SYMPOSIUM

LATENCY and MASKING in VIRAL and RICKETTSIAL INFECTIONS

Symposium

on

LATENCY and MASKING

in

VIRAL and RICKETTSIAL INFECTIONS

The Proceedings of a Conference held at the
University of Wisconsin Medical School,
September 4, 5 and 6, 1957

EDITORS

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Robert P. Hanson Alfred S. Evans

BURGESS PUBLISHING COMPANY
426 South Sixth Street • Minneapolis 15, Minnesota
1958

DEDICATION

To Dr. Francisco Duran-Reynals. His staunch advocation of the role of latent viral infection in the etiology of cancer, his painstaking and inspired research in support of this concept, and his lifetime devotion to a search for truth provide examples to which we all might aspire.

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PREFACE

This volume represents the proceedings of a Symposium on Latency and Masking in Viral and Rickettsial Infections held at the University of Wisconsin Medical School on September 4, 5 and 6, 1957. Increasing attention has been given to viral infections that result in long lasting inapparent infections, prolonged periods of quiescence, or persisting relationships between virus and host in which the presence of the virus is often difficult to demonstrate. Such infections have been found to be relatively frequent, and they have assumed increasingly greater importance as their significance in the maintenance of viruses in nature and in fundamental aspects of viral and cellular biology has gradually been recognized. The first aim of this conference was to discuss and exchange ideas and information on the mechanisms of these infections in animals, insects, plants and bacteria. A second purpose was to clarify terminology relevant to latent infection in these systems. Study of the phenomena of latent infection and exchange of information has been increasingly complicated in recent years by multiple meanings attached to such important terms as 'latent', 'masked', and 'virulent'. Modification of nomenclature to fit the current status of information in the field and some agreement as to the meaning and future application of terms was urgently needed.

The program of the conference was arranged to allow extensive discussion in addition to presentation of formal papers. The discussions were lively and vigorous. Their length, however, required that considerable editing be done to condense the records of discussions into reasonable space. This was done with the approval of the major participants who had an opportunity to inspect the condensed version to be certain that their statements and views were correctly expressed. On the other hand, the papers presented during the symposium have been left essentially in the form in which they were submitted by the authors for publication without any attempt to alter them to conform to a uniform style.

This symposium was made possible through generous financial support from the Rockefeller Foundation and from the Research Committee of the Graduate School of the University of Wisconsin from funds provided by the Wisconsin Alumni Research Foundation.

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Madison, Wisconsin
December, 1957

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POSSIBLE HOST-VIRUS AND CELL-VIRUS RELATIONSHIPS

C. H. Andrewes

The main object of this symposium is, I take it, to clarify our ideas about latency and masking. We cannot do this unless we know what we mean by the words we use: so we have to bring semantics into our discussions. I have been asked to attempt some preliminary definitions to assist our discussions. I am, however, not so much concerned with the actual words to be agreed upon as with agreement as to what are the things we want to name.

In the matter of words we are in this difficulty: many words, such as inapparent, latent, masked are used by different writers in different senses. Are we to scrap them, to avoid perpetuating confusion, or to aim to use them in the future in a more precise sense? Are we to invent a lot of new words with precise meanings or to have pity on the poor student who has words enough to learn already? We shall have to compromise, but I hope that as far as possible we shall make familiar words do. I have already had some talk with some of the virologists on the discussion panel and the words I shall be using can in part be taken as being an agreed compromise between the views of at least some of them.

The whole question of latency and masking in virus infections can be considered at several levels: at that of the whole host and its parasites, or at the levels of organ and virus, cell and virus, or even at a molecular level. We can, however, simplify things by considering two levels only: host-parasite and cell-virus.

The questions can also be considered with two mental attitudes: conservative and radical. One may wish to conserve well-known terms such as latency, using them in a more precise sense, but not pretending to a fundamental understanding which we do not in fact possess. Or, like a logical Frenchman, we may try to build everything upon a firm foundation in terms of the ultimate components of the systems under study, the genomes and the genes and the other bits and pieces of our viruses and our cells. The first attitude is that of the doctor or gardener, trying to describe what he sees: the other that of the academic virologist, probing as deeply as he can.

