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Interferon and recovery from virus infections

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The phenomenon of viral interference is not a new one and an example of it was mentioned by *Jenner* in 1804. He found that when trying to vaccinate people with cowpox virus "takes" did not occur in people infected with what he described as herpes. This may well be an example of virus interference. In the laboratory the phenomenon has been studied for over 25 years. A Swiss microbiologist, Dr. *Jean Lindenmann*, was working with me on the subject of virus interference in 1956/57 when we found that a by-product of the interference reaction, to which we gave the name interferon, had antiviral activity (*Isaacs* and *Lindenmann*, 1957). This substance was first investigated from the point of view of the viral interference phenomenon and our evidence suggested that it played an important role in virus interference. Indeed, some examples of virus interference could be accounted for by interferon alone. However, it was soon realised that the appearance of interferon in virus-infected cells had wider implications. In the first place there was the possibility that interferon could be developed into an antiviral agent for use in man. Secondly, interferon offered a possibility of a clue to the mechanism of recovery from virus infection. This possibility was suggested by the finding that interferon was produced by almost all the animal cells that we have tested, as a general reaction to virus infection both in vitro and in vivo.

Many substances and mechanisms have been implicated in recovery from virus infections. Perhaps the best known is specific antibody but recently arguments have been advanced to indicate that antibody, which clearly plays a most important role in our ability to resist virus infection, (i.e. immunity in the classical sense) may not play such a significant role in our ability to recover from virus infection. Three arguments which support this conclusion are as follows:

1. Antibody may appear very late on the scene at a time when recovery processes have already set in. This point is discussed by *Lwoff* and *Lwoff* (1960).

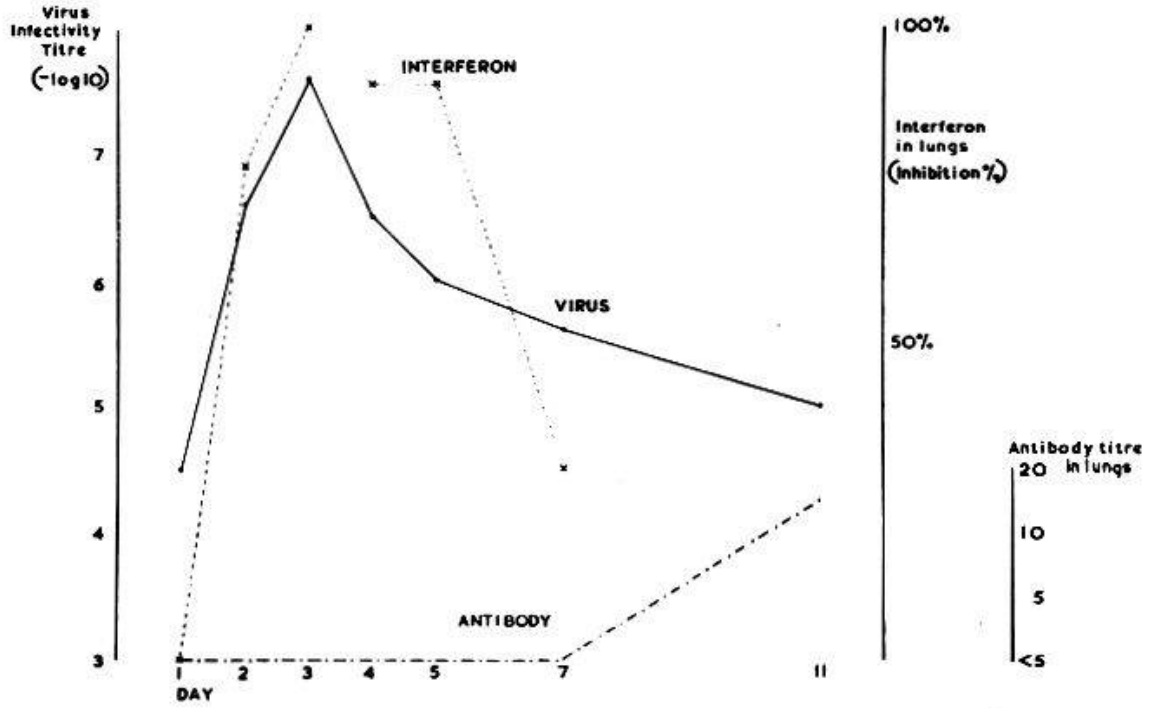

Fig. 1. Appearance of virus, antibody and interferon in the lungs of mice after infection with influenza virus.

