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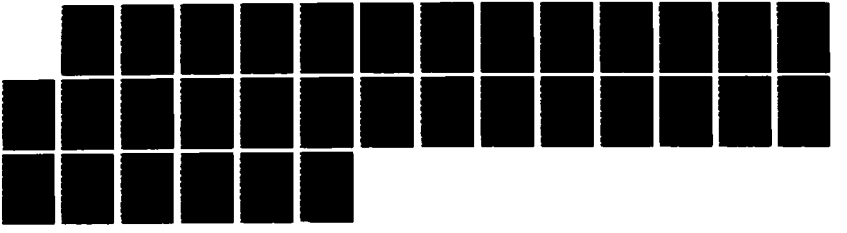

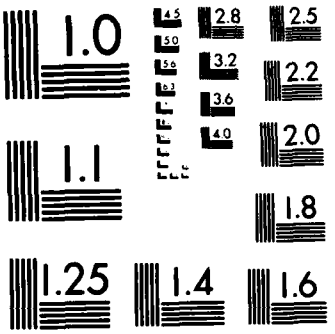

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The retrovirus HTLVIII/LAV, which infects T_4 (helper) cells of the immune system has been implicated as the agent responsible for the acquired immune deficiency syndrome (AIDS). In this paper, we contrast the growth of a 'normal' virus with what we call an Immune System Retrovirus (ISRV): a retrovirus that attacks T_4 cells of the immune system. We show that remarkable interactions with other infections as well as strong virus concentration dependence are general properties of ISRV. Some of the consequences of these ideas are compared with observations.

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THEORY OF AN IMMUNE SYSTEM RETROVIRUS

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ABSTRACT

The retrovirus HTLVIII/LAV, which infects T_4 (helper) cells of the immune system has been implicated as the agent responsible for the acquired immune deficiency syndrome (AIDS). In this paper, we contrast the growth of a 'normal' virus with what we call an Immune System Retrovirus (ISRV): a retrovirus that attacks T_4 cells of the immune system. We show that remarkable interactions with other infections as well as strong virus concentration dependence are general properties of ISRV. Some of the consequences of these ideas are compared with observations.

The retrovirus HTLV III/LAV has been implicated as the agent responsible for the acquired immune deficiency syndrome (AIDS). This virus infects T_4 (helper) cells of the immune system and possibly other cell types as well, and has shown certain pecularities in its life cycle. In particular the simultaneous infection of HTLV III and other viruses or a virus induced sarcoma such as Kaposi's sarcoma are believed to greatly increase the severity of the syndrome.(1) These effects may be due to specific biochemical linkage between the integration and growth of HTLV III and other viruses--or could be the result of a more general interaction between HTLV III and any other agent that stimulates the immune system.

In what follows, using simple models for virus growth and lymphocyte expansion, we contrast the growth of a 'normal' virus with what we call an Immune System Retrovirus (ISRV): a retrovirus that infects T_4 cells of the immune system. We show that remarkable interactions with other infections as well as strong virus concentration dependence are general properties of ISRV. The equations for virus growth and lymphocyte expansion are treated here approximately. A more detailed analysis will be presented elsewhere.

To what extent this account of ISRV provides an accurate description of the life cycle of HTLV III is, of course, an experimental question.

NORMAL VIRUS

The response of the immune system to an invading organism is varied and complex. It is generally believed that one or several binary interactions

results in immune cell proliferation and that this proceeds first by antigen processing by MHC Class II - expressing cells followed by interaction of the appropriate T_4 cell with the processed antigen-cell complex. The transfer of IL-1 between MHC Class II expressing cells and T_4 cells initiates clonal expansion, sustained by IL-2 and IFN-γ.

We first give a brief sketch of these events in a linked-interaction model in which it is assumed that antigen specific T cells must interact with the B-cell processed virus to initiate clonal expansion.(2) We then assume that virus specific antibody is the major component of immune system response that limits virus spread. As will be seen the details of these assumptions do not affect the qualitative features of our conclusions.

