PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Immuno-Modulating Properties of Interferons [and Discussion]

E. De Maeyer, J. De Maeyer-Guignard, Dr. Gresser and Dr. Merigan

Phil. Trans. R. Soc. Lond. B 1982 **299**, 77-90
doi: 10.1098/rstb.1982.0108

Phil. Trans. R. Soc. Lond. B **299**, 77–90 (1982) [77]
Printed in Great Britain

Immuno-modulating properties of interferons

By E. De Maeyer and J. De Maeyer-Guignard
Institut Curie, Biologie, Centre Universitaire, Bâtiment 110, 91405, *Orsay Cedex, France*

Interferons (IFNs), by inducing the antiviral state in cells, are in the first line of defence against virus infections and are therefore part of the immune system as defined in its broadest sense. In addition, IFN-α and β can influence specific functions of lymphocytes and macrophages; moreover, a special class of interferons, called IFN-γ, are produced as a result of antigen recognition by T cells and by the interaction of mitogens and lymphocytes. Interferons influence B and T cell function *in vitro* and *in vivo*, as demonstrated by their effects on antibody formation, specific cytotoxicity of sensitized T cells, allograft survival, delayed-type hypersensitivity and graft–host reaction. They stimulate Natural Killer cell activity and induce functional and morphological changes in mononuclear phagocytes.

There are many examples of disturbed immune reactions as a result of viral infection, implicating interferons as contributing factors; this is a result of the lack of immunological specificity of interferon action. The extent to which interferons have a truly immunoregulatory role is a question currently receiving a great deal of attention, but is still very much unsettled.

1. Introduction

For many years after its discovery (Isaacs & Lindenmann 1957), interferon (IFN) was considered to be one substance with one activity. This view, however, was gradually abandoned as it became increasingly evident that there are many IFNs, exerting a wide variety of interesting biological activities. Of these, the different effects on the immune system are presently attracting much attention, and this review will focus on the interaction of the IFN system and the immune system.

The IFN system is revealing a previously unsuspected complexity, with many different molecular forms of IFN-α, β and probably also γ, with many different genes modulating production as well as action, and with a number of enzyme systems being activated by these IFNs. The complexity of the immune system exceeds by a few orders of magnitude that of the IFN system. It will therefore be a challenging task to probe at the molecular and cellular levels the mechanisms that govern the interactions of these two systems, but at least we are sure at the present time that there is such an interaction. The observations and experiments that have led to this conclusion will be summarized and evaluated in this review. We shall consider the effects of IFN-α and β (formerly type I) on the one hand, and the effects of IFN-γ (formerly type II) on the other.

2. The interaction of IFN-α and β with the immune system

The effects of IFN-α and β have perforce to be discussed together, since, in the murine system and to some extent also in the human, all experiments have been performed with mixtures of both. We shall return to this problem in §6.

(*a*) *Effects on antibody formation*

(i) *Antibody formation* in vitro

Mouse IFNs of different origins inhibit anti-SRBC antibody-forming cells in a Mishell–Dutton (1967) system. The application of a mosaic cell culture system, as developed by Gisler & Dukor (1972), suggests that the effect of interferon is due to an action on B cells and not on T cells or macrophages. In low-responder composite cultures, low doses of IFN stimulate an increase in the number of antibody-forming cells. In all cultures, late addition of IFN results in stimulation of the number of antibody-forming cells if the latter are counted on day 4, but not on day 5. It is therefore evident that the effects of IFN are complex and influenced by the time of addition to the system and the dose used (Gisler *et al.* 1974). Similar results have been obtained by Johnson *et al.* (1974) and Johnson & Baron (1976), who showed that mouse interferon inhibits primary antibody formation in a Mishell–Dutton system. Interferon has to be present at an early stage and the inhibitory effect is obtained regardless of whether a T-cell-dependent antigen or a thymus-independent antigen is used. These same authors also show that IFN is capable of blocking the antibody response of cells that have been primed *in vivo*, suggesting that IFN can block the response of memory lymphocytes. Additional evidence that IFN acts at an early stage in the development of the antibody response to SRBC *in vitro* has been obtained by Booth *et al.* (1976*a*); their results furthermore suggest that IFN inhibits the antibody response *in vitro* by affecting clonal initiation or activation, with little effect on dividing B cells in a developing clone (Booth *et al.* 1976*b*). Härfast *et al.* (1981) have confirmed that IFN acts directly on B cells, and that IFN treatment can either stimulate or inhibit pokeweed mitogen-induced IgG synthesis, depending on the timing of IFN administration to the lymphocyte cultures.

(ii) *Antibody formation* in vivo

Interferon treatment can influence antibody formation in the mouse. Braun & Levy (1972) reported that small amounts of interferon, when given at the time of immunization with SRBC, slightly stimulate the number of antibody-forming cells, whereas higher doses significantly inhibit the number of antibody-forming cells. Both IgM and IgG antibodies to SRBC are suppressed by IFN treatment, and IFN influences the number of memory cells that are generated as a result of the primary immunization with SRBC, if IFN is given before the antigen. Under these conditions, mice rechallenged with SRBC 34 days later show significant decrease of agglutinin titres (Brodeur & Merigan 1974, 1975).

Vignaux *et al.* (1980) were not able to confirm the inhibition by IFN of antibody formation *in vivo* in adult mice. Although they did find an inhibition in suckling mice 14 days old, in somewhat older mice only a delay in the kinetics of the primary antibody response was observed. Thus there is agreement that antibody formation *in vitro* can be influenced by IFN, but the effects of interferon on antibody formation *in vivo* are somewhat controversial.

