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DYNAMIC MODEL OF THE PATHOGENESIS OF MENGO VIRUS INFECTION IN MICE

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Summary. — A mathematical model of the pathogenesis of experimental Mengo virus infection in mice has been developed and fitted using kinetic data of both virus multiplication in different organs and mortality. The behaviour of the model proved to be bistable. In contrast to the widely accepted hypothesis that an acutely virus-infected host dies when virus replication has attained a critical level in the main target organ, the present results showed the following: the maximum virus titre in brain, the main target organ, had been reached already 24 hr post infection (p. i.) but the animals began to die since 60 hr. Hence, it was postulated and confirmed by a good model fit to the experimental data that the so-called AUC (*a*rea *u*nder the *c*urve) of the virus multiplication kinetics may be a critical quantity. From this finding a hypothesis was deduced assuming that in the presence of high amounts of the virus the antiviral effect of IFN wanes with time. Since this process accounts for death, it may be a potential target of antiviral therapy.

Key words: pathogenesis; dynamic modeling; Mengo virus; interferon; bistability; picornavirus; mouse

Introduction

Over half of all viral neurological diseases registered are associated with enteroviruses (Assaad *et al.*, 1980). Mengo virus infection of mice appears to mimic many aspects of human enterovirus diseases involving the central nervous system (CNS) and, therefore, provides a suitable animal model for pathogenetic studies (Stringfellow *et al.*, 1974). The virus causes an acute, generalized and lethal infection, affecting the CNS, salivary glands, exorbital lacrimal glands, thymus, pancreas and kidneys. Animals die consistently of heavy meningoencephalomyelitis (Craighead, 1966; Veckenstedt, 1974; Zschiesche and Veckenstedt, 1974; Veckenstedt *et al.*, 1978; Güttner *et al.*, 1982, Schmidt *et al.*, 1984).

Much attention is now focused on the development of antiviral prophylaxis and therapy. Currently, approved clinical antivirals against picornavirus

Table 1. Published experimental data of Mengo virus-infected mice used for the development and fit of the mathematical model

Experimental data	Figures and Tables	References
Mean values of virus concentration in various organs	Table 2, Figs. 1 and 4	Veckenstedt, 1974
Virus concentration in the brain of individual mice	Table 4, Fig. 2	Veckenstedt and Pusztai, 1981
Number of lymphocytes in the blood	Fig. 4	Zschiesche and Veckenstedt, 1979

infections are not available (Eggers, 1985; De Clercq, 1985). Certainly, only interdisciplinary research can overcome this problem. Such an approach involves mathematical modeling that clearly and accurately defines the details of virus to host interaction. Mathematical models allow important insight into pathogenetic processes and may provide a "template for the design of effective control programmes" as emphasized by Anderson and May (1985) for vaccination policies. Furthermore, such models will be the basis for a computer aided antiviral therapy.

The purpose of the present model study is to define and quantify the crucial processes of the pathogenesis of Mengo virus infection of mice. Therefore, at first, hypotheses will be formulated mathematically and model based predictions will be proved using experimental data. In doing so, it will be demonstrated that the relation between virus dose and outcome of infection can be formulated in simplified terms of both virus multiplication and host defence. This relationship is described by the mathematical model of bistable behaviour. Such models were already fitted to experimental data of fermentation systems (Yang and Humphrey, 1975; Bergter, 1983). For studies of pathogenetic events bistable models were investigated from theoretical point of view without parameter identifications (Belykh and Marchuk, 1982; Stepanova and Chernavsky, 1983). Shortley and Wilkins (1965) used stochastic models instead of deterministic bistable models. The present model is applied for elucidation of crucial processes in the course of pathogenesis of Mengo virus infection in mice.

Materials and Methods

Data used. In addition to the original experimental data, the previously published results summarized in Table 1 were used.

Virus. The origin, methods of preparation and storage of the Mengo virus strain were described (Veckenstedt, 1974; Zschiesche and Veckenstedt, 1979; Veckenstedt and Pusztai, 1981; Güttner *et al.*, 1982). Clarified 10% suspensions of infected mouse brains (w/v) in phosphate-buffered saline (PBS) were used. Virus was titrated by intraperitoneal (i.p.) route in $ABAF_1$ or $ABD2F_1$

mice and the LD_{50}-values per 0.1 g of brain were determined (Reed and Muench, 1938). Mice were infected i.p. with 0.1 ml of different virus doses calculated from the titres of stock virus.