Linked-Interaction Model for Clonal Expansion of Lymphocytes

Let X be the concentration of normal infecting virus displaying its characteristic antigens, B_x the concentration of antigen specific B cells that can recognize and process this antigen, and T_x the concentration of T helper cells that can interact with the B_xX complex. Call the B_xX complex (BX) and the B_xXT_x complex (BXT). [For convenience we suppress the subscript x where no confusion will result.] A set of equations for the immune system response can be written:

$$\begin{aligned} \dot{(BX)} &= \gamma_1 BX - \gamma_2 (BX)T - \lambda_1 (BX) \\ \dot{(BXT)} &= \gamma_2 (BX)T - \lambda_2 (BXT) \\ \dot{B} &= \gamma_3 (BXT) + \varepsilon_B - \gamma_1 BX - \lambda_3 B \\ \dot{T} &= \gamma_4 (BXT) + \varepsilon_T - \gamma_2 (BX)T - \lambda_4 T \end{aligned} \tag{1a}$$

Here it is assumed that, in addition to natural loss, the loss of (BX) complex occurs entirely through the formation of the (BXT) complex and that the loss of B and T cells occurs through the formation of (BX) and (BXT) complex.. The clonal expansion of B and T cells is given by the last two equations which would also contain the production of plasma (non-memory effector) cells. The γ's and λ's are various growth and decay rate factors while ε_B and ε_T give the rate of introduction of new B and T cell from the bone marrow via the 'Bursa' and Thymus.

For a 'normal' virus the rate at which target cells, J, are infected is proportional to the concentration of virus present. The rate at which infected cells die is proportional to the number of infected cells and depends on various factors related to normal cell death as well as the harmful effects of the invading virus. Let J'(t) denote the concentration of infected cells at time, t; the γ's and λ's, as before, are rate factors. We can write

$$\dot{J}'(t) = \gamma_5 JX - \lambda_5 J' \qquad (1b)$$

The rate at which normal virus is produced is proportional to the number of infected cells, while the rate at which virus is destroyed or inactivated

due to immune system response depends on the numbers of B, T and other cells of the immune system and the concentration of immunoglobulin specific to the virus antigens. This represented by I(X,t). The equation for normal virus growth is then

$$\dot{X} = \gamma_6 J' - \lambda_6 X - I(X,t) \qquad (1c)$$

Immune System Action on Virus

The different components of the immune system immobilize or destroy a virus in various ways. In the continued presence of the antigen stimulant there is a very rapid expansion of immune system B and T cells as well as antibody secreting B plasma cells. The destructive effect of antibody is enhanced by interaction with complement and other substances that facilitate identification and destruction of the invading organism.

The action of the immune system on an invading virus can be divided into at least two categories: (1) Antigen non-specific phagocytosis and processing (the various non-specific mechanisms of immune system response) and (2) Antigen specific processing and immunoglobulin identification, followed by immobilization or phagocytosis (mechanisms that are initiated by immunoglobulin attached to the invading organism.)

When the initial concentration of virus is sufficient to evade non-specific immune system defense, target cells are infected, virus production begins and the specific specific immune system response is engaged. In what follows we consider only the specific immune system response. We assume

that virus specific antibody (Ig) provides the major component of immune system response that limits virus spread. (If the antigens of the invading virus are expressed on the surface of the infected cell, cytotoxic T cells would play a complementary role in destruction of infected cells thus further limiting virus spread).

On the average, s immunoglobulin molecules might be required to immobilize a virus or mark it for phagocytosis. However in what follows we are primarily interested in the limiting condition under which the immune system can control a virus. If this exists at all, it will exist for s=1. In this case the function I(X,t) is particularly simple*

$$I_{s=1}(X,t) = nbB(X,t) \qquad (2)$$

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*We assume that some proportion of proliferating B cells are plasma cells and that each plasma cell produces some number, n, of antigen-specific Ig. Then the number of immunoglobulin molecules in some multiple of the number of B cells produced in the clonal expansion. The rate at which individual Ig molecules attach themselves to the virus is denoted by b. (This rate could have some time dependence since the presence of invading antigens might stimulate production of enhancing factors such as complement).