(*b*) *Effects on cell-mediated immunity*

(i) *Allograft survival and delayed-type hypersensitivity*

Our own experiments on IFN and cell-mediated immunity were prompted by the possibility that circulating IFN contributes to the decreased intensity of cell-mediated immune reactions, sometimes observed during or immediately after viral infections. This was first reported by

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

von Pirquet (1908), who described a decreased skin reactivity to tuberculin in patients with measles, and has been repeatedly observed since and confirmed for many other virus infections in animals and in man (Notkins *et al.* 1970). Since circulating IFN production is a common denominator of many, if not all, virus infections, we decided to investigate the effect of IFN on cell-mediated immune reactions, especially since Lindahl-Magnusson *et al.* (1972) had shown that IFN inhibits the mixed lymphocyte reaction, a correlate *in vitro* of allograft rejection. We found that different IFN inducers as well as IFN preparations can prolong allograft survival across the major histocompatibility barrier in the mouse. The most pronounced prolongation is obtained when IFN is administered immediately after grafting, and giving IFN daily until the time of graft rejection does not enhance the effect (Mobraaten *et al.* 1973; De Maeyer *et al.* 1973, 1975*c*). Prolongation after IFN treatment of skin graft survival in mice has also been reported by Hirsch *et al.* (1974), and by Imanishi *et al.* (1977) in a rabbit corneal allograft system. However, the opposite effect, acceleration of graft rejection, has been seen as a result of IFN treatment. Skurkovich *et al.* (1973) reported that IFN treatment of mice, initiated immediately after dorsal skin grafting, significantly accelerates graft rejection. The only explanation that we can advance to account for these seemingly contradictory results is the very low dose of IFN used by Skurkovich *et al.*, since 1 ml of a preparation titring only 200–800 units was given intraperitoneally (i.p.) daily. In accord with this hypothetical explanation is the fact that at the lowest doses used by Imanishi *et al.*, i.e. 200 or 3000 units, acceleration rather than delay of graft rejection is observed in the rabbit corneal allograft system. In our own work, only relatively high doses of IFN, around 50 000 units per mouse per day, were used. It therefore seems likely that in an allograft transplantation system low doses of IFN may accelerate graft rejection, whereas higher doses may delay it. This is a good illustration of the two-sided effect of IFNs, which can either stimulate or depress immune reactions.

The observation that cell-mediated immune reactions *in vivo* can be influenced by IFN was then confirmed and extended in a study of delayed hypersensitivity (d.h.), also in the mouse. This system offers the advantage, at least with some antigens, of making it possible to examine separately the afferent and efferent pathways, so that effects on sensitization on the one hand and on expression of the sensitized state on the other can be readily distinguished. One hapten and two antigens served for sensitization: picryl chloride, with the ear-swelling assay as described by Asherson & Ptak (1968); sheep erythrocytes, with the footpad-swelling test (Lagrange *et al.* 1974); and Newcastle disease virus, also with a footpad-swelling test (De Maeyer 1976). Animals sensitized to any one of these antigens do not react upon challenge with the same antigen if they are treated with at least 10^5 units of IFN at some time during the 24 h preceding the challenge. When less than 10^5 units of IFN are given, some reaction occurs, but to a significantly smaller extent than in control animals. IFN can be administered systemically, and does not have to be injected into the organ that receives the challenge dose of antigen (De Maeyer *et al.* 1975*a*, *b*, *c*, 1976). In addition to this very pronounced effect on the efferent arc of the d.h. reaction, IFN also has an effect on the afferent arc. Experiments with either SRBC or Newcastle disease virus (NDV) as antigen have shown that IFN is capable of either completely inhibiting or decreasing sensitization, provided that it is administered before the antigen (De Maeyer-Guignard *et al.* 1975). The timing of IFN administration is indeed crucial, because when IFN is given at the same time as or after the antigen, there is either no effect, or enhancement. The enhancing effect was observed with SRBC or NDV as antigen (De Maeyer

& De Maeyer-Guignard 1980*a*, *b*), and Knop *et al.* (1981) have provided evidence that inhibition of suppressor cell activity is one of the mechanisms by which IFN stimulates delayed hypersensitivity.

(ii) *Macrophage function*

IFN induces functional and morphological changes in mononuclear phagocytes. Huang *et al.* (1971) reported an enhanced uptake of colloidal carbon by mouse peritoneal macrophages treated with IFN *in vitro* or *in vivo*, and Gresser *et al.* (1970) have reported that phagocytosis of tumour cells by macrophages in the peritoneal cavity is enhanced by IFN treatment of the tumour-bearing mice. Levy & Wheelock (1975) have extended this finding by showing that IFN can restore the activity of macrophages from mice with Friend leukaemia. In such leukaemic mice, macrophages have depressed phagocyte and migratory functions, and these can be restored to normal levels by treatment with IFN. Similarly, IFN treatment transforms resting mouse macrophages to activated cells and renders them cytotoxic for syngeneic lymphoblastic leukaemia cells (Schultz *et al.* 1977). Macrophages are instrumental in host defence against many viruses (Allison 1974), and activation by IFN could conceivably improve the virucidal efficacy of these cells. For the time being there is no direct evidence that this theoretical possibility is realized during infection *in vivo* and contributes to host defence. Lee & Epstein (1980) have recently shown that IFN treatment delays the maturation of human monocytes to macrophages. Monocytes from subjects with trisomy 21 demonstrate an enhanced sensitivity to this maturation-inhibiting effect of IFN, and the authors advance the hypothesis that in view of the important contribution of macrophages to many immune reactions, this increased sensitivity could contribute to the reduced ability of some trisomic individuals to ward off certain infections (Epstein *et al.* 1980).

(iii) *T-effector cell function as monitored* in vitro

IFN enhances the specific cytotoxicity of sensitized mouse lymphocytes against allogeneic tumour cells, and this effect occurs very rapidly, because a few hours of IFN treatment of the lymphocytes are sufficient (Lindahl *et al.* 1972). Similarly, addition of human leucocyte IFN or of human fibroblast IFN results in the enhanced cytotoxicity of human lymphocytes in a mixed lymphocyte reaction (Heron *et al.* 1976; Zarling *et al.* 1978).

The 'spontaneous' cytotoxicity of lymphocytes against allogeneic tumour cells can also be boosted by IFN. This will be discussed below in §v.

(iv) *Enhanced expression of cell-surface components*

Lindahl *et al.* (1973) reported that mouse IFN enhances the expression of alloantigens on L 1210 cells when the latter are cultivated for 24 h in the presence of IFN; antigen expression of L 1210 cells, a subline resistant to the antiviral effect, was not affected. Moreover, exposure to mouse IFN *in vitro* enhances the expression of histocompatibility antigens on thymocytes and on splenic lymphocytes. Treatment with IFN *in vivo* results in comparable effects: when about 10^5–10^6 units of interferon are administered i.p. four times at 12 h intervals, an increased expression of H-2 antigen on thymocytes and splenic lymphocytes, removed 24 or 48 h later, is observed (Lindahl *et al.* 1974, 1976). Lindahl *et al.* believe that IFN treatment of mice is accompanied by a general enhancement of the expression of H-2 antigens, but that this effect is most pronounced on those thymic cells that normally express H-2 antigens poorly. In all these

studies, surface antigens were measured by adsorption of the antisera to the cells and then measuring the remaining, non-adsorbed antibodies through their effect on ^{51}Cr-labelled target cells.