Mice. (AB/Jena $\times$ A/Jena)F_1 hybrids (ABAF$_1$) of both sexes, and male (AB/Jena $\times$ DBA/2. Jena)F_1 hybrids (ABD2F$_1$) 4 to 6-week-old were obtained from SPF colony of the Institute The housing conditions of mice during experiments have been described previously (Veckenstedt, 1974; Veckenstedt and Pusztai, 1981).

Assay for virus content, Randomly selected mice were sacrificed at various intervals after infection (p.i.) and their organs were removed .Pooled or individual organs were weighed, homogenized in PBS to a 10% suspension, and centrifuged. Supernatants were titrated in mice by intracerebral (i.c.) inoculation of 0.03 ml and the LD_{50} — values per 0.03 g of the tissues were determined as above. For details see Veckenstedt (1974) and Veckenstedt and Pusztai (1981).

The LD_{50}-values were designated according to the route of virus inoculation, i.e. units LD_{50} (i.c.) and LD_{50} (i.p.) were introduced. Infectivity titres after i.c. or i.p. inoculation were found to be 5×10^7 LD_{50} (i.c.) /0.03 g and 4×10^7 LD_{50} (i.p.) /0.1 g, respectively (Veckenstedt, 1974). Thus, the virus dose of 1 LD_{50} (i.p.) was considered equivalent to 4.2 LD_{50} (i.c.).

Interferon (IFN) assay. Groups of seven ABD2F$_1$ mice, after i.p. inoculation with 10 LD_{50} (i.p.) of Mengo$_M$ virus were bled at given intervals. Pooled serum samples were dialysed against 0.1 mol/l NaCl/0.01 mol/l HCl (pH about 2) for 3 days, returned to pH 7.2 by dialysis against Hanks' solution, and stored in aliquots at liquid nitrogen until assayed. IFN activity was tested by means of an infectivity inhibition microtest, using vesicular stomatitis virus and L_{929} cells. The highest dilution of the sample causing 50% inhibition of the cytopathogenic effect after 24 hr was considered the titre. In the assay 4.5 units of IFN activity equaled one unit of the international reference unit standard (G-002-904-511) obtained from the National Institute of Health, USA.

Model studies. The dynamic model eq. (8) as well as the integral in eq. (11) were solved as follows:

$$x = x\left(t; x_0, x_m, \frac{\beta}{\mu}, \mu\right) = \frac{x_m}{\left(1 + A \frac{B \exp(A\,\mu\,t) + 1}{B \exp(A\,\mu\,t) - 1}\right)} \qquad (1)$$

and

$$R\left(t_s; x_0, x_m, \frac{\beta}{\mu}, \mu\right) = \int_0^{t_s} x(t)\,dt = \frac{x_m}{2}(1 - A)\,t_s + \frac{x_m}{\mu} \ln\left(\frac{B \exp(A\,\mu\,t_s) - 1}{B - 1}\right) \qquad (2)$$

where

$$A = \sqrt{1 - \frac{4\beta}{\mu\, x_m}} \quad \text{and} \quad B = \frac{1 - 2\,x_0/x_m - A}{1 - 2\,x_0/x_m + A}.$$

Supposing

$$0 < \frac{\beta}{\mu} < \frac{1}{4} x_m$$

x in eq. (1) converges to one of three solutions in dependence on the initial value $x_o = x(0)$:

$$\lim_{t \to \infty} x = \begin{cases} x_{max} & \text{for } x_o > x_{crit} \\ x_{crit} & \text{for } x_o = x_{crit} \\ -\infty & \text{for } x_o < x_{crit} \end{cases}$$

where

$x_{max} = 1/2\ x_m\ (1 + A)$ is the maximum state and $x_{crit} = 1/2\ x_m\ (1 - A)$ is the critical state (tolerance dose). From experimental data of virus multiplication after inoculation of 10 LD_{50} (i.p.) of Mengo virus (Veckenstedt, 1974) it is found that, first, $x_{crit} < x_o = 42$ LD_{50} (i.c.) because x increases and, second, x reaches the maximum value $x_{max} = 5 \cdot 10^8$ LD_{50} (i.c.). Thus, one obtains $x_{crit} \ll x_{max}$ and $\frac{\beta}{\mu} \ll \frac{1}{4} x_m$ so that $x_{crit} \approx \frac{\beta}{\mu}$ and $x_{max} \approx x_m$ are found to be good approximations.