In the equation for normal virus growth (1c), the first (production) term increases no more rapidly than the exponential $X(t) \leq X_0 e^{\gamma_x t}$ where $\gamma_x^2 = \gamma_5 \gamma_6 J$. In the immune response term, B(t) is a monotonically increasing function of time (until the virus is sufficiently depleted and the various feedback mechanisms begin to dampen lymphocyte clonal expansion and degrade X reactive immunoglobulin) and, as shown in the appendix, is singular. Therefore, for the normal virus, X increases monotonically until B(X,t) becomes large enough so that $\dot{X} = 0$. Beyond this turning point, the rate of decrease of the virus depends on various factors including the continued rapid increase of virus specific Ig, the rate of death of infected cells due to natural causes, the adverse effects of the virus infection and, possibly the action of cytotoxic T cells if the virus antigens are expressed on the infected cell surface [These and other such factors are contained in the neglected decay factors $\lambda \neq 0$.] and all of the complex and non-linear feedback mechanisms associated with the immune system response.

At the turning point, t_o, the virus in general will have reached its maximum concentration $X_{max} = X(t_o)$; the value of X_{max} is intimately related to the severity of the infection. To estimate this, we note that B varies slowly at first and then becomes a very rapidly increasing function of t; we therefore replace the continuously varying function B with a step function whose height is just sufficient to reduce $\dot{X}$ to zero at t_o. Beyond t_o, as B increases rapidly X will decrease. With these approximations, for s=1, the turning point occurs when $nbB(X,t) = \gamma_X$ [For $s>1$, the turning point occurs at $nbB = s\gamma_X$].

In the region of rapid (exponential) X growth and slow B cell growth, B cell clonal expansion, as estimated in the appendix, is dominated by the singularity. We then obtain

$$Xmax \simeq \frac{\gamma_x^3}{\gamma_B B_o}\left[1 - \frac{nbB_o}{s\gamma_x}\right] \underline{\sim} \quad \frac{\gamma_x^3}{\gamma_B B_o} \tag{3}$$

We conclude that normal virus concentration is always bounded above: a turning point exists. The essential question is the value of X_{max} (how sick the animal is or indeed whether it survives) when this turning point is reached.

In the above approximation, the maximum virus concentration, Xmax, is not strongly dependent on X_o. This means that if the initial viral infection is sufficient to evade non-specific defenses and to reach target cells the severity of the resulting infection is not strongly dependent on the level of the initial infection. This is so because specific immune system response (involving lymphocyte clonal expansion) becomes probable at some level of virus concentration (and is independent of the intial infection). Thus, once the virus has reached target cells and has begun to multiply it continues to do so until it

reaches a concentration at which it becomes probable that the specific immune system response is triggered. This triggering concentration is not strongly dependent on the concentration of the original infection. Furtner, since in this approximation the growth of B is dominated by the behavior of (A5) near its singularity, so is Xmax. Theretore Xmax is not strongly dependent on s (the number of immunoglobulin molecules required for virus immobilization).

Furtner, the maximum virus concentration, Xmax is proportional to γ_x^3 and inversely proportional to B_o (the initial B cell concentration reactive to X). This shows the expected strong dependence on the rate of virus production as well as the very powerful effect of immunization via the increase of B_o cells.*

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*For a normal virus, immunization via the presence of X reactive Ig would seem to have a much less powertul effect, contributing primarily to the level of initial concentration, X_o of the invading virus required to reach target cells and to begin to reproduce.

IMMUNE SYSTEM RETROVIRUS

An immune system retrovirus (ISRV) is defined as a retrovirus whose target is T_4(helper) cells of the immune system which require stimulation by antigens to reproduce. Its target cells are part of the response mechanism that defends the body against the attacking agents and are stimulated to reproduce by such agents. For a retrovirus, integration does not occur in resting (Go state) cells but rather requires that cells be in the S phase (DNA synthesis state) of their mitotic cycle. Once the viral cDNA integrates, transcription to mRNA proceeds at some rate that depends on details of the infecting virus and the invaded cell.

Since ISRV attacks the immune system itself, we must combine the equations for the immune system response and virus growth. As will become evident, there are two clearly distinct cases (I) pure ISRV infection and (II) mixed infections. These will be treated separately first and then combined.

In the somewhat idealized case of infection by the immune system retrovirus, Y, alone, with no other stimulation of the immune system, the invading virus infects T helper cells each with a potential to respond to a particular antigen but is integrated into T helper cell DNA only when the T helper cell itself recognizes ISRV processed by the appropriate ISRV-specific B cell and participates in the binary event that triggers clonal expansion. Therefore reproduction of ISRV requires

(a) infection of T_y by Y, resulting in T_y^- and

(b) the binary recognition event in which the $(B_yYT^-_y)$ complex formed.