Human IFN has comparable effects and enhances expression of HLA antigens on human lymphoid cells. Both leucocyte and fibroblast IFN enhance the expression of HLA antigens as well as β2-microglobulin, as determined by quantitative immunofluorescence with the fluorescence-activated cell sorter and by the capacity to adsorb out cytotoxic antibodies; membrane immunoglobulins and specific T-cell antigens are not affected by the IFN treatment. The enhanced expression of histocompatibility antigens after IFN treatment is observed on B- and T-enriched lymphocyte populations and is dose dependent. Pretreatment of lymphocytes for 2 h seems to be as effective as having IFN present for longer periods. Of particular interest is the suggestion that the IFN-induced enhancement of antigen expression on cells is dependent on active protein synthesis, as measured by the effect of puromycin treatment (Heron *et al.* 1979).

In a recent study, Sonnenfeld *et al.* (1981) have confirmed that the administration of IFN to mice can enrich the number of high H-2D and H-2K antigen-bearing thymocytes, and they have furthermore extended these findings to IFN-γ. However, these authors feel that this effect of IFN treatment on surface antigen expression could well be due to a selective survival after IFN treatment of cells having already high antigen expression at their surface, rather than to an induction of antigen *de novo*. If this interpretation is correct, an additional, and interesting, question arises: why are high-antigen expressing cells more resistant to IFN treatment than low-antigen expressing cells?

The enhanced expression of Fc-γ receptors on murine (Fridman *et al.* 1980) and human (Iron *et al.* 1980) lymphocytes observed after interferon treatment offers another example of cell-surface changes induced by IFN and suggests one mechanism through which IFN could modulate lymphocyte activity.

(v) *Effects on spontaneous cytotoxicity of lymphocytes* (*Natural Killer cell activity*)

Natural Killer (NK) cells are currently receiving a great deal of attention since there are indications that they may be primarily responsible for natural cell-mediated immunity against tumours, and there is evidence that they are also instrumental in resistance to some virus infections (Kiessling *et al.* 1975; Welsh 1981).

In view of the antitumour effects of IFN, it is therefore of considerable interest that the spontaneous cytotoxicity of lymphocytes (NK cell activity) is enhanced by IFN treatment. In mice, intraperitoneal administration of IFN leads to a marked increase of NK cell activity. Elevated levels of NK activity are found within 3 h after inoculation of as few as 2×10^4 units of IFN per mouse. Likewise, if spleen cells are incubated with IFN *in vitro* for a short while, NK cell activity is increased (Gidlund *et al.* 1979; Djeu *et al.* 1979). Stimulation of NK cell activity has also been observed in man, both with IFN-α and β. Lymphocytes treated with human IFN-α display cytotoxic efficiency up to tenfold higher than that of untreated lymphocytes; these lymphocytes, when tested for various markers, show the characteristics of NK cells. The augmentation of human NK cell activity seems to take place not by enhancing the activity of 'mature' NK cells but rather by recruitment of 'pre-NK' cells (Trinchieri *et al.* 1978; Herberman *et al.* 1979; Heron *et al.* 1979; Saksela *et al.* 1979; Tragan & Dorey 1980; Moore & Potter 1980). An intriguing observation is the protection of target cells as a result of IFN

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

treatment: IFN-treated FS-1 fibroblasts become almost completely resistant to NK cell activity. Furthermore, the fibroblasts are specifically protected against NK cells and not against cytotoxic T-cell or antibody-dependent cytotoxicity. Normal thymocytes are similarly protected against NK cell activity by IFN treatment (Trinchieri *et al.* 1981; Hanson *et al.* 1980). In various tumour-cell lines this protective effect is generally less pronounced, thereby suggesting a selective mechanism through which NK cells could distinguish between normal and tumour cells (Trinchieri *et al.* 1978; Djeu *et al.* 1980). However, this question is presently controversial, and for example Moore *et al.* (1980) find that leukaemic cell lines are quite well protected against NK activity by pre-exposure to IFN. Different experimental protocols, different cell-lines and different IFN preparations are probably responsible for these apparently contradictory results.

NK cell activity is usually measured by the ^{51}Cr release assay, using a limited number of continuous cell lines as targets, and a legitimate question is the relevance of this assay to the phenomenon of natural resistance against tumour development *in vivo*. It is therefore important that Reid *et al.* (1981) have recently shown that the treatment of athymic nude mice with anti-IFN globulin favours the development of persistently virus-infected HeLa or BHK cell-tumours, which normally do not develop in such mice. Although these results do not provide definite proof that the increased tumour growth after the anti-IFN globulin treatment was due to the decreased NK cell activity, they are certainly quite suggestive that this was so. Since in this study allogeneic tumour cells were used, we are still left with the problem of the contribution of IFN to the destruction of autologous tumour cells through NK cell activation. As a matter of fact, some results obtained with IFN-stimulated lymphocytes from tumour-bearing patients are not in line with the hypothesis that the anti-tumour activity of IFN can be ascribed to the stimulation of NK cell activity. Indeed, although a boosting of NK-cell activity was observed as a result of the *in vitro* incubation of lymphocytes with IFN-α, this increased activity could only be demonstrated when allogeneic tumour cells were used as target cell, but not when autologous tumour cells were used (Vanky *et al.* 1980). The hypothesis has therefore been advanced that IFN activation of lymphocytes enhances lytic potential against allogeneic but not against autologous tumour cells (Vanky & Klein 1982).

3. The interaction of IFN-γ's with the immune system

(*a*) *IFN-γ's are lymphokines*

In contrast to IFN-α and β, the relevance of IFN-γ's to the immune system was obvious from the time of their discovery, since these IFNs are the products of mitogen- or antigen-stimulated lymphocytes. They differ from IFN-α and β by a number of physicochemical and antigenic properties, and the nucleotide sequence of the copy DNA (cDNA) of the first recombinant human IFN-γ shows no structural relation to human IFN-α or β (Gray *et al.* 1982). The cellular receptors for IFN-γ's seem to be different from those for IFN-α or β (Branca & Baglioni 1981). Like the other IFNs, this class of IFNs has a relatively species-specific broad-spectrum antiviral activity, and this is the main reason why they were called IFNs at the time of their discovery.