The kinetics of cumulative mortality $M(t, x_0)$ is the estimate of the probability $P(t_s < t)$ that the survival time t_s of mice infected with the virus dose x_0 is smaller than t. For calculations this probability was splitted into a stationary and a time-dependent factor:

$$P(t_s < t) = P\left(\frac{\beta}{\mu} < x_0\right) P\left(t_s < t \,\middle|\, \frac{\beta}{\mu} < x_0\right). \tag{3}$$

Here we used the fact that

$$P\left(t_s < t, \frac{\beta}{\mu} < x_0\right) = P(t_s < t).$$

The distribution function of the tolerance dose $\frac{\beta}{\mu}$

$$F_{\beta/\mu}(x_0) = P\left(\frac{\beta}{\mu} < x_0\right) \tag{4}$$

corresponds to the mortality $M(t, x_0)$ at a given dose x_0 after a sufficient long time ($t \to \infty$). $F_{\beta/\mu}$ was estimated by the relative frequency of animals that died up to day 14 p.i. (end of the observation period) and approximated by a piecewise linear function $F_{\beta/\mu}(x_0)$ to estimate the density function $f_{\beta/\mu}(x_0)$.

The empirical distribution function of the specific multiplication rate

$$\hat{F}_\mu(\mu') = \hat{P}\left(\mu < \mu' \,\middle|\, \frac{\beta}{\mu} < x_0\right) \tag{5}$$

was estimated by the empirical distribution function of virus content x

$$\hat{F}_x(x') = \hat{P}\left(x < x' \,\middle|\, \frac{\beta}{\mu} < x_0\right)$$

obtained by the experimental data published (Veckenstedt and Pusztai, 1981), and transformed by eq. (*1*) with the following parameters:
$t = 12$ hr or $t = 24$ hr when the virus content x in the brain was assayed (Veckenstedt and Pusztai, 1981),

$x_0 = 10\ LD_{50}$ (i.p.) $= 42\ LD_{50}$ (i.c.)

as the dose of virus used (Veckenstedt and Pusztai, 1981)
$x_m = 5 \times 10^8\ LD_{50}$ (i.c.)

as fitted to experimental data (Veckenstedt, 1974), and

$$\frac{\beta}{\mu} \approx \left(\overline{\frac{\beta}{\mu}}\right) = \int_0^{x_0} x' f_{\beta/\mu}(x')\, dx'$$

as the estimate of the conditional expectation $E\left(\frac{\beta}{\mu} \,\middle|\, \frac{\beta}{\mu} < x_0\right)$ approximatively used.

The probability $P(t_s < t)$ was calculated by the following relations: From the empirical distribution function $\hat{F}_\mu$ as defined by eq. (*5*) the conditional probability $P\left(t_s < t \,\middle|\, \frac{\beta}{\mu} < x_0\right)$ was estimated using the transformation

$$t_s = R^{-1}\left(C;\ x_0,\ x_m,\ \frac{\beta}{\mu},\ \mu\right),$$

where R^{-1} is the inverse of eq. (*11*) which was solved by eq. (*2*) for different doses x_0 (= 0.5, 1, 3, 10, 20 LD_{50} (i.p.)), the parameter x_m given above and $\frac{\beta}{\mu}$ calculated by eq. (*6*). Then $P(t_s < t)$ was estimated by eq. (*3*) and compared with experimental data for $M(t, x_0)$ to fit the parameter C.

