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Personal viewpoint

Complexity and the hepatitis viruses

'Complexity' is a contemporary buzzword used in conjunction with conceptual explorations of neural networks, economic models, 'artificial intelligence', evolution, life games, and similar exercises at the intersection of model making and the formulation of complex biological, physical, and economic problems. In this paper I use the term in a more literal sense, that is the complex interactions that are associated with infection by the hepatitis viruses and the subsequent pathology or lack of it.

A goal of medical and public health research is the determination of cause and effect, preferably a single cause with a linear effect or series of effects. This permits a direct attack on cause for which the surgical-military metaphor, 'a quick surgical strike' is sometimes used. But we know that medical problems (as well as military ones) are often far more complex than this hopeful model implies and ideal solutions are not always feasible. From the point of view of interventional medicine, however, an understanding of rich complexity may be more desirable than sterile simplicity. For, the more complex the problem, the greater the possibilities for intervention.

In this paper I plan to briefly discuss the complexities of infection and pathogenesis of hepatitis B virus (HBV) and how this knowledge may be used for prevention and treatment.

Complexity will be considered at several levels.

(1) The five or more viruses that primarily infect the liver.

(2) Examples of adaptation strategies that HBV has developed to conform to particular niches.

(3) Evolutionary strategies that HBV has developed to deal with its host.

(4) Mutation and change.

(5) Host, virus, and environmental interactions that affect infection and pathogenesis.

Possible interventional strategies will be presented to illustrate the wide range of possibilities that are open when the richness of complexity is comprehended. These include a wide range of approaches, for example, the applications of molecular biology, the modification of tattooing practices, and the design of well ventilated and dry storehouses for grains and other comestibles.

There are five named and characterised human viruses, A, B, C, D, and E, whose main tropism is for the liver. Although the outcomes of infection of each of the hepatitis viruses may be similar in terms of symptoms and findings, they are very different from each other and each is classified in a separate category.

There are many parts of the world where two, three, four, or all of these viruses are common in the populations and many potential hosts would be confronted with multiple viruses. It would be rash to assume that the viruses are always competitive; under certain circumstances they can aid each other. For example, infection with other viruses, particularly HDV, usually decreases the replication of HBV in chronic infection. This may at first consideration be thought of as detrimental to HBV, but decreased replication may prolong the life of the host cells and thereby increase the period during which transmission to other hosts may occur and maximise viral survival. This finding has resulted in a body of research whose goal is devising mutant variants of HDV, which would eliminate or decrease the replication of HBV, but be free of the pathogenic effects of HDV.

Another subtle example of apparent cooperation is seen in the interaction of HCV and HIV. As a solo infection, HCV is not readily transmitted from carrier mothers to their newborns and young. If the HCV carrier mother is also infected with HIV, however, then infant infection is much more likely, and would help maintain in the population a virus that is often spread only by transfusion and needle injections.

The interventions to decrease transmission of HBV and HCV by needle injections require public health controls. Tattooing is responsible for the transmission of blood-borne agents, but this can be prevented by the use of disposable needles. And transfusion transmission has been effectively controlled by donor testing. Injection of recreational drugs has proved to be much more difficult to control but it is hoped that public health and educational programmes will eventually help with these problems.

HBV has a remarkable ability to adapt to special 'niche' situations. For example, a large epidemic of HBV infection occurred in Swedish orienteers. (Orienteering is a sport in which contestants run from station to station through forest and field aided by map and compass to achieve the optimum time for the course). The epidemiologists who investigated the outbreak concluded that the contestants, running barelegged through the brush incurred small lacerations. Their blood remained on the foliage and thorns and subsequent runners who also had lacerations became infected. Or, infection could have occurred at the rest stations where the runners washed their legs in a communal tub. Surely a remarkable adaptation for a virus with only four reading frames! In this case preventative intervention was simple; the contestants were required to wear long trousers and the epidemic ceased.

Another niche occupied by the virus arose when a hospital computer system was installed to record and report laboratory results. Several members of the staff incurred HBV infection when they cut their fingers on the edge of computer cards that had become soaked with blood from an HBV carrier. Again, a clever adaptation to the computer age with an obvious and simple method of prevention.

The major strategy of HBV seems to be the maintenance of infective levels in the blood during crucial stages in the hosts life cycle, namely sexual activity and child birth. As these are essential to the perpetuation of the human species, this strategy enhances HBV survivability. The major preventive intervention is the use of the HBV vaccine in newborns and in adolescents before the start of an active sexual career.

In the following section, I will discuss a variety of possible viral mechanisms that have been suggested based on cellular and molecular findings.