Mitogen-stimulated IFN production in spleen cell suspensions was first observed by Wheelock (1965), and in a series of well controlled experiments it was subsequently shown by Epstein *et al.* (1971) that lymphocytes and not macrophages are the source of mitogen-stimulated IFN and that a lymphocyte–macrophage collaboration is necessary for optimal production. The

first evidence that IFN-γ's are produced in lymphocyte cultures on an immune-specific basis was provided by the work of Green *et al.* (1969) who found that after addition of either PPD, diphtheria or pertussis toxoid to human lymphocyte suspensions, IFN only appeared in the supernatants of lymphocytes derived from individuals who had been immunized with the corresponding antigens; thus the production of IFN reflected the immune status of the lymphocyte donor. This was subsequently confirmed by Epstein *et al.* (1972) and Rasmussen *et al.* (1974) and extended to viral antigens. Sensitized human lymphocytes produce IFN *in vitro* if challenged with viral antigens (vaccinia or herpes simplex) in the presence of macrophages; the amount of IFN produced is a reflection of the immune status of the donor. T lymphocytes were demonstrated to be the source of the IFN (Valle *et al.* 1975*a*). The requirement for T cells was also found in a study of mitogen-induced IFN in the mouse, in which it was shown that θ-bearing spleen cells – but not thymocytes – are necessary, suggesting that IFN-γ may be produced by mature T cells (Stobo *et al.* 1974) and this has now been confirmed by the use of cloned T-cell lines (Marcucci *et al.* 1981; Morris *et al.* 1982).

In addition to antigens of bacterial and viral origin, cellular antigens have been shown to stimulate IFN-γ formation, and Virelizier *et al.* (1977*a*) observed production of IFN-γ in one-way-mixed lymphocyte cultures. The viral inhibitor previously observed by Gifford *et al.* (1971), also in mixed lymphocyte cultures of mice, was acid-stable, which makes its nature problematic, since all IFN-γ's described so far are acid-labile.

As in the mouse, IFN-γ is also produced in allogeneic mixed lymphocyte cultures of human lymphocytes (Manger *et al.* 1981). Virelizier & Guy-Grand (1980) have studied the development of memory for IFN-γ production in mice immunized with alloantigens and then tested in the MLR assay. Their results indicate that a population of long-lived, recirculating lymphocytes develops the ability to recognize specifically cell-membrane antigens and to respond with an early and intense secretion of IFN-γ. The importance of H-2 antigens as stimulators of IFN production in the MLR was confirmed in this study.

Studies on the production of IFN-γ's *in vivo* confirm the immune-specific basis for their production, and provide additional evidence that these IFNs are lymphokines (Stinebring & Absher 1970; Salvin *et al.* 1973).

(*b*) *IFN-γ's as immunoregulatory agents*

The fact that IFN-γ's are lymphokines, induced on an immunospecific basis, is indicative of the possible immunoregulatory role of these IFNs. It has not been possible so far to define this role precisely, because the critical reagents, pure IFN-γ and monoclonal antibodies against IFN-γ, have not been available. This situation is now changing rapidly, and, for example, human IFN-γ has recently been purified to electrophoretic homogeneity (Yip *et al.* 1982). In the meantime, the point to be stressed is that there exists as yet no formal proof that the effects on immune reactions described for IFN-γ preparations are due to the same molecules that induce the antiviral state; nevertheless, we believe that the currently available evidence indicates that many of the non-antiviral effects of IFN-γ preparations are due to the interferons present in these preparations.

IFN-γ preparations contain one or several substances capable of either enhancing or depressing antibody formation. In BCG-sensitized mice a correlation has been found between the subsequent induction of IFN-γ with old tuberculin and the suppression of antibody formation to SRBC; the greatest reduction is obtained when IFN-γ is induced 24 h before the SRBC are

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

administered. Furthermore, preparations containing IFN-γ also suppress antibody formation against SRBC *in vitro* and, in fact, are more active in doing so than a mixture of IFN-α and β if the antiviral titre is taken as the basis for comparison. Antibody formation *in vitro* is inhibited if IFN-γ is added to the system before or at the same time as the antigen; if, however, the IFN is added to the system 48 h after the antigen, a definite stimulation of the antibody response is obtained (Sonnenfeld *et al.* 1977*a*, *b*, 1978). Virelizier *et al.* (1977) comparing the immunosuppressive effect of IFN-γ with that of a mixture of IFN-α and β found IFN-γ to be about 20 times as active if the antiviral titre is taken as a reference.

In addition to modulation of antibody formation, other effects, possibly due to immunostimulation, have been described for IFN-γ preparations. Salvin *et al.* (1975) reported on the antitumour effect in mice of IFN-γ-containing sera obtained from BCG-sensitized mice rechallenged with old tuberculin. Similarly, Crane *et al.* (1978), using mouse serum derived from BCG-sensitized animals rechallenged with PPD, observed a significant antitumour effect in C57BL/6 mice inoculated with murine osteogenic sarcoma cells. In this respect, it is of interest that PHA-induced murine IFN-γ preparations are, like IFN-α and β capable of stimulating NK cell activity (Senik *et al.* 1980).

In view of their induction on an immune-specific basis and their immunomodulating effects, it is logical to assume that IFN-γ's play a role in immunoregulation. Brodeur *et al.* (1977), by separating murine spleen cells on histamine columns in different subpopulations, have obtained results suggesting that IFN-γ production is a function of suppressor T cells, and a similar hypothesis has been advanced by Johnson & Baron (1976). Kadish *et al.* (1980) have recently confirmed that both IFN-α and β production by Con A-stimulated human lymphocytes is the mechanism by which these cells suppress lymphocyte activation.

4. Dysfunction of the IFN system, and its possible relation to some immune diseases

(*a*) *Impaired production of IFN*

In view of the compelling evidence for multiple interactions between the IFN and the immune systems, the possibility that an 'abnormal' functioning of the IFN system could be either causally or consequentially related to certain immune diseases is receiving increasing attention. Moreover, decreased IFN production itself, without other concomitant immune deficiencies, may represent a clinical entity. Isaacs *et al.* (1981) have described a deficient production of IFN-α by peripheral lymphocytes in 4 children out of 30 with recurrent respiration infections. The authors believe that this is a specific, primary defect, responsible for the enhanced susceptibility to rhinopharyngeal infection of these individuals. Virelizier *et al.* (1978) have described a case of deficient IFN-γ production in a child with hypergammaglobulinaemia and immunoblastic proliferation. In this patient, humoral, cellular and non-specific immunities were found to be normal, with the exception of NK cell activity. Leucocytes from patients with multiple sclerosis have a decreased IFN-α response to measles and NDV, and it was therefore suggested that this reduced IFN-α production constitutes an immunoregulatory defect that may be one of the predisposing factors in the development of this disease (Neighbour & Bloom 1979; Neighbour *et al.* 1981). This point of view, however, has been challenged by Santoli *et al.* (1981), who examined a large series of patients with multiple sclerosis and found no evidence for im-

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

paired IFN production by peripheral blood lymphocytes of these individuals. Further work is clearly required to settle this important issue.