Each approach has its advantages and disadvantages. I suggest that we can best combine them by starting at the two ends and hoping, one day, to meet in the middle. Let us use a conservative approach to the problem at the host-parasite level, not venturing further than we can see. Let us at the cellular end be a little bold, constructing a logical system even though our factual information is rather incomplete. It may for example be of value to try to explain phenomena of animal virology in terms of activating a pro-virus, as one activates a prophage -- even though nobody has yet certainly demonstrated that a provirus actually exists.

I will begin at the host-parasite level with a few tentative definitions. All the phenomena we are interested in concern infection without evident disease, inapparent infection. Nicolle used the term to mean an acute disease running a regular course leading to recovery and immunity, but all below the level of clinical symptoms. I rather think we do need a separate word for this type of infection and I feel that "subclinical" exactly expresses what we mean in human disease; in its derivation, "clinical" implies a bed, and you don't put diseased caterpillars and potatoes to bed; but the original meaning has for all practical purposes been forgotten. I am inclined to use "inapparent" to include the whole field under discussion and "subclinical" for the inapparent infection of brief evolution in human and veterinary medicine. I doubt if insect and plant pathologists need a separate word, for I am not aware that short inapparent infections of brief evolution occur in their fields. We have of course to qualify the term inapparent. An infection

may be inapparent to a lay observer but obvious to a trained clinical observer; even to him it may be apparent or not according to whether he does or does not use a clinical thermometer, a haemocytometer, a laboratory test for viraemia or whether he examines serial sections with the aid of an electron microscope. We cannot have separate words for these degrees of inapparency. We shall have, but fortunately not very often, to use an appropriate qualifying phrase.

There are other inapparent infections besides that running a definite course: the infection is not clinically apparent during the incubation period of measles; and virus may persist in the stools in poliomyelities after the disease has passed. But of primary importance are latent infections. I use this term, and others do the same, to denote inapparent infections which are chronic, and in which a state of equilibrium between host and parasite has been established. New techniques are constantly revealing more and more such infections, first the use of serial blind passages in mice and other species, latterly the use of cultures of tissues of monkey and other species. We are probably wise to eschew the use of the term "latent virus" as such and to speak only of "latent virus infection." Otherwise we might well find ourselves using latent in a different sense according to whether it was qualifying infection or virus.

The term masked virus presents particular difficulties. It means, according to Shope (1950), virus not directly demonstrable as an infectious agent but revealed by indirect tests and circumstantial evidence. Clearly, all depends on what tests one uses and on the delicacy of the test. Should a virus be called "masked" merely because it is present in a very small quantity, or must it either be qualitatively modified or rendered undetectable for the time being by mixture with antibody or other inhibitor? Rowe, Huebner, et al. (1953) with human adenoids, and my colleagues Pereira and Kelly (1957) with rabbit spleen, have been able to make adenoviruses manifest by tissue culture techniques when more direct methods failed. Beard (1956) had adduced evidence that in the particular instance of rabbit papilloma the apparent masking can be explained purely on the basis that infectiveness is a relatively insensitive test for presence of virus: but that, with animal viruses, is probably an unusual state of affairs.

Masking has been used to mean so many things that I feel it wise not to try at this date to give it too precise a meaning. Just as "inapparent" may prove a useful word to cover all forms of infection which are not obvious, so a general term like "masking" could prove very useful to describe a virus which is detectable with difficulty or only by indirect means. This can even include virus present in very small amount and not detectable for that reason. After all a needle in a haystack is masked by an awful lot of hay. There will be so many instances of viruses which are hard to detect but where the cause of their elusiveness needs much further work. We can later propose words with precise definitions for particular kinds of masking when we have certainly established their nature.

Activation

Latent infections may be activated in the infected host by a variety of stimuli: in the case of herpes simplex in man by sunlight, fever and a host of other things: in swine influenza by chilling and injections of killed bacteria: in mice carrying the Bittner virus by hormonal factors: and so on.