2. Patients with hypogammaglobulinaemia generally recover from virus infections in the same way as normal individuals do, but without producing more than traces of antiviral antibody.

3. *Friedmann* and *Baron* (1961) have recently shown experimentally that guinea pigs treated with large doses of X-rays, which greatly inhibited the production of antibody, nevertheless recovered normally from infection with vaccinia virus.

Thus, there is evidence that antibody may not play such an important role in recovery from virus infections as had been thought earlier and this makes us search for alternative mechanisms which could be important. Recently evidence has come to light from 6 different experimental systems suggesting that interferon may play an important role in recovery from virus infections. These results will now be discussed:

1. A study was made of infection of mice with influenza virus (*Isaacs* and *Hitchcock*, 1960). The daily content of virus, interferon and antibody in the lungs of infected mice was measured and the results are shown in figure 1. Shortly after infection there was a sharp rise in the content of virus in the lungs and this began to decrease by the third day. The interferon content of the lungs closely followed the content of virus. However, antibody appeared late on the scene and no antibody was detectable at a time when the virus present in the lungs was decreasing. The decrease in virus content was not due to exhaustion of the supply

of available cells and must therefore have been due to recovery mechanisms which set in before antibody was demonstrable. This suggests that interferon, unlike antibody, was present at the right place and at the right time to influence recovery from virus infection.

Recently *Hitchcock* and *Porterfield* (1961) have studied infection of the mouse brain with an arbor virus. The results which they have found in regard to the appearance of virus, interferon and antibody closely parallel those found for infection of the mouse lung.

2. In the course of studying the mechanism of action of interferon, some evidence arose to suggest that interferon might act by inhibiting an oxidative process needed to supply energy for viral synthesis. In order to test this hypothesis experiments were carried out on embryonic cells. These have a high anaerobic glycolysis, and if this theory were correct, one would expect that they should be resistant to the antiviral action of interferon. We therefore tested the sensitivity to interferon of chick embryonic tissues of different ages and found that the tissues of very young embryos were, in fact, very resistant to the antiviral action of interferon (*Isaacs* and *Baron*, 1960). If interferon were important in recovery from virus infection one should therefore expect that the ability to recover from infection with different viruses might be related to the age at which the embryos developed sensitivity to interferon. We therefore infected chick embryos of different ages with 4 different viruses, two strains of influenza virus, an arbor virus and vaccinia virus, and observed the mortality daily during a period of observation of 7 days. It was found that the younger embryos showed a much higher mortality than the older embryos. This finding has been described previously in the laboratory (*Beveridge* and *Burnet*, 1946) but what was most interesting was to observe that there was a very close correlation between the age at which embryos developed sensitivity to interferon and the age at which they showed increased resistance to the antiviral action of interferon (*Baron* and *Isaacs*, 1961 a). This correlation derives added significance from the fact that the chick embryo is unable to make antibody and shows no delayed hypersensitivity reaction to infection.

The critical period at which the change occurred was the first third of the embryonic development period. This seems to be a most interesting time in embryonic development and it may be more than a coincidence that women who get infected with rubella during the first three months of pregnancy frequently show embryos with congenital malformations of different kinds (*Gregg*, 1941; *Swan*, 1949). The implication is that during the first three months of embryonic development the foetus is unable to protect itself owing to the fact that its cells are insensitive to the anti-

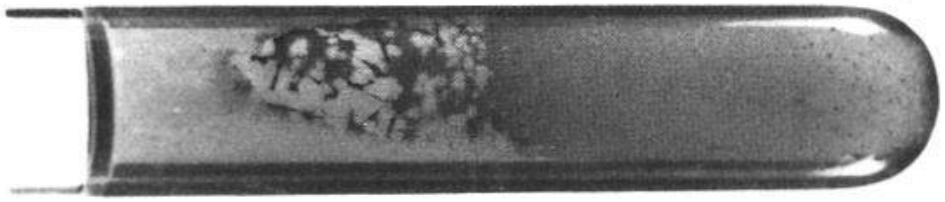

Fig. 2. Plaque formation by Newcastle disease virus in test-tube cultures of chick embryo fibroblasts with an agar overlay.

viral action of interferon. This is very difficult to test experimentally, but the preliminary indications that we have could support this viewpoint.