The recent report that intrathecal administration of IFN-β to five patients with multiple sclerosis caused a significant reduction in the exacerbation rates compared with these rates before treatment is potentially very important and supports the concept that IFN treatment may find its place in the therapy of dysimmune diseases (Jacobs *et al.* 1981). Obviously, in view of the small number of patients involved, the special characteristics of this disease, and its notoriously irregular and unpredictable evolution, this report needs confirmation and extension.

(*b*) *Autoimmune disease*

The production of IFN-γ on an immune-specific basis provided the rationale for Hooks *et al.* (1979) to investigate its possible presence in several autoimmune disorders. Interestingly, they did find that 'spontaneous' IFN-γ was present in the circulation of 71% of the patients examined with active disease and in 21% of those with inactive disease. Hooks *et al.* therefore advance the possibility that the continuous presence of the immune IFN may contribute to immunological aberrations in autoimmune diseases. It is, however, difficult for the time being to distinguish between cause and effect, and one cannot exclude that the presence of the IFN-γ is just another symptom of these diseases, without being causally related to their pathogenesis. However, it is conceivable that once IFN-γ is for some reason being produced continuously in the body, it may become an aggravating factor in the disease. This possibility receives experimental support from the observation that administration of mixtures of mouse IFN-α and IFN-β to NZB mice can accelerate the onset and increase the severity of the spontaneous autoimmune disease in these animals (Heremans *et al.* 1978; Adam *et al.* 1980), and more recently the same effect has been obtained with IFN-γ.

In contradistinction to IFN-γ, IFN-α production by peripheral leucocytes of patients with systemic lupus erythematosus appears to be impaired (Neighbour *et al.* 1981).

5. IFN-α and β: regulators or disturbers?

Not everything capable of influencing immunity by definition also participates in its regulation, and a substance can have immunomodulating effects without being a normal component of an immune reaction. From the preceding sections, it is clear that IFN-α and β exert a variety of immunomodulating activities, but however interesting and important these may be, this does not necessarily imply that IFN-α and β participate in the regulation *sensu stricto* of the immune response.

A distinguishing characteristic of these IFNs is that they can be produced by practically any cell of the organism. Unlike IFN-γ or lymphokines in general, production of IFN-α and β does not require previous contact of the host with the virus, nor is it a specialized function of a given class of cells. Most virus-infected cells are capable of producing IFN-α or IFN-β, or a mixture of both, and they can thus directly influence the activity of the immune system. This influence is not necessarily immunoregulatory and there are many instances of disturbance of immune reactions as a result of viral infection in which IFN-α and β can be implicated as a contributing factor. Viral infections are often associated with suppressed delayed-type hypersensitivity, and infection with certain viruses can delay allograft rejection; furthermore, depressed lymphocyte reactivity to antigens *in vitro* and abnormalities in antibody response can occur in patients or be

experimentally obtained in animals as a result of viral infection (see review by Woodruff & Woodruff 1975). Obviously, viruses that infect lymphocytes and macrophages disturb directly the function of these cells; however, the various effects of IFN on lymphocyte and macrophage function clearly indicate that viral infection of these cells is not a prerequisite for dysfunction, since IFN released by other cells can reach macrophages or lymphocytes. In addition, virus-infected lymphocytes or macrophages themselves release IFN, which then can act on other non-infected lymphoid cells.

The IFN-caused dysfunction of the immune system is a result of the lack of immunological specificity of IFN action and, as such, an epiphenomenon of many viral infections. The balance of this phenomenon on the whole is beneficial to the host, since the main effect of this generalized action of IFN is to render non-infected cells resistant to virus replication and hence to limit the severity of the disease.

The multiple effects of IFN-α and β on T-cell function imply that these IFNs can also influence cell-mediated immunity to viruses; these effects are important in view of the contribution of cell-mediated immunity to the recovery from many virus infections (Blanden 1974). In the mouse, several loci, designated as *If*-loci, influence levels of circulating IFN production (De Maeyer & De Maeyer-Guignard 1979). We have previously shown that IFN-α and IFN-β can exert a specific regulatory role on viral immunity through these loci. This was examined by studying the effect of endogenous IFN-α and β production on cell-mediated immunity by using the NDV-mouse model and comparing *If-1*^{h} and *If-1*^{l} animals. This study showed that delayed hypersensitivity to NDV is influenced by the levels of IFN produced, and the alleles at the *If-1* locus influence the extent of delayed hypersensitivity to NDV, in that *If-1*^{h} mice develop stronger delayed hypersensitivity than *If-1*^{l} mice. Furthermore, anti-IFN globulin given immediately after immunization decreases sensitization to NDV, whereas additional, exogenous, IFN given to low IFN producers stimulates sensitization to NDV (De Maeyer & De Maeyer-Guignard 1980). In view of the evidence for the contribution of cell-mediated immunity to the resistance to viral infection, the enhancement of effector T-cell function by IFN can generally be considered to be beneficial to the host. However, the action of sensitized T cells against virus-infected target cells sometimes has adverse effects, and may even be the cause of the main pathology of the viral infection, as with lymphocytic choriomeningitis virus (LCM) (Oldstone 1979), and in those circumstances, IFN, through stimulation of effector T cells, may be an aggravating factor. In this respect, it is relevant to mention the beneficial effect of treatment with anti-IFN serum on the course of LCM infection in mice (Gresser *et al.* 1978). This raises the interesting possibility that in some diseases anti-IFN globulin might constitute an appropriate therapeutic agent.