Table 2. Maximum virus concentrations (Veckenstedt, 1974) and virus contents in various organs of mice infected with 10 LD_{50} (i.p.) of Mengo virus

Organ		Time p.i.	Virus	
Type	Mean weight		Concentration	Content
	(g)	hr	LD_{50}(i.c.)/0.03g	LD_{50}(i.c.)
Brain	0.30	24	5×10^7	5.0×10^8
Pancreas	0.13	72	4×10^6	1.7×10^7
Blood	2.00	60	1×10^5	6.7×10^6
Liver	1.50	72	2×10^4	1.0×10^6
Spleen	0.09	72	5×10^4	1.5×10^5

Results

Development of the mathematical model

As was shown in antiviral studies Mengo virus titres in the brain and other organs of mice corresponded to the mortality (Veckenstedt and Pusztai, 1981). Consequently, the kinetics of the virus content in the host can be assumed to be a meaningful characteristic of the pathogenesis and,

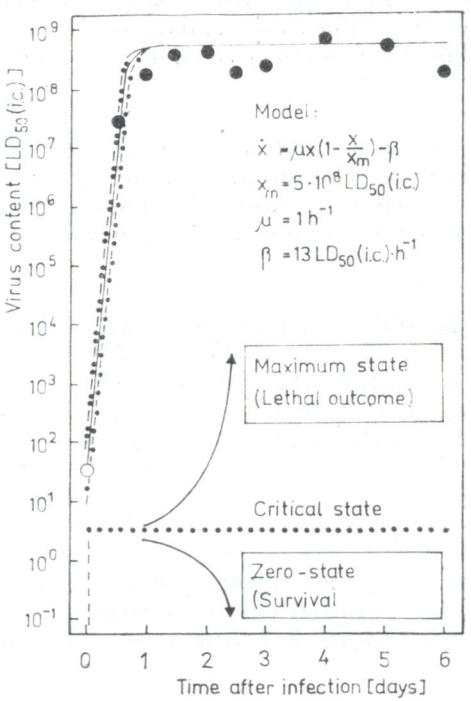

Fig. 1.

Kinetics of Mengo virus content x in mice versus the time t

● experimental data from Veckenstedt (1974); mean values after inoculation of 10 LD_{50} (i.p.) of the virus; ○ inoculated dose of the virus (42 LD_{50} (i.c.) corresponding to 10 LD_{50} (i.p.));

————, fitted model kinetics with $x_0 = 42$ LD_{50} (i.c.).

Predicted model kinetics x for different virus doses x_0:

— — —, 0.5 LD_{50} (i.p.); . . . . . , 1 LD_{50} (i.p.); —.—.—, 3 LD_{50} (i.p.); —..—.., 20 LD_{50} (i.p.).

Model parameters: $\mu = 1$ hr^{-1}, $x_m = 5 \times \times 10^8$ LD_{50} (i.c.), $\beta = 13$ LD_{50} (i.c.) $\times \times$ hr^{-1} (expectation of β/μ) for the fit and $\beta = 4.2$ LD_{50} (i.c.) $\times$ hr^{-1} (median of β/μ) for the prediction.

Table 3. Mortality 14 days p.i. of mice infected i.p. with different doses x_0 of Mengo virus and the fit of the distribution function $F_{\mu/\beta(x_0)}$ using eq. (9)

Dose of virus x_0		Number of mice	Mortality M (%)	Distribution function $F_{\beta/\mu}$ (%)
LD_{50}(i.p.)	LD_{50}(i.c.)			
0.5	2.1	273	23.5	24.6
1[a]	4.2	200	45.0	49.1
1[a]	4.2	186	54.3	49.1
3	12.5	200	63.0	63.0
10	42.0	510	96.9	96.9
20	84.0	20	100.0	100.0

[a] Separate experiments

therefore, can be used for development of a mathematical model. Beginning already 12 hr after i.p. infection with Mengo virus, the virus content in the brain was significantly greater then in other organs (Veckenstedt, 1974). For the maximum virus content in various organs this is shown in Table 2. Thus, virus content of the whole body was approximately equal to that of the brain beginning 12 hr p. i. For the development of the mathematical model, therefore, virus content of the whole body was considered. This model variable was symbolized by x.