(It does not yet seem to be known whether reproduction of HTLVIII requires continued stimulation of the infected cell or whether virus reproduction
proceeds as soon as the virus is integrated into cell DNA. We will assume here that no continued stimulation is required. If such stimulation turns out to be necessary, the conclusions below will be strengthened.)

Using the same notation as before but letting T′ be the concentration of virus infected helper T cells, for the binary response model we write

$$\begin{aligned}
\dot{(BY)} &= \gamma_1 BY - (BY)(\gamma_2 T + \gamma_2' T') - \lambda_1 (BY) \\
\dot{(BYT)} &= \gamma_2 (BY)T - \lambda_2 (BYT) \\
\dot{B} &= \gamma_3 (BYT) + \varepsilon_B - \gamma_1 BY - \lambda_3 B \\
\dot{T} &= \gamma_4 (BYT) + \varepsilon_T - \gamma_2 (BY)T - \gamma_4' TY - \lambda_4 T_y \\
\dot{(BYT')} &= \gamma_2' (BY)T' - \lambda_2' (BYT') \\
\dot{T}' &= \gamma_4' TY - \gamma_2' (BY)T' - \lambda_4' T'
\end{aligned} \tag{4a}$$

Here (BY) and (BYT) denote the B_yY and B_yYT_y complex, T′ denotes the ISRV infected T cell and (BYT′) denotes the complex of B_y cell, ISRV and <u>ISRV infected</u> T_y cell. In this case the equation for ISRV growth is

$$\dot{Y} = \gamma_6' (BYT') - \lambda_6 Y - I(Y,t) \tag{4b}$$

The more realistic situation is that in which the immune system is excited by the presence of another antigen system: a growing normal virus, X, for example, or is subject to constant turnover. We must then

add to the above equations (1a) for the clonal expansion of B and T cells reactive to the normal virus, X, and, in addition, equations for the infection of T cells reactive to X by ISRV, Y, and for the formation of the mixed complex ($B_X X T_X''$):

$$\dot{T}_x'' = \gamma_4'' T_x Y - \gamma_2''(B_x X) T_x'' - \lambda_4'' T_x''$$

and (4c)

$$(B_x \dot{X} T_x'') = \gamma_2''(B_x X) T_x'' - \lambda_2''(B_x X T_x'')$$

where γ'' and λ'' are rate factors for mixed production and decay and T_x'' denotes the Y infected T_x cell. The fundamental equation for ISRV becomes

$$\dot{Y} = \gamma_6'(B_y Y T_y') + \gamma_6''(B_x X T_x'') \qquad (4d)$$

$$- \lambda_6 Y - I(Y,t)$$

The first production term is non-linear in Y. The second production term, linear in Y, is due to the fact that ISRV growth can occur due to infection by Y of T helper cells reactive to the X antigen followed by Y integration into the infected T_4 cell DNA that occurs when it enters the mitotic state that is initiated by binary recognition to form the complex ($B_X X T_X$).

Due to the non-linearities the many variables and rate factors these equations are too complex to analyze completely here. However we can separate various regions of growth and point out several of their most relevant properties.

Pure ISRV Infection or Virus Production Dominated by Non-Linear Term.

This most difficult region to analyze, in which virus growth is dominated by the non-linear term, occurs for the idealized situation of pure ISRV infection, or for a mixed infection for which Y and/or B_y have reached sufficiently high concentrations. In this case virus production is dominated by $\gamma_6' (B_y Y T_y')$. As shown in the appendix, this term is bounded by $c\gamma_y B^2 Y^2 \geq \gamma_6' (B_y Y T') \leq 2\gamma_y \gamma_B^{-1} YB$ where c is a constant determined by the various decay terms.

From this we conclude that for low concentrations of Y and/or B (until YB reaches some critical value) non-linear virus production is very low. Since I(Y,t) is linear in Y, for low enough concentration of Y and/or B we expect no increase of Y. [Strictly, this conclusion is dependent on the rates of attrition of the various complexes.]

