolongation in Tilorone treated rats. Transplantation 21: 129-134.

Wiramowska-Stewart, M. and Stewart II, W. E. (1977) The role of human chromosome 21 in sensitivity to interferons. J. gen. Virol. 7: 629-634.

Wong, P. K. Y., Yuen, P. H., Macleod, R., Chang, E. H., Myers, M. W. and Friedman, R. M. (1977) The effect of interferon on de novo infection by Moloney murine leukemia virus. Cell. 10: 245-263.

Worthington, M. and Baron, S. (1971) Late treatment with an interferon stimulator in an arbovirus encephalitis in mice. Proc. Soc. exp. Biol. Med. 136: 323-327.

Worthington, M. and Hasenclever, H. F. (1972) Effect of an interferon stimulator, polyinosinic acid on experimental fungus infections. Infect. Immun. 5: 199-211.

Worthington, M., Levy, H. and Rice, J. (1973) Late therapy of arbovirus encephalitis in mice with interferon and interferon stimulators. Proc. Soc. exp. Biol. Med. 143: 638-643.

Wu, A. M., Schultz, A. and Gallo, R. C. (1976) Synthesis of type C virus particles from murine-cultured cells induced by iododeoxyuridine. Virology 74: 71-76.

Yabrova, A. V. (1966) The enhancement of the stability of cells to the dipheria toxin under the influence of a latent viral infection. Cytology 8: 767-769.

Yabrova, A. A. (1967) A nonspecific stability of cells to bacterial toxins. The idea of cell stress. Citologia, Leningrad 9: 692-706.

Yabrova, A. A. (1975) Influence of interferon on the disturbance of protein synthesis. Proc. Symp. Clin. Use of Interferon, Zagreb, Yugoslavia.

Yabrova, A. A. (1976) Prevention of the disturbance of protein synthesis is a possible mechanism of interferon protective activity. Life Sci. 18: 1397-1404.

Yabrova, A. A., Yekimova, V. A. and Zeiteleenok, N. A. (1971) The effect of dibazole on interferon activity. Leningrad Nauka 14: 62-74.

Yakobson, E., Prives, C., Hartman, J. R., Winocour, E. and Revel, M. (1977a) Inhibition of viral protein synthesis in monkey cells treated with interferon late in Simian virus 40 lytic cycle. Cell 12: 73-82.

Yakobson, E., Revel, M. and Winocour, E. (1977b) Inhibition of Simian virus 40 replication by interferon treatment late in the lytic cycle. Virology 80: 225-228.

Yamamoto, K., Yamaguchi, N. and Oda, K. (1975) Mechanism of interferon-induced inhibition of early Simian virus 40 (SV40) functions. Virology 68: 58-69.
prostaglandin E. production in cultured human fibroblasts by poly I:C and human interferon. Nature, Lond. 267: 457.

YOKOTA, Y., KISHIDA, T., ESAKI, K. and KAWAMATA, J. (1976) Antitumor effects of interferon on transplanted tumors in congenitally athymic nude mice. Biken J. 19: 125–139.

YOUN, J. K. and BARKSI, G. (1966) Interference between LCM and Rauscher leukemia in mice. J. natn. Cancer Inst. 37: 381–388.

YOUN, J. K., BARKSI, G. and HUPPERT, J. (1968) Inhibition of viral leukemogenesis in mice by treatment with synthetic polynucleotides. C. r. hebd. Séanc. Acad. Sci., ser. D 267: 816–829.

YOUNG, C. H. S., PRINGLE, C. R. and FOLLETT, E. A. C. (1975) Effect of interferon in enucleated cells. J. Virol. 15: 428–441.

YOUNGNER, J. S. and HALLUM, J. V. (1969) Inhibition of induction of interferon synthesis in L cells pretreated with interferon. Virology 37: 473–475.

YOUNGNER, J. S., THACORE, H. R. and KELLY, M. E. (1972) Sensitivity of ribonucleic acid and deoxyribonucleic acid viruses to different species of interferon in cell cultures. J. Virol. 10: 171–178.

ZEMLA, J. and SEHRAMEK, S. (1962) The action of interferon under anaerobic conditions. Virology 16: 204–205.

ZILBERSTEIN, A., DUDOCK, B., BERISSI, H. and REVEL, M. (1976a) Control of messenger RNA translation by minor species of leucyl-transfer RNA in extracts from interferon-treated cells. J. molec. Biol. 108: 43–49.

ZILBERSTEIN, A., FEDERMAN, P., SHULMAN, L. and REVEL, M. (1976b) Specific phosphorylation in vitro of a protein associated with ribosomes of interferon-treated mouse L cells. FEBS Lett. 68: 119–127.