The mathematical model is a differential equation

$$\dot{x} = f(x)$$

where $\dot{x}$ is the first derivative of x by time t and f(x) is a function of the virus content x. The initial value of x, symbolized by $x_0 = x(0)$, is given by the inoculated virus dose. To define the function f(x) the virus multiplication is considered exponential for unlimited conditions.

$$\dot{x} = \mu x \tag{7}$$

is the differential equation which gives an exponential increase of virus content, where μ is the specific multiplication rate. In contrast to eq. (7), virus multiplication is limited under natural conditions. Maximum value of $x_m = 5 \times 10^8$ LD_{50} (i.c.) was found in mice (Table 2). Therefore, instead of the Malthusian law eq. (7) the so-called Verhulst-equation is used (Verhulst, 1838):

$$\dot{x} = \mu \left(1 - \frac{x}{x_m}\right) x$$

gives a logistic solution instead of the exponential one. It tends to x_m for all positive initial values x_0. However, one has to take into account the tolerance dose x_{crit}. For virus doses x_0 smaller than x_{crit} the virus content will

Table 4. Virus content in brains of mice 12 and 24 hr p.i.

Time t hr	Virus content x LD_{50} (i.c.)	Specific multiplication rate μ hr^{-1}
12	1.1×10^7	1.07
12	8.4×10^6	1.04
12	6.5×10^6	1.02
12	3.2×10^6	0.97
12	2.1×10^6	0.93
12	1.4×10^6	0.89
12	5.2×10^5	0.81
24	2.4×10^8	0.69
24	5.8×10^7	0.61
24	2.7×10^7	0.57
24	2.2×10^7	0.56
24	6.3×10^6	0.51
24	4.5×10^5	0.40
24	3.1×10^5	0.38
24	1.1×10^5	0.34
24	1.1×10^4	0.24
24	6.2×10^3	0.22

Mengo virus inoculation dose of 10 LD_{50} (i.p.) (Veckenstedt and Pusztai, 1981) and the corresponding parameters μ as the results of model fit using eq. (*1*) and
$x_0 = 42$ LD_{50} (i.c.), $x_m = 5 \times 10^8$ LD_{50} (i.c.)
$\beta/\mu = 11$ LD_{50} (i.c.)

be markedly reduced due to the host defence. Introducing a parameter β that quantifies the defence system and is considered to be constant, one obtaines the dynamic model of virus multiplication in the host:

$$\dot{x} = \mu \left(1 - \frac{x}{x_m}\right) x - \beta \,. \qquad (8)$$

The model eq. (*8*) contains the exponential virus multiplication, its limitation and the host defence, defined by the specific multiplication rate μ, the maximum virus content x_m and the virus reduction rate β, respectively. Note, that eq. (*8*) and its so ution are valid only for positive x, i.e. for $x = 0$ the parameter β must be set equal zero. Then the solution converges to the maximum value if the initial value x_0 was overcritical ($x_0 > x_{crit} \approx \frac{\beta}{u}$), whereas the solution tends to zero if x_0 was undercritical ($x_0 < x_{crit}$). For $x_0 = x_{crit}$ the solution is a constant: $x(t) = x_{crit}$ for all t. Thus, the dynamic model has three stationary states: one unstable, the critical state x_{crit}, and two stable, namely the zero- and maximum states, which will correlate to survival or lethal outcome of infection, respectively.

For consistency with experimental findings a stochastic approach to the mathematical model must be applied, as the individual course of the virus

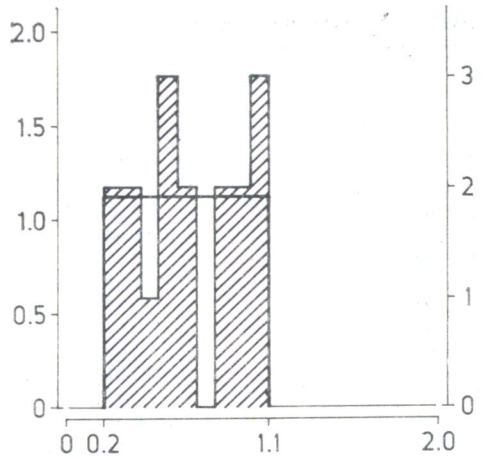

Fig. 2.
Distribution of model parameter μ (specific multiplication rate)
Dashed area: frequency according to Table 4; experimental data from Veckenstedt and Pusztai, (1981);
——, empirical density function f_μ according to eq. (*10*).
Abscissa: specific multiplication rate (hr^{-1}); left ordinate: empirical density function (hr); right ordinate frequency.