6. What is the function of each individual molecular IFN species?

As a result of the considerable progress in purification of human and murine IFNs, it is now possible to perform experiments with essentially pure IFN-α and β. Earlier experiments, done with relative impure IFN preparations, had been open to the criticism that the antiviral and immunomodulating effects could be due to different substances present in these preparations. This has stimulated us, and others, to devote a great deal of time and effort to the purification of murine IFNs. As soon as electrophoretically pure preparations were obtained (De Maeyer-Guignard *et al.* 1979), the effect of these preparations on various functions of T and B cells were

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

examined. As a result of this, we can now conclude that several previously described immunomodulating activities are indeed due to IFN (Gresser *et al.* 1980). In addition, NK cell activity has been stimulated with recombinant human IFN-α (Masucci *et al.* 1980). However, a new and important question has arisen, since, as a result of recombinant DNA technology, it has become evident that IFNs are a family of related proteins, and in man there are at least 11 different IFN-α genes (Brack *et al.* 1981). Moreover, all experiments in the mouse have so far been done with mixtures of IFN-α and IFN-β, since mouse cells, contrary to most human cells, make both IFN-α and IFN-β concomitantly. Experiments in cell cultures with the different recombinant human IFN-α's are revealing different target cell affinities and different relative antiviral activities for each IFN-α species (Stewart *et al.* 1980; Weck *et al.* 1981). This raises the possibility that each IFN-α and β species will have different effects on the different lymphocyte populations.

We are therefore convinced that for further work on immunomodulation by IFN in the murine, and obviously also the human, system, the different IFN-α and IFN-β species must be used separately. This poses no problem for experiments with human cells, since the different cloned IFN-α's are available, and we hope that this will soon be true for murine IFN as well. We have recently succeeded in isolating two partial cDNA clones of murine IFN-β; both are derived from IFN mRNA coding for a 34000 Da protein that is neutralized by an anti-mouse IFN-β serum. The nucleotide sequence of the cDNA inserted into the plasmids of both clones, however, is significantly different, suggesting the existence of two rather different murine IFN-β proteins (Skup *et al.* 1982). These first results suggest that murine IFN-β, like human IFN-α, may consist of a family of related, but structurally different, proteins, and the same is probably true for murine IFN-α, by analogy with the human system. The possibility that these various molecular forms will all show different target cell affinities when tested on different lymphocytic populations and their subsets is very real, and, when interpreting the results of the experiment on immunomodulation by IFN that have been published so far, it should be borne in mind that, at least in the murine system, mixtures of IFN-α and β, each one containing different molecular species, have been used. It therefore becomes imperative to isolate and characterize each individual murine IFN-α, β and γ molecular species, and examine its immunomodulating properties separately. There is no longer any doubt that IFN-α, β and γ do have immunomodulating properties; the next step will be to sort out the various effects of the individual molecular species on well defined subsets of the different lymphocyte classes. Only then will it become possible to draw a coherent picture of the interrelation between the interferon and the immune systems.

References

Adam, C., Thoua, Y., Ronco, P., Verroust, P., Tovey, M. & Morel-Maroger, L. 1980 *Clin. exp. Immunol.* **40**, 373–382.

Allison, A. C. 1974 *Prog. med. Virol.* **18**, 15.

Asherson, G. L. & Ptak, W. 1968 *Immunology* **15**, 405–416.

Blanden, R. V. 1974 *Transplant Rev.* **19**, 56.

Booth, R. J., Booth, J. M. & Marbrook, J. 1976*a* *Eur. J. Immun.* **6**, 769–772.

Booth, R. J., Rastrick, J. M., Bellamy, A. R. & Marbrook, J. 1976*b* *Aust. J. exp. Biol. med. Sci.* **54**, 11–25.

Brack, C., Nagata, S., Mantei, N. & Weissmann, C. 1981 *Gene* **15**, 379–394.

Branca, A. A. & Baglioni, C. 1981 *Nature, Lond.* **294**, 768–769.

Braun, W. & Levy, H. B. 1972 *Proc. Soc. exp. Biol. Med.* **141**, 769.

Brodeur, B. R. & Merigan, T. C. 1974 *J. Immunol.* **113**, 1319.

Brodeur, B. R. & Merigan, T. C. 1975 *J. Immunol.* **114**, 1323.