The virus in a latently infected host may be made manifest by passage to a sensitive indicator host, as with lysogenic bacteria, Traub's latent lymphocytic choriomeningitis virus and the latent paracrinkle virus in King Edward potatoes. In other cases we may be able to reveal it by serial passage in hosts of the original sort or in tissue culture.

Examples of Types of Infection

The examples in Figure 1 indicate (1) whether the infection is apparent or inapparent according to whether the threshold (dotted line) is passed; (2) whether the inapparent infection persists, i.e. becomes truly latent; (3) whether it can be activated in the original host (shown by an arrow) and (4) whether the virus is masked (shown by shading).

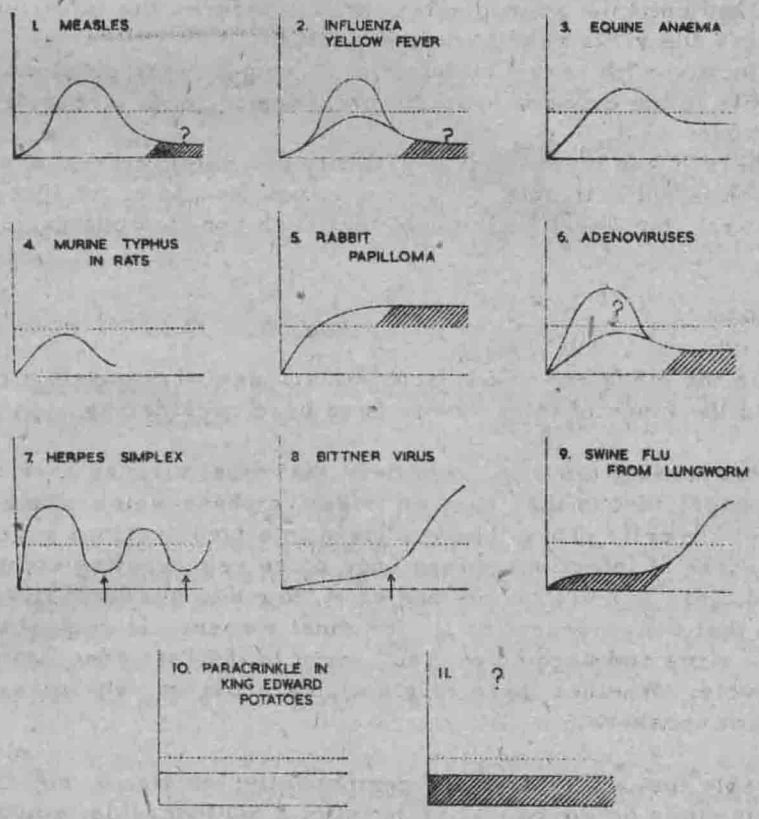

Figure 1

Examples of types of infection

Eleven examples are depicted.

1. Measles runs an acute, almost always clinical course. Views differ as to whether long-lasting immunity is associated with persistence of latent infection possibly with masked virus.
2. Yellow fever and influenza show a similar pattern except that infection is as often or more often subclinical than clinical.
3. In equine infectious anaemia and perhaps infectious hepatitis in man recovery from clinical disease is associated with latent infection in which fully active virus persists in the blood, sometimes in considerable amounts.
4. Some infections are, in a particular species, always subclinical. Examples are equine encephalitis in some species of birds, and murine typhus in rats.
5. In rabbit papilloma, the course of the infection is chronic and chronicity is associated with masking of the virus, using the term in its broadest sense.
6. Infection of man with adenoviruses types I and II may be clinical or subclinical -- we are not sure which; type V infection in rabbits is certainly subclinical, there seems to be a long latent infection with virus present in small quantity and only detected by the sensitive technique of tissue culture.