multiplication in the host differs from mouse to mouse. It is assumed that the variability is due to both conditions of virus multiplication and state of host defence. Therefore, the two density functions f_μ and $f_{\beta/\mu}$ are introduced for the specific multiplication rate μ and for the tolerance dose $\frac{\beta}{\mu}$ which are considered as random parameters. To quantify these density functions they are approximated by piecewise constant ones.

Model fit to experimental data

The condition for survival or lethal outcome of infection is defined by $\frac{\beta}{\mu} > x_0$ and $\frac{\beta}{\mu} < x_0$, respectively. Thus, the distribution function $F_{\beta/\mu}(x_0)$ defined by eq. (*4*) can be estimated by the mortality M at day 14 p.i. for different doses x_0 of Mengo virus as shown in Table 3. The corresponding density function $f_{\beta/\mu}$ can be approximated by the piecewise constant function:

$$f_{\beta/\mu}(x_0) = \begin{cases} 0.117 & [LD_{50}(i.c.)]^{-1} \text{ for } 0 \quad LD_{50}(i.c.) < x_0 < 4.6\ LD_{50}(i.c.) \\ 0.0115 & [LD_{50}(i.c.)]^{-1} \text{ for } 4.6\ LD_{50}(i.c.) < x_0 < 45\ LD_{50}(i.c.) \\ 0 & [LD_{50}(i.c.)]^{-1} \text{ else.} \end{cases} \quad (9)$$

The estimate of expectation $E(\frac{\beta}{\mu})$ as calculated by eq. (*9*) is 13 LD_{50} (i.c.). This value for $\frac{\beta}{\mu}$ is used for the fit of model kinetics $x(t; x_0, x_m, \frac{\beta}{\mu}, \mu)$ as calculated by eq. (*1*). For the fit experimental data of virus content in the brain for different periods p.i. with $x_0 = 10$ LD_{50} (i.p.) are used (cf. Fig. 1). In doing so, for x_m the estimate 5×10^8 LD_{50} (i.c.) and for μ the estimate 1 hr^{-1} have been found. The experimental data (Fig. 1) represent arithmetical means (n = 4). Therefore, the estimated μ-value represents an upper value of the randomly distributed parameter μ. The distribution function F_μ for

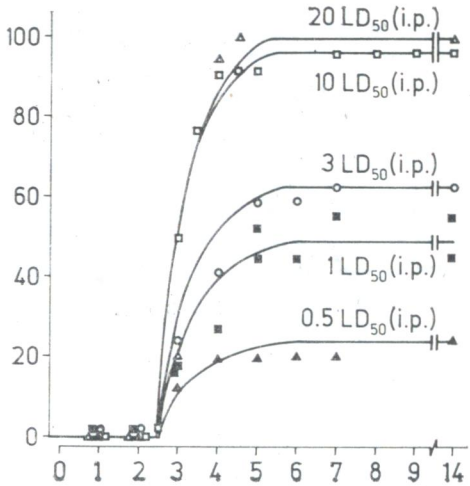

Fig. 3.
Mortality M(t, x_0) after inoculation of different doses x_0 of Mengo virus to mice ▲, ■, ○, □, △, experimental data; for number of mice see Table 3;
——, fitted model kinetics according to eqs. (*8*) — (*11*).
Abscissa: time post-infection (days); ordinate: mortality rate (%).

the parameter μ is estimated by eq. (*5*) using 17 not averaged, individual data of virus content x found at 12 and 24 hr (Table 4). According to Table 4, the empirical distribution of the random parameter μ is shown in Fig. 2. It can be approximated by an uniform distribution function:

$$f_\mu(u') = \begin{cases} 1.1 \text{ hr for } 0.2 \text{ hr}^{-1} < \mu' < 1.1 \text{ hr}^{-1} \\ 0 \quad \text{hr else.} \end{cases} \qquad (10)$$

The μ-values for t = 24 hr have been found to be smaller than for t = 12 hr. This significant* finding may be interpreted by increasing host defence, such as IFN and natural killer (NK) cell activity (Stanton and Baron, 1984; Hassin *et al.*, 1985). For the sake of simplicity of the modeling this was neglected.