For YB larger than critical we have $\dot{Y} \leq (2\gamma_y\gamma_B^{-1} - nb)YB$. Since control of the virus seems possible under some circumstances (Antibodies to HTLVIII appear with no symptoms), we conjecture that the term in brackets is smaller than zero.

The situation in the region dominated by the non-linear term thus appears as follows. For low virus concentration, since virus production in this region increases no more rapidly than B^2Y^2 while virus destruction by the immune system increases as BY, for low enough values of Y and/or B for a pure IRSV infection there is not likely to be any virus growth. The details depend on how rapidly the various complexes (BY), (TY) and (BYT′) decay. Given the normal attrition in systems of this type it appears likely that for low enough concentrations of either Y or B_y there will be no growth of Y even though the specific mechanisms of the immune system are engaged. Thus one might expect antibodies to Y to appear accompanied by no symptoms of the disease.

For large virus and/or B cell concentration (BY larger than critical) virus growth is no more rapid than BY. Immune system control is thus

possible, but critically dependent on the various rate factors and the depleting effect of the virus on healthy T_4 cells. It thus appears that even under these relatively favorable assumptions (letting s be larger than one, and/or including the depleting effect of Y on the T_4 cells would make it more difficult to achieve the turning point) that once Y is large enough virus control by the immune system is only marginally possible. Since the growth rate of Y depends on B, once the concentration of infected T_4 cells (T') reaches a critical value (dependent on the various rate constants) compared to the concentration of healthy T_4 cells increasing B makes matters worse. In this non-linear region characteristic of ISRV, there is strong dependence of growth on concentration of Y as well as on the B (and T_4) cells specific to Y. Thus Y_o, B_o and T_o (the initial concentration of infection and B and T cells reactive to Y) are critical in determining whether virus control is possible.

Mixed Infections: Virus Production Dominated by Linear Term

This will be the situation when the immune system is excited by the presence of another antigen system (a growing normal virus, for example) or is subject to a constant turnover and when the concentrations of ISRV and lymphocytes reactive to ISRV are sufficiently low. It is likely the usual situation early in virus production in those situations when ISRV and B and T cells reactive to Y concentrations are low. In these circumstances the dominant production term is $\gamma_6''(B_x X T'' _x)$.

There are two distinct cases. Probably most frequently occurring is that for which X is a chronic controlled infection, a roughly constant allergic antigen, or represents natural turnover of the immune system. Then, as in the appendix, the dominant production term, is $\gamma_6''(B_x X T_x'')$. This is linear in Y and has the form $\gamma_y Y$, where γ_y, the mixed production rate, depends on the equilibrium values of X reactive B and T cells. In this case initial Y growth is like that of a normal virus with growth rate of γ_y. Depending on the magnitude of this growth rate, Y will either increase until the Y^2 term dominates or may be controlled by the immune system response while still in the linear region.

In the region where the equations are dominated by the exponential virus growth, (4b) becomes

$$\dot{Y} = \gamma BTY^2 + \gamma_y Y - I(Y,t) \qquad (5)$$

If the linear term dominates ($\gamma BTY < \gamma_y$) until the turning point (due to immune system action) we have as before, for the turning point $nbB \simeq s\gamma_y$. In this region B and T cell clonal expansions are like that for the normal virus, so that as for the normal virus

$$Y_{max} \simeq \frac{\gamma_y^3}{\gamma_B B_{oy}} \qquad (6)$$

where now B_{oy} is the initial concentration of B cells specific to Y. It therefore appears that in a very likely situation (that which would result from an infection with a relatively low dose of virus in an otherwise healthy individual whose immune system is not too active so that γ_4 is not too large) ISRV growth would be like that of a normal virus and could be controlled, resulting in ISRV reactive I, but no easily visible symptoms of the disease.

In striking contrast is the case in which X represents a rapidly growing normal virus or other infection. For initial low Y concentration that could be the result of a simultaneous new Y infection (or a chronic Y infection resulting in a continuing low Y concentration) virus growth is dominated by the linear term. But in this case, B_x and T_x grow very rapidly and the growth of Y is like that of a normal virus with a rapidly increasing rate of growth; the (non-linear) term will become important increasing the rapid rate of growth. Thus, for a simultaneous Y and X infection we almost certainly will be faced with catastrophic Y growth with consequent destruction of T helper cells and immobilization of the immune system.