7. The periodical activation of latent herpes simplex in man often follows an initial acute episode of stomatitis in childhood.
8. In many other instances infection is wholly latent for a long time before it is activated -- examples are afforded by mice carrying the Bittner mammary cancer virus and caterpillars carrying polyhedrosis viruses.
9. Swine 'flu' virus in pigs which have eaten virus-bearing lung worms seems to be quite masked until the appropriate stimulus induces the infection and simultaneously makes the virus readily demonstrable.
10. Latent infection with paracrinkle virus in King Edward potatoes does not seem to be activable in the original host; its presence is readily revealed by transmission to an indicator host.
11. Finally there is the theoretical possibility of a latent infection with a masked virus which is not activable. We do not know how to prove that such a virus is present at all, but I feel little doubt that such non-demonstrable viruses must exist.

Cell-Virus Relations

Let us turn to the other end of our problem and see what possible cell-virus associations could lead to the kinds of infection we have been considering.

There is an increasing tendency to believe that most viruses have a developmental cycle like that of phage, that is they have an infective phase which attaches to and permits entry into a susceptible cell. They then replicate in a noninfectious vegetative phase (the so-called eclipse phase of infection) before once more regenerating complete infective particles. It would make our arguments easier if we could unswervingly believe all that, but I must confess that the evidence for it, for most viruses, is very scanty. However, the terms infective virus and vegetative virus seem to indicate adequately the two main phases in such a cycle. Whether there exists also a provirus, analogous to prophage, I leave to subsequent speakers.

It is conceivable that a virus may be permanently, or almost so, in the vegetative phase: such a virus could be the causative agent of a nonfilterable tumour (or a filterable tumour in a nonfilterable phase). Many years ago I (Andrewes, 1939) described such an hypothetical agent as a toothless virus, one unable to get out and about and bite another cell. Hereditary transmission of such a virus has to be considered.

There is also the question of production of incomplete virus, one lacking an essential component because of abnormal or arrested development. Incomplete viruses are nowadays very familiar to those who play games with viruses in laboratories. They may be important also in the pattern of infectious disease in real life. For example where a virus reaches an abnormal host it may fail to undergo the successive serial complete replications necessary for its continued existence, yet may cause disease, even fatal disease. (This happens in the laboratory where many influenza A strains are inoculated into mouse brains.)

Causes of Virus-Masking

We can now enumerate some of the possible reasons why a virus infection may fail to yield viruses when conventional techniques are employed, why in fact virus is masked or demonstrable with difficulty.

1. It may be incomplete and wholly noninfectious, whatever the technique used for the test.
2. It may be present in amounts too small for detection by the technique used. This may be the case with papilloma in domestic rabbits.

3. It may be mixed with antibody but cultivable in tissue culture where antibody can be gradually got rid of without disturbance of a small amount of virus within a few cells: or other methods may avail to separate it from antibody.

   Here perhaps we should include cases of fatal brain infections from which no virus is recovered, the "neuro-infections mortilles auto-sterilisables" of French writers.

4. It may have been sought for at an inopportune moment in the development when it was all in the vegetative phase.
5. It may be a virus which is permanently in the vegetative (toothless) phase as in nonfilterable tumours. (This is admittedly a hypothetical case.)
6. It may be a prophage and perhaps also pro-virus.
7. It may be a moderate virus -- a term proposed by Dulbecco and which I shall discuss later.

Factors Tending to Latency of Infection

Let us now turn our myopic gaze once more from the intimacies of the cell and consider how the ideas we have encountered will help to explain how a virus infection may remain latent.

Virus may exist in the body, as in a tissue culture, in a suppressed state, able to infect and perhaps destroy, a small group of expendable, perhaps unduly susceptible, cells here and there, but unable to establish or re-establish a general or widespread infection. This possibility may be blocked by active specific immunity of the host, usually mediated by the presence of antibody; or by genetic or species resistance to the infection; or, as with some phages and plant viruses and perhaps some animal viruses too, by interference by another virus, pre-empting the site of attack.