Application of the model

The model presented will be applied for elucidation of the kinetics of mortality of mice that were infected with different doses of Mengo virus. Therefore, a relation between the kinetics of virus content in mice x(t) and the survival time t_s must be introduced. The widely accepted understanding that animals die when the virus content in the main target organ has reached a critical value C', found to be as high as 10^8 TCD_{50} for echovirus 9 in newborn mice (Eggers and Sabin, 1959), can be formulated by

$$x(t_s) = C' .$$

For the present case, such a criterion must be rejected: The maximum virus titre in the main target organ of the infection, the brain, was reached already 24 hr after virus inoculation but the animals did no die before 60 hr. Hence,

* Mann-Whitney-test with $\alpha = 0.01$

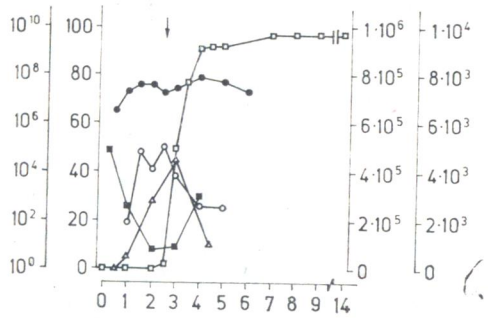

Fig. 4.
Experimental data found after inoculation of 10 LD_{50} (i.p.) of Mengo virus to mice
□, mortality as shown in Fig. 3;
●, virus concentration in the brain
○, virus concentration in the blood
↓ (Veckenstedt, 1974);
△, IFN concentration in the serum;
■, number of peripheral lymphocytes (Zschiesche and Veckenstedt, 1979);
↓, first cases of death.
Abscissa: days post-infection; ordinates: in the left — virus concentration (LD_{50} i.c./0.03 g), mortality (%); in the right: number of lymphocytes per ml, IFN concentration in IU per ml.

not the virus multiplication itself but its sequels account for death. This sequence can be formulated in the simplest manner by the differential equation

$$\dot{y} = -x$$

that defines the survival time t_s by boundary conditions

$$y(0) = C\,,\ y(t_s) = 0\,.$$

The formulation is equivalent to an integral criterion: animals die when the time integral of x(t), the so-called AUC (*a*rea *u*nder the *c*urve), reaches a critical value C,

$$AUC = R(t_s\,;\, x_0,\, x_m,\, \frac{\beta}{\mu},\, \mu) = \int_0^{t_s} x(t)\,dt = C\,. \qquad (11)$$

It is worth mentioning that in pharmacokinetics the AUC is used to quantify the potential efficacy of the regime of drug administration (Mellett, 1975). The dynamic model, eqs. (*8*)—(*10*), along with the hypothesis on the survival time t_s, formulated by eq. (*11*), is fitted to the experimental data of mortality $M/t, x_0)$ shown in Fig. 3. When doing so, C was found to be as high as $2.2 \times \times 10^{10}$ LD_{50} (i.c.) × hr. Model kinetics and experimentally found kinetics as well showed that the kinetics of mortality; $M(t, x_0)$ were delayed and limited in time: The animals died 2.5 to 7 days p.i. (Fig. 3).

To find alternative, more complex hypotheses on the relation between virus multiplication and survival time, other virus-dependent state variables were considered. Fig. 4 shows that mice did not die before day 2.5 p.i., when both the virus and the IFN concentrations in the blood reached maximum values whereas the lymphocyte number was minimal. If any of these three findings would account for death, then the model should involve equations for virus in the blood as well as for IFN, lymphocytes or other defence factors. Considering IFN as a virus-induced product and certain lymphocytes

as a substrate for virus multiplication, the model of Guthke and Knorre (1980) would be applicable. However, the experimental data presently available are not sufficient to fit such a model.