Brodeur, B. R., Weinstein, Y., Melmon, K. L. & Merigan, T. C. 1977 *Cell. Immunol.* **29**, 363.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Crane, J. L., Glasgow, L. A., Kern, E. R. & Youngner, J. S. 1978 *J. natn. Cancer Inst.* **61**, 871.
De Maeyer, E. 1976 *J. infect. Dis.* **133**, A63.
De Maeyer, E. & De Maeyer-Guignard, J. 1979 In *Interferon 1979* (ed. I. Gresser), vol. 1, pp. 75–100. London: Academic Press.
De Maeyer, E. & De Maeyer-Guignard, J. 1980*a* *Nature, Lond.* **284**, 173.
De Maeyer, E. & De Maeyer-Guignard, J. 1980*b* *Ann. N.Y. Acad. Sci.* **350**, 1.
De Maeyer, E., De Maeyer-Guignard, J. & Vandeputte, M. 1975 *Proc. natn. Acad. Sci. U.S.A.* **72**, 1753.
De Maeyer, E., Mobraaten, L. & De Maeyer-Guignard, J. 1973 *C.r. hebd. Séanc. Acad. Sci., Paris* D **227**, 2101–2103.
De Maeyer, E., Mobraaten, L. & De Maeyer-Guignard, J. 1975 In *Effects of interferon on cells, viruses and the immune system* (ed. A. Geraldes), pp. 367–379. London: Academic Press.
De Maeyer-Guignard, J., Cachard, A. & De Maeyer, E. 1975 *Science, Wash.* **190**, 574.
De Maeyer-Guignard, J., Tovey, M. G., Gresser, I. & De Maeyer, E. 1978 *Nature, Lond.* **271**, 622.
Djeu, J. Y., Heinbaugh, A., Holden, H. T. & Herberman, R. B. 1979 *J. Immunol.* **122**, 175.
Djeu, J. Y., Huang, K. Y. & Herberman, R. B. 1980 *J. exp. Med.* **151**, 781.
Engelman, E. G., Sonnenfeld, G., Dauphinee, M., Greenspan, J. S., Talal, N., McDevitt, H. O. & Merigan, T. C. 1981 *Arthritis Rheumatism* **24**, 1396–1402.
Epstein, L. B., Cline, M. J. & Merigan, T. C. 1971 *J. clin. Invest.* **50**, 744–753.
Epstein, L. B., Lee, S. H. S. & Epstein, C. J. 1980 *Cell. Immunol.* **50**, 191.
Epstein, L. B., Stevens, D. A. & Merigan, T. C. 1972 *Proc. natn. Acad. Sci. U.S.A.* **69**, 2632.
Farkas, T. V., Argov, S. A., Einhorn, S. A. & Klein, E. 1980 *J. exp. Med.* **151**, 1151–1165.
Fridman, W. H., Gresser, I., Bandu, M. T., Aguet, M. & Neauport-Sautes, C. 1980 *J. Immunol.* **124**, 3436.
Gidlund, M., Orn, A., Wigzell, H., Senik, A. & Gresser, I. 1978 *Nature, Lond.* **273**, 759.
Gifford, G. D., Tibor, A. & Peavy, D. L. 1971 *Infect. Immun.* **3**, 164–166.
Gisler, R. H. & Dukor, P. 1972 *Cell. Immunol.* **4**, 341.
Gisler, R. H., Lindahl, P. & Gresser, I. 1974 *J. Immunol.* **113**, 438–444.
Gray, P. W., Leung, D. W., Pennica, D., Yelverton, E., Najarian, R., Simonsen, C. C., Derynck, R., Sherwood, P. J., Wallace, D. M., Berger, S. L., Levinson, A. D. & Goedel, D. V. 1982 *Nature, Lond.* **295**, 503.
Green, J. A., Cooperband, S. R. & Kibrick, S. 1969 *Science, Wash.* **164**, 1415.
Gresser, I., Bourali, C., Chouroulinkov, I., Brouty-Boyé, D. & Thomas, M. 1970 *Ann. N.Y. Acad. Sci.* **173**, 694.
Gresser, I., De Maeyer-Guignard, J., Tovey, M. G. & De Maeyer, E. 1979 *Proc. natn. Acad. Sci. U.S.A.* **76**, 5308.
Gresser, I., Morel-Maroger, L., Verroust, P., Rivière, Y. & Guillon, J. C. 1978 *Proc. natn. Acad. Sci. U.S.A.* **75**, 3413.
Hansson, M., Kiessling, R., Andersson, B. & Welsh, R. M. 1980 *J. Immunol.* **125**, 2225.
Harfast, B., Huddlestone, J. R., Casali, P., Merigan, T. C. & Oldstone, M. B. A. 1981 *J. Immunol.* **127**, 2146.
Herberman, R. R., Ortaldo, J. R. & Bonnard, G. D. 1979 *Nature, Lond.* **277**, 221.
Heremans, H., Billiau, A., Colombatti, A., Hilgers, J. & DeSomer, P. 1978 *Infect. Immun.* **21**, 925–930.
Heron, I., Berg, K. & Cantell, K. 1976 *J. Immunol.* **117**, 1370.
Heron, I., Hokland, M. & Berg, K. 1978 *Proc. natn. Acad. Sci. U.S.A.* **75**, 6215.
Heron, I., Hokland, M., Moller-Larsen, A. & Berg, K. 1979 *Cell. Immunol.* **42**, 183.
Hirsch, M. S., Ellis, D. A., Black, P. H., Monaco, A. P. & Wood, M. L. 1974 *Transplantation* **17**, 234–236.
Hooks, J. J., Moutsopoulos, H. M., Geis, S. A., Stahl, N. I., Decker, J. L. & Notkins, A. L. 1979 *New Engl. J. Med.* **301**, 5–8.
Huang, K. Y., Donahoe, R. M., Gordon, F. B. & Dressler, H. R. 1971 *Infect. Immun.* **4**, 581–588.
Imanishi, J., Oishi, K., Kishida, T., Negoro, Y. & Izuka, M. 1977 *Archs Virol.* **53**, 157–161.
Isaacs, D., Clarke, J. R., Tyrrell, D. A. J., Webster, A. D. B. & Valman, H. B. 1981 *Lancet* ii, 950.
Isaacs, A. & Lindenmann, J. 1957 *Proc. R. Soc. Lond.* B **147**, 258.
Itoh, K., Inoue, M., Kataoka, S. & Kumagai, K. 1980 *J. Immunol.* **124**, 2589–2595.
Jacobs, L., O'Malley, J., Freeman, A. & Ekes, R. 1981 *Science, Wash.* **214**, 1026–1028.
Johnson, H. M. & Baron, S. 1976*a* *Cell. Immunol.* **25**, 106–115.
Johnson, H. M. & Baron, S. 1976*b* *J. med. Sci.* **4**, 50.
Johnson, H. M., Smith, B. G. & Baron, S. 1974 *IRCS* **2**, 1616.
Kadish, A. S., Tansey, F. A., Yu, G. S. M., Doyle, A. T. & Biloom, B. R. 1980 *J. exp. Med.* **151**, 637.
Kiessling, R., Hochman, P. S., Haller, O., Shearer, G. M., Wigzell, H. & Cudkowicz, G. 1977 *Eur. J. Immunol.* **7**, 655.
Knop, J., Stremmer, R., Neumann, C., De Maeyer, E. & Macher, E. 1982 *Nature, Lond.* **296**, 775–776.
Lagrange, P. H., Mackannes, G. B. & Miller, T. E. 1974 *J. exp. Med.* **139**, 528–542.
Lee, S. H. S. & Epstein, L. B. 1980 *Cell. Immunol.* **50**, 177.
Levy, M. H. & Wheelock, E. F. 1975 *J. Immunol.* **114**, 962.
Lindahl, P., Gresser, I., Leary, P. & Tovey, M. 1976 *Proc. natn. Acad. Sci. U.S.A.* **73**, 1284.
Lindahl, P., Leary, P. & Gresser, I. 1972 *Proc. natn. Acad. Sci. U.S.A.* **69**, 721–725.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Lindahl, P., Leary, P. & Gresser, I. 1973 *Proc. natn. Acad. Sci. U.S.A.* **70**, 2785.
Lindahl, P., Leary, P. & Gresser, I. 1974 *Eur. J. Immunol.* **4**, 779.