3. It has been known for some years that viruses depend on oxidative processes to supply the energy for viral synthesis. We have recently carried out experiments by a new technique which is illustrated in figure 2. In this technique cells are grown in a test tube, infected, and then overlaid with agar so that the oxygen tension varies greatly at different heights within the tube. It was found, as shown in figure 2, that virus plaque formation occurs only to a particular depth (*Baron*, *Porterfield* and *Isaacs*, 1961). What was most surprising was that different viruses were found to differ in their requirements for oxygen and this difference in oxygen requirement closely paralleled the differences among viruses in their sensitivity to interferon, i.e. viruses with a high oxygen requirement were very sensitive to interferon and viruses with a low requirement of oxygen were very resistant to the antiviral action of interferon. In addition it was found that the antiviral action of interferon could be inhibited by increasing the available oxygen supply (*Isaacs*, *Porterfield* and *Baron*, 1961). These findings, incidentally, support the idea that interferon acts by inhibiting an oxidative process.

If interferon played an important role in recovery from virus infections, one should expect, therefore, that increased oxygen tension might inhibit the processes of viral recovery. This was tested experimentally by infecting mice with influenza virus and keeping half of them in an atmosphere of 50% oxygen while the controls remained in air (*Sawicki*, *Baron* and *Isaacs*, 1961). It was found that the mice kept in oxygen died much earlier than the controls and showed a higher final mortality rate. These findings support the idea that interferon may be important in recovery from virus infections. From the practical point of view they also suggest that it may be wise to re-examine the treatment of infants suffering from viral pneumonias by putting them in oxygen tents.

4. Another substance which has been found to inhibit the action of interferon in vitro is cortisone, as was reported by *Kilbourne* et al.

(1961). This is a very interesting observation as it has been known for the last few years that patients receiving cortisone treatment for arthritis, for example, are often in serious danger from infection from otherwise mild viruses such as varicella. Indeed some fatal cases of varicella have been reported in patients under cortisone treatment (*McMath*, 1959). It is also known that cortisone in doses used in therapy in man does not inhibit antibody formation (*Havens* et al., 1951; *Larson* and *Tomlinson*, 1951). This evidence therefore parallels the evidence from the oxygen experiments and shows that treatment which reduces or abolishes the action of interferon has a detrimental effect on virus infections.

5. Recently *Enders* (1960) has found an inverse relationship in some viruses between virus virulence and ability to stimulate production of interferon. He has pointed out that avirulent viruses stimulate greater production of interferon than virulent strains. The mechanism of this most interesting effect remains to be determined but this would seem to be a very important association between virus virulence and interferon production.

6. Finally, Dr. *Baron* and I have very recently found evidence that in a number of patients who have died of influenza there was either no interferon or only traces of interferon present in their lungs. The lungs had been sent to us by other investigators who had shown them to contain influenza virus (*Baron* and *Isaacs*, 1961b). We are left with the question in mind whether some patients die of influenza when they cannot make interferon.

In summary, therefore, there is growing evidence of the importance of the interferon mechanism in the ability of man and animals to recover from virus infections. This point has theoretical importance and it may indeed have practical importance, as any attempts to use interferon therapeutically would be attempts to capitalise on a natural mechanism of recovery from virus infections. It may be useful, therefore, to think of the use of interferon in man as a way of increasing his normal supplies of a natural antiviral substance rather than as injecting him with a foreign substance.

Summary

There is growing evidence that antibody, which plays the dominant role in resistance to virus infections, may not play such an important role in the process of recovery from virus infections. In seeking for alternative factors which may be important in recovery from virus infections, we have studied the role of interferon. The following findings are reported in this paper:

1. Interferon is present at the right place and at the right time for influencing recovery from two different virus infections in mice.

2. In the chick embryo the age at which ability to resist the lethal action of four different viruses was closely related to the age at which the embryo developed sensitivity to interferon.

3. High oxygen concentration, which was found to inhibit the antiviral action of interferon in vitro, had a detrimental effect on influenza virus infection in mice.

4. Cortisone has been found to inhibit the production and action of interferon in vitro and also to have a detrimental effect on virus infections in man.

5. Production of interferon by some viruses was found to be inversely related to the virus virulence.

6. No interferon was found in the lungs of some patients who died of influenza.

These findings support the conclusion that interferon may play an important role in the process of recovery from virus infections.