Such incomplete suppression of the virus is probably the commonest state of affairs in latent infections. There is no need to postulate any qualitative change in the virus. It simply ticks over at a low level. It may destroy the occasional cell or groups of cells as readily as in a florid infection. Or it may avoid neutralization by antibody, by skulking from one cell to another along secret intercellular passages. Or, in the special instance of growth within tumours, by increasing pari passu with the cell divisions which make the tumour grow. Here one may note that some viruses can be carried indefinitely as "passengers" in transplantable tumours, while for others this is only possible when the host is not actively immune.

Infection probably remains subclinical in some instances because the virus simply grows rather slowly and production of specific resistance occurs before any vast liberation of virus can take place and lead to disease. A few years ago it was believed that animal viruses all grew in cells and grew and grew till the cell burst and liberated a shower of particles. A slow growth of virus would then have been associated with a longer period before the effective cell burst, or with longer intervals between bursts: and this may indeed happen. We now realize, however, that with many animal viruses, such as influenza, virus may be shed from the cell surface over a period of time without cell death as a necessary consequence. There is here clearly much more scope for variations in behaviour of viruses in cells, and for the possibility of immunization and infection continuing side by side. Resistance of some species of birds to equine encephalomyelitis viruses can be cited. This species resistance may not be absolute. Thus hares normally resist experimental infection even with heavy doses of myxoma virus: but in the field an occasional hare proves susceptible, probably only one in many thousands exposed. Resistance of this kind doubtless has a biochemical-physiological basis: Dr. Chaproniere and I (1957) have lately found that tissues of species which are apparently quite resistant to myxoma

and some other viruses are highly susceptible in tissue culture and even in homografts. In these conditions cell-metabolism must be greatly changed, evidently with resulting great differences in ability to support virus growth. One can easily imagine therefore how a latent infection might be turned into an active one through the agency of all sorts of different disturbing influence, affecting the same variables.

Apart from these quantitative aspects of the relation between a potentially fully active virus and the host-cell, there remains the question of the existence of a qualitatively different virus peculiarly apt to establish an equilibrium with the host -- something like a temperate phage. Dulbecco (1955) suggests with a slightly different connotation the term "moderate virus" as something analogous to temperate phage. The word temperate cannot itself be used since it carries implications concerning lysogeny which are not, so far as we know, appropriate for animal virus infections.

I feel rather definitely that viruses exist in this "moderate" state, producing latent infections, and that once we have activated them, we do not know, as a rule, how to get them back into the moderate state. For instance, ectromelia is latent in some stocks of mice, only activated unwittingly by workers passaging some other virus. To get the ectromelia virus back into the submerged condition is, at least with most strains, very difficult.

Japanese and Chinese workers have independently reported that Sendai virus, sometimes called Influenza D, is latent in stocks of mice but can be activated by serial passage and made to cause a fatal infection: it can also cause disease in man and in swine: apparently it caused recently an epidemic of clinical influenza in Vladivostock. I thought this to be of great interest as a possible model virus to study in hope of shedding light on what happens to influenza A virus in between epidemics. I have therefore in unpublished experiments made three attempts to establish a latent Sendai virus infection in mice, infecting with doses of different sizes, killing at intervals and passing. I have used the Chinese virus and two lots from Japan, one of them very little removed from the original mice. I also tried to establish a latent infection in suckling mice. I have failed: the virus produces a clinical -- or a subclinical -- infection and then in 10 days or so disappears: no amount of blind passage will bring it out again. I suspect that it has been brought from the moderate phase, inducing latent infection to a virulent phase and that I am ignorant of how to get it back again.

Here I think is the difficulty about studying these moderate viruses. We cannot see what they are doing while they are moderate: we can only induce virulence and then study the virulent virus. We can perform a one-way magic: our laboratory incantations will get the genie out of the bottle: they cannot make it go back in again.

CONCLUSIONS

I have suggested two approaches -- to study and name the phenomena we observe, avoiding the temptation to use, in advance of precise knowledge, words which purport to describe fundamental mechanisms.