DISCUSSION

The above argument is based on the following assumptions: an immune system retrovirus (ISRV) is a retrovirus that infects T_4 (helper) cells of the immune system. The retrovirus can invade the cell upon proper receptor contact but is integrated into cell DNA only in the mitotic phase. Since the mitotic phase is induced by a binary recognition event, integration and (possibly) virus reproduction requires that the invaded target T cell interact with the appropriate B cell-processed antigen complex.

In contrast with a normal virus, for ISRV we see a complicated pattern of growth regions depending critically on the concentration of ISRV, B and T cells reactive to ISRV and on activity of the immune system due to other infections or natural turnover.

For a first-time low concentration infection with low $B_y(o)$ and $T_y(o)$ populations (with little or no other stimulation of the immune system) ISRV is produced very slowly since most of the T_4 (helper) cells infected <u>will not be stimulated to reproduce.</u> For such first-time infections we might expect to remain either in the linear growth region or (for the idealized pure ISRV infection) in the low growth non-linear region. Thus one would expect some antibody response but low virus growth. Since the level of ISRV antibody as well as the number B_y and T_y cells determine the rapidity of immune system response immunization to the virus for this situation seems possible. This is consistent with

puzzling presence of ISRV Ig in so many individuals who, in spite of the extraordinarily rapid production rate of HTLVIII, show no symptoms.

A further infection by ISRV (as long as Y_0 is not too large and possibly also as long as B_y and T_y are not too large - since ISRV growth rates depend on these quantities) if not accompanied by a rapidly growing 'normal' infection could then be controlled by the immune system so that the individual would appear to be immunized to ISRV.

If ISRV comes in several genetic variations (each of which contain a site reactive to the same Ig) further infection by a new variety of ISRV after an initial controlled infection (if not accompanied by a rapidly growing normal infection) could be controlled by the immune system so that it would not appear as virus in the individual. Therefore an individual already showing virus (likely in an ISRV chronic state) will in effect be immunized to other strains of the virus so that one would not be likely to find more than one very distinct genetic variation in a single individual(3)

However, for an ISRV infection simultaneous with another rapidly growing virus or other infection, [The second infection could be a chronic illness such as malaria; it could occur at the same time as the ISRV infection or at some later time when the individual still has ISRV invaded T cells.] there is rapid growth of ISRV resulting almost certainly in destruction of immune system response.

Thus, in striking contrast to a normal virus, no level of initial B and T memory cells can give complete protection since simultaneous 'normal' and ISRV infection (if one is not already immunized to the normal infection) leads to catastrophically rapid ISRV growth rates, destruction of T_4 cells and no possible immune system control. Because of this each repeated infection of ISRV exposes the individual to this risk in spite of his level of 'immunization'.

Once the concentration of infected T_4 cells grows large enough compared to the concentration of healthy T_4 cells, since the growth rate of ISRV depends on concentrations of B_y cells, it appears that, again in contrast with a normal virus, for ISRV increasing the level of B_y becomes counterproductive.

It is possible that for an initial controlled infection the virus can lurk unintegrated or possibly integrated and non-producing (if reproduction, as has been suggested, requires some other signal) in those T_4 helper cells not stimulated to reproduce. Thus even with an effective immune system response resulting in appropriate B and T cells and Ig, virus can continue to exist in infected T_4 cells. If these cells are stimulated by some other infection (or even a subsequent IRSV infection) virus can again be produced, again entering the blood so that the infection appears once more. In the absence of further infection the virus will continue to exist in infected T_4 cells until these cells die naturally. Thus one might speculate that an otherwise healthy individual exposed to ISRV could show an immune system response (ISRV Ig) no easily visible symptoms, and with no further infection, might rid himself of the virus in the time due to the natural turnover of T cells.

When a sufficient number of T_4 cells are infected by ISRV an intermediate situation could result in a chronic infection: continual low production of ISRV and reinfection of T_4 cells due to slow stimulation of the immune system by ISRV itself but no catastrophic growth of ISRV.