Zusammenfassung

Es häufen sich die Anhaltspunkte dafür, daß die Antikörper, welche die Hauptrolle bei der Abwehr gegen Virusinfektionen spielen, nicht eine gleich wichtige Rolle in der Erholungsphase von Virusinfektionen spielen können. Auf der Suche nach anderen Faktoren, die für die Überwindung von Virusinfektionen wichtig sein könnten, haben wir die Rolle des Interferons untersucht. Die folgenden Befunde werden in diesem Vortrag mitgeteilt:

1. Interferon ist am rechten Ort und zur rechten Zeit vorhanden, um die Erholung von zwei verschiedenen Virusinfektionen bei Mäusen zu beeinflussen.

2. Beim Hühnerembryo steht das Alter, in dem dieses die tödliche Wirkung von vier verschiedenen Virusarten überwinden kann, in direkter Abhängigkeit vom Alter, in welchem der Embryo Empfindlichkeit für Interferon entwickelte.

3. Hohe Sauerstoffkonzentration, welche bekanntlich die antivirale Tätigkeit des Interferons *in vitro* hemmt, hatte eine nachteilige Wirkung auf die Influenzavirusinfektion bei der Maus.

4. Cortison hemmt die Bildung und die Wirkung des Interferons *in vitro* und hat zudem eine schädliche Wirkung auf Virusinfektionen beim Menschen.

5. Die Fähigkeit einiger Virusarten, die Interferonbildung zu stimulieren, steht in umgekehrtem Verhältnis zur Virulenz dieser Viren.

6. Kein Interferon wurde in den Lungen einiger Patienten gefunden, die an Influenza starben.

Diese Befunde stützen die Schlußfolgerung, daß das Interferon beim Heilungsvorgang von Virusinfektionen eine wichtige Rolle spielen muß.

Résumé

Il se confirme de plus en plus que les anticorps, qui jouent un rôle dominant dans la résistance aux infections à virus, ne jouent pas un rôle aussi important dans les processus de guérison après les infections virales. En recherchant quels autres facteurs ont de l'importance dans la guérison après infections virales, nous avons étudié le rôle de l'«interferon». C'est le résultat de nos recherches que nous exposons dans cet article:

1. L'interferon apparaît au bon moment et au bon endroit pour amener la guérison de deux infections à virus différentes chez la souris.

2. Dans l'embryon de poule, le moment, auquel cet embryon est capable de résister à l'effet léthal de quatre infections à virus différentes, est en relation étroite avec l'âge auquel cet embryon a développé une sensibilité à l'interferon.

3. Des concentrations élevées en oxygène, qui sont capables d'inhiber l'action antivirale de l'interferon *in vitro*, ont un effet défavorable sur une infection à virus de l'influenza chez la souris.

4. La cortisone a le pouvoir d'inhiber la production et l'effet de l'interferon *in vitro*, et l'on a trouvé qu'elle avait aussi un effet défavorable sur l'infection à virus chez l'homme.

5. La production d'interferon par certains virus est en relation inverse avec la virulence de ces infections virales.

6. L'on n'a pas pu mettre en évidence de l'interferon dans les poumons de certains malades, qui ont succombé à une influenza.

Ces quelques résultats permettent de conclure que l'interferon peut jouer un rôle important dans les phénomènes de guérison après infections virales.

Riassunto

E sempre più evidente che gli anticorpi che hanno un ruolo dominante nel fenomeno della resistenza alle infezioni virali non necessariamente hanno una parte egualmente importante nel processo di guarigione delle infezioni stesse. Nell'intento di trovare fattori, escludentisi a vicenda,

che possono avere importanza nella guarigione delle infezioni virali, abbiamo studiato l'azione dell'interferon. I risultati seguenti sono consegnati in questo lavoro:

1. L'interferon è presente nel luogo giusto ed al momento giusto per influenzare la guarigione di due differenti affezioni virali nel topo.

2. Nell'embrione di pollo esiste una stretta relazione tra l'età in cui esso è in grado di resistere all'azione letale di quattro differenti virus e l'età in cui detto embrione manifesta una sensibilità all'interferon.

3. Elevate concentrazioni di ossigeno, che, come fu constatato, inibiscono l'azione antivirale dell'interferon *in vitro*, hanno un'azione dannosa sull'infezione del topo da virus influenzale.

4. Il cortisone inibisce la produzione e l'azione dell'interferon *in vitro*, ed esercita inoltre un effetto nocivo sulle affezioni da virus dell'uomo.

5. La produzione di interferon in alcuni virus risultò essere inversamente proporzionale alla virulenza dei virus stessi.

6. Non fu possibile trovare interferon in polmoni di alcuni pazienti deceduti per influenza.

Questi risultati suffragano la conclusione che l'interferon può avere una parte importante nel processo di guarigione delle infezioni da virus.

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