Discussion

A mathematical model of pathogenesis of murine Mengo virus infection has been developed using experimental data. An one-compartment model was assumed, because already since 12 hr after i.p. infection the virus content in the brain was found to be significantly greater than in the other organs. The kinetics of this model proved to be bistable. Contents of Mengo virus below a critical value $\frac{\beta}{\mu}$, differing strikingly from mouse to mouse, vanish with time; in such cases animals survive. Virus amounts administered above the critical value increase up to a maximum; as a consequence, the outcome of infection is lethal.

To formulate these relations between virus dose and outcome of infection, the understanding of virus multiplication and host defence is sufficient. This knowledge could be important for prophylactic antiviral treatment. However, for design of an antiviral therapy the crucial process that accounts for death, i.e. the process that is responsible for the survival time, has to be quantified and controlled. Therefore, the application of the mathematical model presented was focused on that point. It has been postulated and confirmed by a good model fit that the survival time can be defined by the AUC--criterion eq. (*11*). This criterion could be found only because the specific multiplication rate μ was extremly high for the Mengo virus strain used (about 1 hr^{-1} corresponding a doubling time of 42 minutes). Thus, the virus multiplication was limited before reaching the critical AUC-value C. The specific multiplication rates μ of echovirus 9 and of encephalomyocarditis (EMC) virus strain used by other authors (Eggers and Sabin, 1959; Heremans *et al.*, 1980) were smaller and, therefore, the critical AUC-value C was reached before the virus multiplication is limited and the AUC-criterion could not be detected. Nevertheless, even these cases can be interpreted in this way, indicating that the AUC-criterion may generally be accepted.

Probably, the AUC-criterion means that defence mechanisms are continuously impaired in the presence of high amounts of the virus. The earliest host defence mechanisms found for Mengo virus are IFN and NK cells (Stanton and Baron, 1984, Hassin *et al.*, 1985). A close correlation between the concentration of serum IFN during the early course of infection and the survival of EMC virus-infected mice was previously demonstrated (Gresser *et al.*, 1976; Pozzetto and Gresser, 1985). However, it is well documented that during progressed stages of infection high levels of serum IFN are not sufficient for survival as animals died even at peak IFN titres (cf. Fig. 4 as well as Murphy and Glasgow, 1968; Gresser *et al.*, 1968; Olsen *et al.*, 1976; Heremans *et al.*, 1980; Baron *et al.*, 1985; Billiau, 1985). Probably, the presence of high amounts of virus points to diminution of antiviral effectiveness of

IFN (Stanton and Baton, 1984). The assumed wane of antiviral effect of IFN may be due to autoimmunosuppressive events such as (a) damage of the thymus as early as 2 days p.i. (Güttner *et al.*, 1982) resulting in the failure of production of a thymic factor found to enhance the protective effect of IFN in Mengo virus-infected mice (Klein *et al.*, 1984), b) loss of active macrophages that were found to be necessary for antiviral activity of IFN in EMC virus-infected mice (Stebbing *et al.*, 1978), (c) decrease of the number of peripheral lymphocytes (cf. Fig. 4), (d) production of inhibitors of IFN action which were found in Mengo virus-infected mice (Campbell, 1976), or/and (e) down regulation of IFN receptors (Zoon and Arnheiter, 1984).

All these events are caused or enhanced by high amounts of virus. Consequently, the AUC-criterion formulated by eq. (*11*) is consistent with these experimental findings.

Whatever the reason for the suggested wane of antiviral activity of IFN in the presence of high amounts of virus, the model approach presented offers the chance of providing insight into the crucial factors that affect the course of infection. Particularly, the dynamic model of virus multiplication eq. (*8*) and the introduced AUC-criterion eq. (*11*), defining the relation between the virus multiplication kinetics and the survival time, allow an elucidation of mortality kinetic data in the pathogenesis of viral infections.

As the assumed loss of antiviral activity of IFN in the presence of virus accounts for death, this wane should be considered a potential target of antiviral therapy. Hence, model aided analysis will be a helpful tool for design and evaluation of strategies in antiviral therapy.

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