One of the consequences of these arguments is that a high concentration of Ig reactive to ISRV can serve to control the ISRV infection while a high concentration of T_y and B_y (the natural source of ISRV reactive Ig) works in the opposite direction since it increases the ISRV growth rate. This suggests that increasing the level of Ig reactive to ISRV while at the same time dampening immune system activity would aid in controlling the growth of ISRV. [One would, of course, have to deal with the growth of other infections.]

In the above analysis no assumptions have been made concerning biological co-factors and/or latency or incubation periods. If these exist they would modify but not negate our discussion. However, a consequence of our arguments is that there can be delays between infection and syndrome even though there is no intrinsic prolonged latency period; any immune system stimulant acts as a co-factor.

As one application of these ideas consider Kaposi's sarcoma. Among the earliest observations in AIDS patients was the increased virulence of this sarcoma. It has further been observed that this increase in virulence is correlated to the presence of the HTL VIII antibody.

It is believed that Kaposi's sarcoma is caused by a virus (a virus independent of HTLV III) and it seems likely that the spread of this sarcoma is mediated by the virus as much as by migration of malignant cells.

Following the above arguments, this can be analyzed as follows. In a patient, not infected with ISRV the spread of Kaposi's sarcoma is inhibited by normal immune system function -- the immune system preventing the spread of the virus. In the patient infected with HTL VIII, the virus that produces the sarcoma acts as a 'normal' virus described above. The stimulation this virus provides for the immune system increases the growth of the ISRV. This destroys the capacity of the immune system to respond thus allowing the spread of the normal virus resulting in the increased virulence of Kaposi's sarcoma. [This, of course, would also be true for other infections spread by 'normal' viruses.]

In this case, we may be seeing the interaction of the immune system retrovirus with a normal virus that would under ordinary circumstances be controlled by the immune system. However, the interaction of these two viruses results in destruction of the immune system and the increased virulence of a normally controllable disease.

APPENDIX

Because of the non-linearities, the number of variables and growth and decay rates, the equations for virus and lymphocyte growth are too complex to analyze exactly here. In what follows, we make precise the approximations on which our arguments are based.

Lymphocyte Clonal Expansion and Normal Virus Turning Point

We approximate the equations for B cell clonal expansion by dividing them into two regions: (1) rapid virus growth, slow B cell growth, (2) virus concentration stationary, rapid B cell growth. We believe that these approximations capture the qualitative features of B cell growth which are dominated by a singularity in the region of very rapid expansion. The position of this singularity is most important in determining the dependence of Xmax on the various parameters of interest. Neglecting the decay terms and assuming that $B(t\simeq o) = T(\simeq o) \equiv B_o$, $(BX)_o = (BXB)_o = o$ and that $\gamma_3 = \gamma_4$, B cell and T cell proliferation proceed at the same rate so that $B(t) = T(t)$. Equations (1a) become

$$\begin{aligned} \dot{(BX)} &= \gamma_1 BX \\ \dot{(BXB)} &= \gamma_2 (BX)B \\ \dot{B} &= \gamma_3 (BXB) \end{aligned} \qquad \text{(A1)}$$

[Here X represents either a normal virus or ISRV until explicit assumptions are made on the rate of virus growth.]

These yield

$$\dot{B} = \gamma_B \int_o^t B(t')Z(t')dt'$$

(A2)

where

$$Z(t) = \int_o^t X(t')B(t')dt'$$

We employ the rapid virus, slow B cell growth, approximation until virus growth becomes stationary. Then we employ the stationary virus, rapid B cell growth approximation. The maximum virus concentration is obtained from the singularity in the first approximation. The singularity in the second approximation indicates that the B cell clonal expansion continues so that the virus concentration diminishes rapidly.

Since B is monotomically increasing (A2) yields

$$\dot{B} \leq \gamma_B B^2 \int_o^t dt'' \int_o^{t''} dt' X(t') \qquad (A3)$$

where $\gamma_B = \gamma_1\gamma_2\gamma_3$. It follows that

$$B(t) \simeq B_o [1 - \gamma_B B_o \int_o^t dt''' \int_o^{t'''} dt'' \int_o^{t''} dt' X(t')]^{-1} \qquad (A4)$$

Approximating X(t) by its value neglecting the effect of the immune system (rapid virus growth region) $X(t) \simeq X_{oe}^{\gamma_x t}$ gives

$$B(t) \simeq B_o(1-\gamma_B\gamma_X^{-3}\ B_oX(t))^{-1} \qquad (A5)$$

The singularity occurs at $X(t) \simeq \gamma_X^3\ (\gamma_B B_o)^{-1}$.