Inapparent infection can, I suggest, be used to mean just what it says -- covering the whole field of study: subclinical (at least in human and veterinary medicine) should describe (with necessary qualifications) inapparent infections running a definite limited course below the clinical level; latent infection should include all those silent, host-virus associations which are chronic, and, at least for a time, balanced. Masking and masked virus can denote all those infections in which virus is hard to demonstrate or has to be revealed by indirect tests; and moderate virus can describe virus which is qualitatively

changed so that it readily forms stable associations with host-cells. Moderate virus will prove, I surmise, to be normal avirulent and masked. At the intimate and logical end of the subject the terms prophage, perhaps provirus, vegetative and infective virus may be used just as soon as we are sure that they are appropriate. Other words call out to be defined and other things call out for precise names: I have only tried to make a start on the most fundamental ones. I do not hold passionately to my own suggestions as to words: I am happy to fall in (within limits) to other suggestions which meet general approval.

Two things have in the past evoked all mankind's basest passions: religious intolerance -- and nomenclature. Let us, as regards the latter of these anyway, set a new precedent. We cannot by choosing and defining words, settle all the problems of virus latency, but we can at least clarify our thoughts.

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INTERRELATION BETWEEN BACTERIA AND BACTERIOPHAGE

André Lwoff

INTRODUCTION

According to the program, I am to discuss "the factors involved in the interrelations between Bacteria and Bacteriophage." I shall do my best to perform my task for I am, like every Frenchman, highly disciplined.

Since 1953, the various aspects of bacteriophage have been reviewed and discussed adequately and extensively a number of times. So far as virulent phages are concerned, the subject has been dealt with by Hershey (1957), Stent (1958) and S. Cohen (1953).

The interactions of temperate phages and bacteria, and especially the problem of lysogeny, have been analysed and a doctrinal corpus put forward on three occasions by A. Lwoff (1953), F. Jacob (1954), F. Jacob and E. L. Wollman (1956). Moreover particular aspects of phage biology have been examined: induction by F. Jacob and E. L. Wollman (1953), genetics by A. D. Hershey (1957), S. Benzer (1956) and by M. Delbruck (1957), phage in its relations with bacterial genetics by E. L. Wollman, F. Jacob and W. Hayes (1956) and by Hartmann (1956), phage in its relations with disease by A. Lwoff (1955), S. S. Cohen (1955) and phage in its relations with viruses in general by Hershey (1956) and A. Lwoff (1957).

When considering the situation on September the 4th 1957, the conclusion is obvious: there is no real need for an additional paper on the subject. Scientists however, do not write papers because of a need, but because they are asked to do so. Although most scientists generally feel they should refuse, most of them generally accept. It is why we are here.

In order to close this introduction on a less pessimistic note, I should like to add two remarks. The first is that in the last few months some important discoveries have been made which have neither been published nor reviewed. This is an abnormal situation about which something will be done. The second is that each symposium has its specific leitmotiv. Today, we are assembled under the sign, or should we say the iron rule, of latency. Of course, bacteriophage provides remarkable models for all sorts of possible and impossible situations encountered by animals and plants virologists, and it is worthwhile summarizing them as a basis for the discussion of latency. For those who have not followed the latest developments of the subject, let me first recall briefly the actual state of our knowledge concerning bacteriophage. I have first to produce three preliminary remarks: 1) in order to avoid confusion, a bacterium will be called a bacterium and not a cell (this is not an attack on the cellular theory). 2) As it is fashionable to make use of groups of initials instead of perfectly understandable expressions, a few abbreviations will be used: D. N. A. for desoxyribo-nucleic acid, R. N. A. for ribonucleic acid, G. M. P. for genetic material of the phage. 3) Only one new term is proposed in this review: the phoron (bearer or carrier). The phoron is the unique and specific site or locus of the bacterial chromosome on which the G. M. P., that is to say the genetic material of the phage, has to be attached in order to be a prophage.

CYCLE OF BACTERIOPHAGE

When bacteria and bacteriophage are mixed, two things may happen: either the bacterium is killed, and is therefore called sensitive, or it survives and is therefore called resistant. As will be seen throughout the paper, the term sensitivity and resistance cover a variety of situations.