Slow Viruses

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PREFACE

One of the major and probably fairly exceptional problems we have encountered in our attempt to write an essay on slow viruses is the almost complete absence of any solid body of accepted evidence which could be used as a basis. In the first place it has been necessary to try to make our own definition of both the topic and the area involved.

We have for example begun from the conclusion that if the term 'slow virus' is to be meaningful it must be restricted to viruses which are 'slow growing' (or 'slow replicating'), and consequently that the term 'slow virus diseases' should properly apply to diseases resulting from infection with slow growing viruses. The reasons for this view will be given in the early part of this volume. We have also tried, because it seemed essential, to begin from both the disease standpoint and that of fundamental principles of viral replication and to direct the two lines of thought towards common ground. Although to a greater or lesser extent it is always difficult to bridge such a gap it has become more and more obvious to us during our enquiries that the gap in this case is very

large. It seems quite clear in fact that any better understanding of slow viruses and the mechanisms associated with them will depend on the ability of future investigators to extend the boundaries.

The clinical symptoms of the slow virus diseases tend to be ill defined and variable, particularly in the early stages, and while much has been written about the associated pathological changes they are not always clearly reconcilable with the clinical symptoms. Also, many of the biochemical and virological considerations have of necessity been extrapolated from first principles by a combination of experience, educated guess work and sheer speculation. Bearing all this in mind, we hope that it will be understood that it is a daunting problem to attempt to integrate the biochemical, virological, cell-virus relationship and disease aspects of slow viruses. Particularly in a volume of this size we realize that at best we can do little more than scratch the surface. We make no apology therefore for the fact that this volume has an unusually high content of personal opinion, and we accept that some at least of our views will be considered controversial. All that we can say is that we have made an honest and painstaking effort to deal with the slow virus problem as we see it, in as many aspects as possible, and in an overall way which does not seem to have been attempted before. We hope that the blunders, errors and omissions which we have no doubt made will at least be measured against the difficulties involved.

We also hope that what we have written will help others, not only to learn something, but also to recognise the problems and pitfalls which beset the study of these fascinating infective agents. Particularly we hope that some may be

stimulated to take up the challenge - and to do better!

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CHAPTER 1

INTRODUCTION

Over the last 20 years a multitude of review articles has appeared covering virtually all aspects of the nature, composition, structure and mechanism of replication of viruses. However, the experimental studies on which these have been based have largely centred on a few fast acting common viruses. Recently, an increasing amount of work has been directed towards a small group of infective agents whose most obvious characteristic is that they are unusually slow growing. In comparison with the fast growing viruses our knowledge of the nature and properties of these slow infective agents is fragmentary and it is not even entirely accepted at present that they are 'viruses' in the classical sense. However it is becoming more and more urgent to try to begin to find answers to the problems posed by them because it is clear that they are the cause of an ever widening number of rare, but unusually severe diseases. Apart from their intrinsic interest in this respect, one of the major questions which arises is 'why are they slow'? So far as we can see, current literature provides few direct

clues because despite wide coverage of the work on almost all aspects of virology virtually no attention seems to have been given to parameters which may govern the rates of viral replication and the lengths of the time interval between infection and the appearance of viremia or disease.

We shall begin on the tacit assumption that the slow (growing) infective agents probably are 'viruses' in the classical sense, but with special properties. Because of present divergencies of opinion (48, 78, 80) we will attempt to make an exclusive definition of what is meant by the terms 'slow virus' and 'slow virus disease' in relation to other virus groups and diseases. Then we shall examine the steps involved in the replication of classical virus particles (virions) to determine their potential ability for rate limitation, in an attempt to see how 'slowness' might arise. We shall next consider the properties of a typical slow virus (that producing the disease of scrapie) in the light of conclusions drawn from the classical viruses. Finally, we shall consider the implications of 'slowness' for the disease producing capability of the viruses involved and conclude with a primarily clinical description of the definite and putative individual slow virus diseases of man.

The time interval between infection and appearance of viremia or disease - defined as the 'incubation period' - may in general be divided into two relatively rapid phases. During the first phase, the latent period, little or no active virus is produced. The second phase - which may begin quite suddenly - is that in which viral replication occurs, and this may be followed by a recognisable disease state. In most instances, and fortunately for the host, the second phase is followed by an equally rapid decrease in virus titer and recovery. Although typically the whole

process occupies only a few days and rarely extends beyond a four week period, it is nevertheless quite clear that a minority of viral agents do not fit this pattern and, if viral agents are taken as a whole, then both latent periods and rates of replication in the infected tissues vary enormously.

At one end of the scale lie such agents as the murine virus, first discovered by Riley as a contaminant of transplanted tumors, which has the interesting property of elevating plasma lactate dehydrogenase activity in infected animals, but without causing any obvious disease. After intraperitoneal inoculation into mice this virus remains latent for a period of about 6 hours, and then a rapid viremia develops. The plasma concentration increases 10 fold (1 $\log_{10}$) every hour for the next 10 to 11 hours, and then decreases more slowly by about 5 logs over the next two to three weeks. At the other end of the scale, in mice inoculated intracerebrally with the infective agent of scrapie, the titre in the brain remains almost unmeasurable for 2-4 months and then increases by 1 log/10-20 days for a further 3-6 months. These time periods are very approximate for the development of scrapie and may be influenced in many ways which will be dealt with later. There is no decrease in agent titre at any stage, except perhaps shortly before the death of the animal, which occurs usually about 6-12 months after inoculation. In sheep, the natural scrapie host, the time course of the disease can be even longer, with the period between infection and death extending to as much as three years.

It may be pointed out here that 'slowness' per se is by no means an unknown biological phenomenon, and diverse examples can be given. Some seeds take a long time to

germinate and the time required for germination may be increased by subjecting them to adverse conditions such as storage. Carcinogens may not produce malignant growth for very prolonged periods - twenty years or more in some cases in man. Diseases ascribed to genetic defects may not make their appearance until late in life, and although it may be said that the eventual disease has always been present but without showing itself, the evidence for such a conclusion is often poor or non-existent.

So far as viruses, taken in their entirety, are concerned a whole spectrum may be plotted of the incubation periods between infection and onset of disease or peak of virus titer (Fig. 1). The great majority of the common viruses of which examples are given in Fig. 1 do in fact have short incubation periods, and consequently lie towards the left hand part of the Figure. Incidentally, it is important to remember that the majority of the individual lines in Fig. 1, designating the members falling within this short incubation period, cover a larger or smaller group of more or less closely related viruses - as many as 40 in some instances. As one proceeds towards the right the number of examples sharply decreases, and it becomes more uncertain how many variants there are in each. Moving even further to the right there is an amorphous collection of 'latent' viruses which remain apparently inactive in their hosts for an indefinite period. How many there are in this group we do not know - partly because they are difficult to detect - but they may be very numerous. They must, of course, be differentiated from viruses which, after infection, disappear from, or are eliminated by, their hosts. The essence of latency is the continuing presence in the host of virus, or at least of viral components, which are

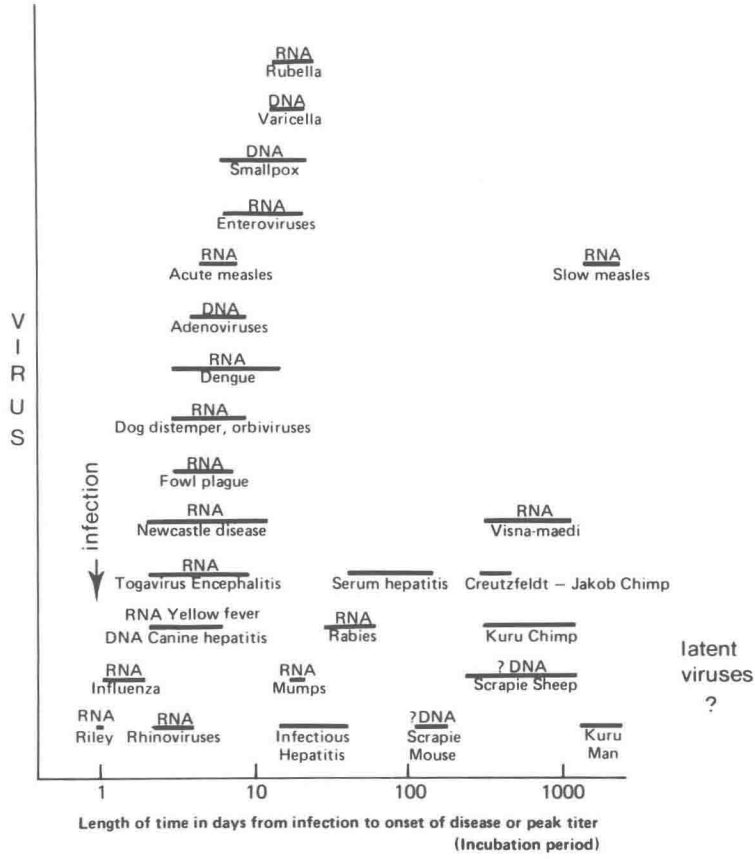

Fig. 1

The lengths of the incubation periods (the time between infection and disease or peak viremia) for different viruses. The approximate range of the incubation periods for each virus or group of viruses is given by ——. The nature of the core material (RNA or DNA) is stated for those viruses in which the information is available.

potentially capable of replication - rather like a seed kept in conditions which are unfavourable to germination. How many such agents are completely latent in the sense that they do not replicate at all, and how many could, but have no chance to do so because their latent period is longer than the lifetime of their host, is an open question. Some latent viruses may come to light only because their replication is 'triggered' by other events which 'help' latent viruses to emerge - such as the infection of their hosts by other, active, viruses, or alteration of the hosts' immune status.

As with the length of the incubation period, it is also clear that viruses can be arranged in a relatively continuous spectrum concerning their effects on individual cells in culture. Some (lytic) agents rapidly fill the host cell with new particles until it 'bursts' and releases its contents, while others produce a range of more or less subtle morphological changes, in some cases without causing cell death. Many latent, persistent and slow virus infections cause either no or very slight cytopathological effects, even after a prolonged period.

In summary then, the spectrum of virus incubation periods in their host animals runs a course from the very fast acting agents to those whose replicative ability is virtually zero under the circumstances applied to them. Slow viruses may be provisionally considered as those with exceptionally long incubation periods, which possibly merge into the 'latent' group in the way mentioned above. Also, for the moment let us assume that 'slow viruses' are the cause of 'slow virus infections', although as will be seen subsequently the tendency to equate these two terms has caused a good deal of confusion.

CHAPTER II

DEFINITION OF SLOW VIRUSES

The idea that 'slow virus' diseases formed a distinct group was first put forward by the late Bjorn Sigurdsson in 1954 (17) and he defined them in terms of the following criteria:-

1. A very long initial period of latency lasting from several months to several years.
2. A rather regular protracted course after the appearance of clinical signs, usually ending in serious disease or death.
3. Limitation of the infection to a single host species, with anatomical lesions occurring in only a single organ or tissue system.

One difficulty which arises over Sigurdsson's original list is that the disease nomenclature which he used has changed over the intervening years. Basically however his list comprised scrapie; maedi, which is also a disease of sheep but involving the lungs as well as the central nervous system; and a number of tumour viruses such as those concerned in the development of mouse mammary

carcinoma and avian and murine lymphomatosis. Sigurdsson recognised that his criteria might require modification in the light of future knowledge, and, as will be seen later it seems clear that his original list must also be amended.

Since this initial description, the terms 'slow virus infection' and 'slow virus disease' have been used to describe a wide range of conditions, many of which are obviously not caused by 'slow viruses'. Because of its construction, the term "slow virus disease" can obviously be interpreted in two ways. It may mean either a disease resulting from infection with a slow growing agent which takes a long time to accumulate a sufficiently high titer to damage enough cells to cause clinical symptoms, or a disease resulting from the long term persistence in tissues of a virus which may have replicated rapidly and reached peak titer without hours or days of infection, but which the host has been unable to eradicate. In the latter group clinical symptoms may also appear after a long interval, but the underlying pathological changes are usually due to tissue destruction by virus-antibody complexes rather than to an increase in the number of virus-infected cells.

Following Sigurdsson's initial description there has been an increasing tendency to group together the clinical syndromes resulting from both the above processes under the heading of "slow virus diseases". In fact, since we began to write this monograph, at least two separate volumes entitled "Slow Virus Diseases" have appeared (49, 80) in which disease processes resulting from slow growing and persistent viruses are considered together almost without discrimination. A typical example has been the inclusion of the pathological changes occurring in mice a comparatively long time after infection with Riley (lactate dehydrogenase