In the region of rapid B cell, slow or stationary virus growth (A2) has a solution as an elliptic integral for which B becomes infinite for finite t. Since B can be shown to be larger than such a solution, it follows that B is singular for finite t.

ISRV EQUATIONS

Neglecting decay terms, the non-linear term for ISRV production is obtained from

$$\begin{aligned} (\dot{BY}) &= \gamma_1 BY \\ \dot{T}' &= \gamma_4' TY \\ (\dot{BYT'}) &= \gamma_2' (BY)T' \\ \dot{Y} &= \gamma_6' (BYT') \end{aligned} \qquad (A6)$$

where all implied subscripts have been suppressed. As before we assume $B_o \simeq T_o$ and equal rates of growth for B and T (thus before serious T_4 cell depletion due to the action of the virus). We obtain for the non-linear production term

$$Y_{p'} = \gamma' \int_o^t dt' (Z(t'))^2 = 2\gamma' \int_o^t dt'' \int_o^{t''} Y(t')B(t')Z(t')dt' \qquad (A7)$$

where $\gamma' = \gamma_1\gamma_2'\gamma_4'\gamma_6'$, $Y_{p'} = \gamma_6'(B_yYT_y')$ and now $Z = \int_o^t Y(t')B(t')dt'$

In the region in which Y is monotonically increasing

$$\dot{Y}_{p'} \leqslant 2\gamma' \int_o^t Y(t'')dt'' \int_o^{t''} B(t')Z(t')dt' \\ = 2\gamma' \gamma_B^{-1} \int_o^t Y(t')\dot{B}(t')dt' \tag{A8}$$

Therefore

$$\dot{Y}_p \leqslant 2\gamma' \gamma_B^{-1} YB \tag{A9}$$

It follows in any case that

$$\dot{Y}_{p'} \leqslant c\gamma' B^2 Y^2 \tag{A10}$$

where the constant, c, is determined by the rates of decay (λ_1, λ_2. etc.) of the various complexes.

The linear virus production term (due to a simultaneous 'normal' infection or to background immune system turnover) again neglecting decay and letting $B_x = T_x$ is

$$\dot{Y}_{p''} = \gamma_2'' (B_x X T_x'') = \\ \gamma_2'' \int_o^t dt' \int_o^{t'} dt'' B_x Y \int_o^{t''} dt''' B_x X \tag{A11}$$

where $\gamma'' = \gamma_1\gamma_2'\gamma_4''\gamma_6''$ and $\dot{Y}_p'' = \gamma_6''(B_X X T_X'')$.

In this case (A8) is replaced by

$$\dot{Y}_p'' \ll 2\gamma'' \gamma_B^{-1} \int_0^t Y(t')\dot{B}_X(t')dt' \qquad \text{(A12)}$$

where now, of course, B_X denotes B or T lymphocytes reactive to X, the 'normal' antigen.

In the absence of a simultaneous rapidly growing infection, background immune system turnover might be approximated by $\dot{B}_X \approx$ constant so that Y_p' increases as a normal virus $\dot{Y}_p'' \approx \gamma_y^2 \int_0^t Y(t')dt'$ where

$$\gamma_y \approx (2\gamma''\gamma_B^{-1}\dot{B})_X^{\cdot}.$$

When there is a simultaneous growing infection (in the region where X is increasing rapidly) when $\dot{B}_X$ given by (A3) and estimating the increase of X by an exponential we have $\dot{B}_X \approx \gamma_B\gamma_X^{-2} B_X X$ which gives a very rapid growth of Y.

When virus production is dominated by the linear term we estimate the non-linear term (in the region of rapid virus - slow lymphocyte growth) letting $Y = Y_o e^{\gamma_y t}$. We then obtain $\dot{Y}_p' \approx \gamma\gamma^2 B^2$ where $\gamma = 2\gamma'\gamma_y^{-3}$. All together

$$\dot{Y} = \gamma\, Y^2 B^2 + \gamma_y Y - nb\, BY \qquad \text{(A13)}$$

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