The virus fully utilises the small number of proteins it can produce from its limited genetic repertoire, but it also enlists the capabilities of its host. For example, HBV produces an excess amount of viral surface antigen

particles (HBsAg), which can interact with the protective anti-HBs generated by the host after infection and prevent the destruction of the whole virus particles. Or, in utero it can render the foetus tolerant. Then, after infection by the mother, the infant will not respond immunologically at the time of infection or later, and the probability of becoming a carrier will increase.

Much of the pathology of HBV infection arises from the host immune response to the core antigen of the virus (HBcAg), which is expressed in an available position on infected liver cells. The virus has developed a clever molecular mechanism to delay the destruction by the host immune system of the infected cell and thus maintain its replication capability. The C reading frame has two start codons. If transcription is initiated at the second start codon the smaller protein, HBcAg, is produced, which encapsulates the viral DNA but also is expressed on the infected hepatitis cells. If transcription commences at the first start codon then a larger protein, HBeAg, is produced. It can be transported from the cells and render the immune system tolerant to the core antigen (HBcAg) with which it shares most of its amino acid sequences. As a consequence, the host does not destroy the infected liver cells for a long period, and viral replication is assured. HBeAg may also have an effect in utero, and may render the newborn tolerant.

The virus proteins can inhibit the effects of interferon. Treatment with interferon, probably the major form of therapeutic intervention now in use, acts to overcome this effect. It stimulates the immune system to destroy the cells burdened with virus. This leads to an acute increase in symptoms and chemical abnormalities. In some cases, unfortunately a few, it may also help to clear the body of virus or significantly decrease replication, or both.

There does not seem to be a receptor site on liver cells with a strong affinity for HBV. If this is the case, then high levels of virus would be maintained in the blood where it would be available for transmission.

After host reproductive and sexual activity have decreased significantly, or stopped, there is little reason for the virus to maintain its benign attitude to the survival of the host. Loss of the immune effects, mutation late in the life of the infection, and other changes may then be set in place to increase the rate of cell death with the consequent increase in risk for the development of hepatocellular carcinoma.

The molecular biology of HBV suggests many areas where intervention can take place; inhibition of the reverse transcriptase, DNA polymerase and other enzymes required for replication of the virus, interference with the receptor site(s), disruption of assembly, decreasing or increasing the immune response to HBsAg, HBcAg, HBxAg or some of the other products of the genes. But, before these individual effects are considered it must be kept in mind that the whole life cycle of the virus is part of a system, and any attempt at treatment would have to regard the evolutionary and adaptive features of the virus, not only at the moment of treatment but during its whole life history.

But there are other complexities of the interactions of HBV with its host and environment. Sex has an important influence; men are more likely to become carriers than women, and male carriers are more likely than females to remain carriers and to develop chronic hepatitis and primary cancer of the liver. There is an even more curious relation; in families in which parents are carriers, the sex ratio (number of male divided by number of female offspring multiplied by 100) is higher than in families in which the mother has developed anti-HBs. That is, the offspring of carrier families are more likely to be males. This may account, in part, for the high sex ratio and apparent paucity of female newborns in south China; HBV carriers are extremely common in this area. In fact, the effect on sex ratio, if confirmed, could represent one of the most important biological characteristics of the virus because it could significantly effect human evolution.

There is an additional environmental factor in the development of hepatocellular carcinoma in regions of the world where this deadly cancer is most common. Aflatoxin is a potent animal carcinogen produced by fungi that thrive on improperly stored grains and other foodstuffs such as peanuts. Studies in China, where both HBV and aflatoxin are common, have shown that, although HBV or HCV infection, or both is necessary for the development of most of the hepatocellular carcinoma in the population, the presence of increased aflatoxin considerably increases the probability of hepatocellular carcinoma. Also, cases of hepatocellular carcinoma in which HBV and aflatoxin are both present are more likely to have specific p53 mutations, which in turn are associated with the presence of the cancer.

The genes of the human host are also involved. There are two human loci for genes that are responsible for the detoxification of aflatoxin. At both locations there are alleles that confer deficient detoxification, and these alleles are more common in patients with the p53 mutation and with hepatocellular carcinoma.

Intervention for this 'cause' would be quite different than the molecular solutions described. As noted, aflatoxin contamination often results from improper storage of grains, peanuts, and other edible agricultural products. Adequate, well ventilated storage, and strict food inspection are the appropriate interventions in this case.

This brief description provides only a limited insight into the complexity of infection and disease with HBV. Continued research will show other aspects of the responses of this fascinating virus and the more we know the greater the possibilities of devising treatments and preventions.

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