Lindahl-Magnusson, P., Leary, P. & Gresser, I. 1972 *Nature, new Biol.* **237**, 120–121.
Manger, B., Kalden, J. R., Zawatzky, R. & Kirchner, H. 1981 *Transplantation* **32**, 149–152.
Marcucci, F., Waller, M., Kirchner, H. & Krammer, P. 1981 *Nature, Lond.* **291**, 79–81.
Masucci, M. G., Szigeti, R., Klein, E., Klein, G., Gruest, J., Montagnier, L., Taira, H., Hall, A., Nagata, S. & Weissmann, C. 1980 *Science, Wash.* **209**, 1431–1435.
Mishell, R. I. & Dutton, R. W. 1967 *J. exp. Med.* **126**, 423.
Mobraaten, L., De Maeyer, E. & De Maeyer-Guignard, J. 1973 *Transplantation* **16**, 415–420.
Moore, M. & Potter, M. R. 1980 *Br. J. Cancer* **41**, 378.
Moore, M., White, W. J. & Potter, M. R. 1980 *Int. J. Cancer* **25**, 565.
Morris, A. G., Lin, Y. L. & Askonas, B. A. 1982 *Nature, Lond.* **295**, 150.
Neighbour, P. A., Miller, A. E. & Bloom, B. R. 1981 *Neurology* **31**, 561–566.
Neighbour, P. A. & Bloom, B. R. 1979 *Proc. natn. Acad. Sci. U.S.A.* **76**, 476–480.
Neighbour, P. A. & Grayzel, A. I. 1981 *Clin. exp. Immunol.* **45**, 576–582.
Notkins, A. L., Mergenhagen, S. E. & Howard, R. J. 1970 *A. Rev. Microbiol.* **24**, 525.
Oldstone, M. B. 1979 In *Comprehensive virology*, vol. 15, pp. 1–36. New York: Plenum Press.
Rasmussen, L. E., Jordan, G. W., Stevens, D. A. & Merigan, T. C. 1974 *J. Immunol.* **112**, 728.
Reid, L. M., Minato, N., Gresser, I., Holland, J., Kadish, A. & Bloom, B. R. 1981 *Proc. natn. Acad. Sci. U.S.A.* **78**, 1171–1175.
Saksela, E., Timonen, T. & Cantell, K. 1979 *Scand. J. Immunol.* **10**, 257.
Salvin, S. B., Youngner, J. S. & Lederer, W. H. 1973 *Infect. Immun.* **7**, 68.
Salvin, S. B., Youngner, J. S., Nishio, J. & Neta, R. 1975 *J. natn. Cancer Inst.* **55**, 1233.
Santoli, D., Hall, W., Kastrukoff, L., Lisak, R. P., Perussia, B., Trinchieri, G. & Koprowski, H. 1981 *J. Immunol.* **126**, 1274–1278.
Schultz, R. M., Papamatheakis, J. D. & Chirigos, M. A. 1977 *Science, Wash.* **197**, 674.
Senik, A., Stefanos, S., Kolb, J. P., Lucero, M. & Falcoff, E. 1980 *Ann. Immunol.* C **131**, 349–361.
Skup, D., Windass, J. D., Sor, F., George, H., Williams, B. R. G., Fukuhara, H., De Maeyer-Guignard, J. & De Maeyer, E. 1982 *Nucl. Acids Res.* **10**, 3069–3084.
Skurkovich, S. V., Klinova, E. G., Aleksandrovskaya, I. M., Levina, N. V., Arkhipova, N. A. & Bulicheva, T. I. 1973 *Immunology* **25**, 317.
Sonnenfeld, G., Mandel, A. D. & Merigan, T. C. 1977 *Cell. Immunol.* **34**, 193.
Sonnenfeld, G., Mandel, A. D. & Merigan, T. C. 1978 *Cell. Immunol.* **40**, 285.
Sonnenfeld, G., Meruelo, D., McDevitt, H. O. & Merigan, T. C. 1981 *Cell. Immunol.* **57**, 427–439.
Sonnenfeld, G., Salvin, S. B. & Youngner, J. S. 1977 *Infect. Immun.* **18**, 283.
Stinebring, W. R. & Absher, P. M. 1970 *Ann. N.Y. Acad. Sci.* **173**, 714.
Stobo, J., Green, I., Jackson, L. & Baron, S. 1974 *J. Immunol.* **112**, 1589–1593.
Streuli, M., Hall, A., Boll, W., Stewart, W. E. II, Nagata, S. & Weissmann, C. 1981 *Proc. natn. Acad. Sci. U.S.A.* **78**, 2848–2852.
Targan, S. & Dorey, F. 1980 *J. Immunol.* **124**, 2157–2161.
Trinchieri, G., Granato, D. & Perussia, B. 1981 *J. Immunol.* **126**, 335.
Trinchieri, G., Santoli, D., Dee, R. R. & Knowles, B. B. 1978 *J. exp. Med.* **147**, 1299.
Valle, M. J., Bodrove, A. M., Strober, S. & Merigan, T. C. 1975 *J. Immunol.* **114**, 435.
Vanky, F. & Klein, E. 1982 *Immunogenetics* **15**, 31–40.
Vignaux, F., Gresser, I. & Fridman, W. H. 1980 *Eur. J. Immunol.* **10**, 767–772.
Virelizier, J. L., Allison, A. C. & De Maeyer, E. 1977 *Infect. Immun.* **17**, 282–285.
Virelizier, J. L., Chan, E. L. & Allison, A. C. 1977 *Clin. exp. Immunol.* **30**, 299.
Virelizier, J. L. & Guy-Grand, D. 1980 *Eur. J. Immunol.* **10**, 375.
Virelizier, J. L., Lenoir, G. & Griscelli, C. 1978 *Lancet* ii, 231–234.
Von Pirquet, C. 1908 *Dt. med. Wschr.* **34**, 1297.
Weck, P. K., Apperson, S., May, L. & Stebbing, N. 1981 *J. gen. Virol.* **57**, 233–237.
Welsh, R. M. 1981 *Antiviral Res.* **1**, 5–12.
Wheelock, E. F. 1965 *Science, Wash.* **149**, 310.
Woodruff, J. F. & Woodruff, J. J. 1975 In *Viral immunology and immunopathology* (ed. A. L. Notkins), pp. 393–418. New York: Academic Press.
Yip, Y. K., Barrowclough, B. S., Urban, C. & Vilček, J. 1982 *Science, Wash.* **215**, 411–413.
Zarling, J. M., Sosman, J., Eskra, L., Borden, E. C., Horoszewicz, J. S. & Carter, W. A. 1978 *J. Immunol.* **121**, 2002.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Discussion

Dr Gresser expressed the opinion that the effects of interferons on the immune systems, though varied, are so small compared with the antiviral effects that in many situations the antiviral effects must be far more important than any immunomodulating effects. Dr Merigan thought that if immunoregulatory effects occur they are likely to be local.

Tests so far have shown no correlation between clinical responses to tumours and effects on the patient's NK cell activity in myelomas (Strander) or lymphomas (Merigan).

In discussions on tumour regression it was pointed out that tumours may regress owing to loss of fluid or host cell infiltration, but in some instances regression of tumour cells had been shown by biopsy. Animal models with the use of transplantable tumours do not show regression on treatment, but these are not comparable with man in whom the tumour is partly controlled, and the interferon has only to 'tip the balance'. Not much work is done on more relevant mouse models, such as spontaneous mammary carcinoma, which are not so easy to get results with.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES