Pathogenesis of Scrapie (Strain 263K) in Hamsters Infected Intracerebrally, Intraperitoneally or Intracocularly

By RICHARD H. KIMBERLIN* AND CAROL A. WALKER

AFRC & MRC Neuropathogenesis Unit, West Mains Road, Edinburgh EH9 3JF and 1AFRC Institute for Research on Animal Diseases, Compton, Newbury RG16 0NN, U.K.

(Accepted 14 October 1985)

SUMMARY

After intracerebral (i.c.) infection of hamsters, the 263K strain of scrapie replicated at a nearly constant exponential rate until clinical disease developed when titres in brain averaged 9.8 log_{10} LD_{50} i.c. units/g. After intraperitoneal infection, scrapie replication was first detected in spleen, then in thoracic spinal cord and finally in lumbar cord and brain. This pattern suggests that invasion of the central nervous system occurs by spread of infection along certain visceral autonomic nerves. Infectivity was detected in the thoracic cord only 3 to 4 weeks after infection (incubation period 16 weeks) indicating the exceptional neuroinvasiveness of this scrapie model. This observation and the failure of splenectomy to lengthen incubation period raises the possibility of direct infection of nerve tissue in the peritoneum and transport to the thoracic cord with minimal prior replication of scrapie agent extraneurally. After intraocular infection of the right eye, replication (or accumulation) of scrapie was detected in the right optic nerve and left superior colliculus, then in the right superior colliculus and finally in the left optic nerve and medulla. This pattern shows that scrapie infection can spread along nerves, possibly by intra-axonal transport. The duration of agent replication in brain (between detectable onset of replication and clinical disease) was shortest after intraperitoneal infection (51 to 58 days), longer after intracerebral infection (81 to 88 days) and longest after intraocular infection (>121 days). These differences may reflect the relative efficiency of the neural pathways by which infectivity spreads from different sites of entry in the brain to the postulated ‘clinical target areas’.

INTRODUCTION

Present understanding of scrapie pathogenesis is based on a variety of murine models which differ mainly in the strain of scrapie and the Sinc genotype of the mouse [Sinc being a gene that controls scrapie incubation period (Dickinson & Fraser, 1979)]. A considerable body of evidence indicates that the slowness of scrapie is not due to host defences but is predetermined by mainly genetic factors in agent and host which control the overall dynamics of scrapie replication and produce predictable incubation periods that are characteristic for each model (Dickinson & Outram, 1979).

Because the target system for clinical scrapie to occur is the central nervous system (CNS), the intracerebral route of infection generally gives much shorter incubation periods that peripheral routes. With the latter, agent replication in certain lymphoid tissues (e.g. spleen and lymph nodes) seems to be a necessary prelude to invasion of the CNS (Kimberlin, 1979) based on the models of mouse scrapie studied.

Neuroinvasion of 139A scrapie in peripherally injected CW mice has been investigated by measuring (i) the onset of agent replication in extraneural tissues and in dissected areas of brain and spinal cord (Kimberlin & Walker, 1979, 1980, 1982) and (ii) the sequential development of vacuolar lesions in parts of the CNS (Cole & Kimberlin, 1985). The data suggest that infection spreads from visceral sites of replication along sympathetic nerves to the mid-thoracic cord and
tence to the rest of the CNS (Kimberlin & Walker, 1982) and to other peripheral nerves (Kimberlin et al., 1983a, b). Direct evidence that infection can enter the CNS via peripheral nerves has come from studies of intraneural injection of 139A scrapie in sciatic nerves (Kimberlin et al., 1983b) and of intraocular injection using several mouse scrapie models (Fraser, 1982; Fraser & Dickinson, 1985). The intraocular experiments also strongly suggest that scrapie can be transported within axons.

The present work investigates a different scrapie model, strain 263K in hamsters, which is widely used in scrapie research because of the very high infectivity titres produced in clinical brain (about \(10^{10}\) \(LD_{50}/g\)) and the exceptionally short incubation times (Kimberlin & Walker, 1977). Even after intraperitoneal infection, incubation periods are remarkably short. This implies a high degree of neuroinvasiveness which is in marked contrast to the situation in some other scrapie models; for example, the 87V strain persists in the spleens of IM mice for over a year before any infection can be detected in the CNS (Collis & Kimberlin, 1985; Bruce, 1985).

**METHODS**

**Infection of animals.** Outbred, female golden hamsters (from a colony at Compton and from a local supplier) were injected as adults with the 263K strain of scrapie (see Kimberlin & Walker, 1977, 1978). Inocula were prepared from the brains of clinically affected hamsters and stored at \(-20^\circ\)C as intact tissue or as \(10\%\) (w/v) homogenates of whole tissue in sterile, physiological saline. The 4th to 12th serial intracerebral passage of 263K in hamsters was used, either uncloned or cloned by five consecutive passages at dilutions of \(10^{-9}\) or \(10^{-10}\). Animals were injected with \(1\%\) (w/v) or less concentrated brain homogenates diluted in saline or, in the case of intragastric (i.g.) infection, distilled water. Intracerebral (i.c.) and intraperitoneal (i.p.) injections of 50 \(\mu l\) or 200 \(\mu l\) of inocula, respectively, were made using 26-gauge needles and light anaesthesia with ether. A long round-ended needle was used for the i.g. administration of 1 ml of inoculum to hamsters which had been deprived of food and water the night before. Intraocular (i.o.) injections of 2 \(\mu l\) of inoculum were made using a Hamilton syringe with a 30-gauge needle inserted dorso-ventrally behind the lens; the animals were anaesthetized with halothane. Adults were splenectomized or sham-operated and injected i.p. 2 weeks later. All injected hamsters were kept singly in coded cages and observed for clinical signs of scrapie for up to 300 days. Incubation periods were calculated to the time of the first positive clinical score (Kimberlin & Walker, 1977).

**Dissection of tissues.** Great care was taken in the removal of tissues to minimize cross-contamination between samples with scrapie agent: separate sets of dissection instruments were used to remove each tissue from each donor group of two or three hamsters (Kimberlin & Walker, 1979). Left and right superior colliculi and the medulla were dissected from coronal slices of brain using scalpel blades. Optic nerves were taken from each eye to within 2 mm of the optic chiasma. Thoracic cord was taken between the 5th and 11th thoracic vertebrae and lumbar cord was taken between the 1st and 5th lumbar vertebrae by expulsion under gentle pressure from syringes filled with saline (Kimberlin & Walker, 1979). Pools of tissue were weighed and homogenized in saline (using separate homogenizers) at a weight concentration of \(5\%, 1\%\) or \(0.5\%\), depending on the experiment.

**Assays of infectivity.** In one experiment (Fig. 2) infectivity was measured directly by titrating, i.c. in hamsters, tenfold dilutions of \(1\%\) homogenates in saline and calculating titres by the Karber (1931) method. In other experiments (Figs. 3 and 4) an indirect assay of infectivity in tissue was used which requires fewer animals than titration. Five \(\%\) (Fig. 3) and \(0.5\%\) (Fig. 4) tissue homogenates were injected i.c. into groups of recipient hamsters and incubation periods were measured. The assay is based on the inverse relationship between dose and incubation period which was originally described for this scrapie model by Kimberlin & Walker (1977) and subsequently by others (Prusiner et al., 1980, 1982). Fig. 1 shows a dose-incubation curve derived from the results of 34 experiments using clinical brains taken at the 4th to 12th serial passage of 263K in hamsters and injected i.c. The data include 26 titrations of infectivity in clinical scrapie brain which gave an average concentration (± S.E.M.) of 8.3 (±0.1) \(LD_{50}\) i.c. units/0.05 g of brain. This value was used to calculate the average number of \(LD_{50}\) i.c. units/0.05 ml of each dilution of brain (Fig. 1, right-hand ordinate). The seven arrows show the incubation periods corresponding to \(10^0\) to \(10^6 LD_{50}\) i.c. units and this is the derivation of the right-hand ordinates in Fig. 3 and 4. Fig. 1 shows that the average incubation period for 1 \(LD_{50}\) i.c. unit of infectivity in 0.05 ml of brain homogenates is 150 days (and a similar value is assumed for 1 \(LD_{50}\) i.c. unit of infectivity in homogenates of other tissues). The sensitivity of the assay method was about 40 \(LD_{50}\) i.c. units/100 mg of tissue using \(5\%\) (w/v) homogenates and about 400 \(LD_{50}\) i.c. units/100 mg of tissue using \(0.5\%\) (w/v) homogenates.

**RESULTS**

**Intracerebral infection**

Hamsters were injected i.c. with \(3.9 \log_{10} LD_{50}\) i.c. units of scrapie. After 7 days the concentration of infectivity in brain was \(2.3 \log_{10} LD_{50}\) i.c. units/0.05 g which represents a total
infectivity titre of 3.6 log_{10} units in a hamster brain weighing 950 to 1000 mg. How much of this value is due to the persistence of the original inoculum or to replication occurring before 7 days is not known because titres were not measured earlier. However, Fig. 2 shows that the agent replicated at an almost constant exponential rate between 7 days and 88 days when clinical disease developed. The minimum duration of replication in brain was therefore 81 days (i.e.
Fig. 3. Replication of cloned 263K scrapie (a) in spleen (■) and cervical lymph nodes (□) and (b) in thoracic spinal cord (○), lumbar spinal cord (●) and brain (▲) of hamsters infected i.p. with an estimated dose of 50 to 500 LD₅₀ i.p. units. The average incubation period of the donor animals was 114 ± 4 days (± S.E.M.). At weekly intervals, 5% (w/v) homogenates of pooled tissues from three hamsters were injected i.c. into groups of four recipient (assay) hamsters and the average incubation period was determined (left-hand ordinate). The right-hand ordinate shows the estimated titre based on the dose-incubation curve in Fig. 1.

88 - 7 days) and the concentration of infectivity increased 10⁶-fold in this period. At the clinical stage of scrapie, the average titre (± S.E.M.) of cloned 263K measured in ten experiments on individual brains or brain pools was 9.8 (± 0.1) log₁₀ LD₅₀ i.c. units/g.

Intraperitoneal infection

Hamsters were injected i.p. with between 50 and 500 LD₅₀ i.p. units of scrapie and the time of onset of agent replication was determined in five tissues. As expected, infectivity was detected first in spleen where replication of agent was evident after 7 days (Fig. 3a). Replication in cervical lymph nodes started later, at 28 to 35 days. After 49 days, infectivity in both extraneural tissues reached similar plateau concentrations.

In the CNS, agent replication was first detectable in thoracic cord at 28 days. This was 5 weeks before replication was detected in both lumbar cord and brain at 63 days (Fig. 3b). In contrast to spleen and lymph nodes, replication continued to occur in all three areas of the CNS for the remaining period studied and much higher concentrations of infectivity were reached. It is probable that replication in brain continued beyond the period of study to the end of incubation because, at the clinical stage, the concentration of infectivity after i.p. infection is the same as in the brains of hamsters that were infected i.c. (Kimberlin & Walker, 1977).

In the present experiment, the incubation period of the i.p. infected hamsters was 114 days. Since infectivity was detected in the brain at 63 days but not at 56 days the minimum duration of
Pathogenesis of scrapie in hamsters

Table 1. Effect of splenectomy and of different routes of injection on incubation period

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>Treatment of hamsters</th>
<th>Route of injection</th>
<th>Vol. of inoculum (μl)*</th>
<th>No. of hamsters</th>
<th>Incubation period (days ± S.E.M.)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sham-operated</td>
<td>i.p.</td>
<td>200</td>
<td>9</td>
<td>127 ± 2</td>
</tr>
<tr>
<td>1</td>
<td>Splenectomized</td>
<td>i.p.</td>
<td>200</td>
<td>11</td>
<td>122 ± 5</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
<td>i.g.</td>
<td>1000</td>
<td>10</td>
<td>125 ± 12</td>
</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>i.o. (R)‡</td>
<td>2</td>
<td>14</td>
<td>132 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>i.o. (R)</td>
<td>2</td>
<td>8</td>
<td>138 ± 7</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>i.o. (L)‡</td>
<td>2</td>
<td>5</td>
<td>183 ± 8§</td>
</tr>
</tbody>
</table>

* All hamsters were injected with 1% (w/v) homogenates of scrapie brain containing cloned 263K, except in experiment 5 where the incubation period (§) shows that a more dilute inoculum was used by mistake.
† All injected hamsters developed scrapie.
‡ Right (R) or left (L) eyes injected.

agent replication in the brain was 51 days (i.e. 114 – 63 days) and the maximum was 58 days. These values are considerably shorter than the minimum (81 days) and maximum (88 days) values found for i.c. injected hamsters.

The data in Fig. 3 suggest a sequential spread of infection from spleen to thoracic cord and thence to the rest of the CNS. This sequence points strongly to an initial invasion of the CNS by scrapie within certain visceral autonomic nerves. However, in confirmation of an earlier finding (Kimberlin & Walker, 1977), Table 1 shows that prior splenectomy of hamsters had no effect on the incubation period of 263K scrapie after i.p. injection. These findings suggest that spleen is not an obligatory source from which infection spreads to the thoracic spinal cord.

Intraocular infection

Table 1 shows that i.o. injection of either eye produced scrapie in hamsters with reproducible incubation periods. This enabled us to seek other evidence for the neural spread of scrapie by investigating agent replication in optic nerve (distal to the optic chiasma) and brain after unilateral i.o. infection. In hamsters (Chalupa & Thompson, 1980; Pickard & Silverman, 1981) as in many other vertebrates, the majority of retinal ganglion cells in the eye project directly to the contralateral superior colliculus. Intra-axonal transport of scrapie would be the most likely explanation if infectivity were detected contralaterally before it occurred ipsilaterally.

Hamsters were injected in the right eye. Agent replication was first detected in the right optic nerve and in the left superior colliculus after 62 days (there were insufficient sampling times to establish a real difference between these two curves; Fig. 4). Replication in the left superior colliculus clearly preceded that in the right superior colliculus which in turn preceded replication in the left optic nerve. The latter started at 82 days which was when replication started in the medulla (data not shown). The medulla was selected because it is remote from the optic system but would have been involved in any early dissemination of infectivity entering the CNS from the spleen etc. via the spinal cord. In fact no infectivity was detected in spleen at 21 to 62 days and at 82 days infectivity in the spleen must have been very low because only 60% of the assay hamsters developed scrapie. This finding suggests that very little of the original inoculum escaped from the site of injection to be taken up by the spleen. Therefore, the data in Fig. 4 are entirely consistent with intra-axonal spread of infection to the brain from the injected eye.

Scrapie replication in brain was first detected (in the left superior colliculus) between 34 and 62 days after i.o. injection. Since the incubation period averaged 183 days, the duration of agent replication in brain was in the region of 121 to 149 days. Even the lower value is much greater than the corresponding estimates for hamsters infected i.c. (81 to 88 days) or i.p. (51 to 58 days) and, in fact, a value of 121 days is likely to be an underestimate because the infectivity assays in the i.o. experiment were performed with 0.5% tissue homogenates, compared to the 5% homogenates used in the i.p. experiment.
Fig. 4. Replication (or accumulation) of cloned 263K scrapie in right optic nerve (○), left superior colliculus (■), right superior colliculus (□) and left optic nerve (●) of hamster injected in the right eye with 2 μl of 1% scrapie homogenate. The average incubation period in the donor hamsters was 183 ± 8 days (+ s.e.m.) (see Table 1). After 21, 34, 62, 82, 103 and 146 days, 0.5% (w/v) homogenates of pooled tissues from three hamsters were injected i.e. into groups of five recipient (assay) hamsters and the average incubation period was determined (left-hand ordinate). The right-hand ordinate shows the estimated titre based on the dose-incubation curve in Fig. 1.

DISCUSSION

Studies of short incubation models of mouse scrapie have shown that infectivity titres in brain increase progressively, starting soon after i.c. infection, but the rate of increase, expressed exponentially, tends to slow down in the later stages of incubation (Haig & Clarke, 1965; Dickinson et al., 1969; Kimberlin, 1976 and unpublished). This situation contrasts with the nearly constant exponential rate of replication of 263K scrapie in hamster brain shown in Fig. 2 and reported by Moreau-Dubois et al. (1982). In addition, the overall rate of replication of 263K scrapie in hamsters seems to be higher than with other scrapie models but careful comparisons have not been made to establish this point firmly. However, it is likely that both factors contribute to the exceptionally short incubation periods of 263K in hamsters and to the very high infectivity titres in clinical brain which average 9.8 log₁₀ LD₅₀ i.c. units/g. This is eight times higher than the mean (+ s.e.m.) of 8.9 ± 0.1 log₁₀ LD₅₀ i.c. units/g brain (n = 9) obtained under identical titration conditions for 139A scrapie in CW mice (R. H. Kimberlin & C. A. Walker, unpublished), one of the quickest models of mouse scrapie. It would be interesting to investigate titres in clinical brain in models of scrapie with much longer incubation periods.

Intraperitoneal infection of hamsters produced results identical, in many respects, to what has been shown with 139A scrapie in CW mice. For example, agent replication in spleen started soon after infection (Kimberlin & Walker, 1979), and replication in cervical lymph nodes started later (R. H. Kimberlin & C. A. Walker, unpublished). In both tissues, infectivity reached plateau concentrations which were lower than the eventual concentrations of infectivity in the CNS (Kimberlin & Walker, 1979; Kimberlin et al., 1983b).

In the CNS of hamsters, scrapie replication was detected in the thoracic spinal cord 5 weeks before it occurred in lumbar cord or brain (Fig. 3). This interval was longer than the average of 3 weeks seen in CW mice infected i.p. (Kimberlin & Walker, 1979, 1983). It is suggested that the rate of spread of infection in the CNS, estimated in the mouse studies to be 0.5 to 1.0 mm/day (Kimberlin & Walker, 1982), is similar for both scrapie models and that the greater interval in hamsters is due to their spinal cords being longer than those of mice.
The earlier onset of agent replication in hamster thoracic cord, compared to brain and lumbar cord, is evidence that scrapie infection invades the CNS via autonomic (probably sympathetic) fibres innervating spleen and other visceral sites of replication. Haematogenous spread of infection to the CNS is not excluded by the data but it does not easily explain why scrapie replication in the CNS starts in the thoracic cord or why, in the mouse studies, the onset of replication is so predictable with all four peripheral routes of infection tested (Kimberlin & Walker, 1979, 1983).

A primary viraemia has been shown to occur with 139A scrapie in CW mice which can account for the initial spread of infection to spleen etc., but it was not detectable later (Millson et al., 1979). Recently, more sensitive methods have been used to show a viraemic phase in hamsters which lasted for at least 40 days after the i.p. injection of 263K scrapie (Diringer, 1984). The same methods revealed that low levels of scrapie infectivity were present in hamster brain 5 days after infection and it is likely that scrapie spread there via the blood supply. However, the concentration of infectivity in brain remained at the same low level for the rest of the 40 day observation period, a remarkable situation given that 263K injected into the brain would have increased by 100- to 1000-fold in the same period of time (Fig. 2). It seems almost certain that the cells in brain which became infected haematogenously could not support the replication of 263K or be a source of infection to other cells in the brain. Diringer's interesting study (Diringer, 1984) strengthens our view that neural spread of infection to the thoracic cord is the main route by which infection eventually reaches the brain.

One main difference between our results in mice and hamsters lies in the timing of events. In hamsters, the replication of 263K in thoracic cord started about 3 weeks before infectivity reached a plateau in spleen (Fig. 3) whereas in mice, the replication of 139A started 5 to 6 weeks afterwards (Kimberlin & Walker, 1979). This difference is presumably a reflection of the high neuroinvasiveness of 263K in hamsters which results in shorter i.p. incubation periods than with any other scrapie model, despite the fact that the i.p. route of infection is exceptionally inefficient; about 40000 LD_{50} i.c. units of 263K are required to give 1 LD_{50} unit by the i.p. route in hamsters (Kimberlin & Walker, 1977) compared to an average of 430 LD_{50} i.c. units of 139A in CW mice (Kimberlin & Walker, 1983).

The other main difference between our results in mice and hamsters concerns the effects of splenectomy on scrapie. Splenectomy of CW mice before i.p. infection with 139A prolongs the incubation period (Clarke & Haig, 1971). This is good evidence that replication in spleen directly contributes to the subsequent invasion of the CNS although this has yet to be tested. The failure of splenectomy to alter the i.p. incubation period of 263K in hamsters (Table 1) was previously attributed (Kimberlin & Walker, 1977) to the inefficiency of the i.p. route reducing the effective dose below the point where the absence of a spleen is a limiting factor, i.e. other lymphoid organs could functionally replace spleen. Results from the present study raise the possibility of an alternative explanation. Fig. 3(b) shows that replication was detectable in thoracic cord between 21 and 28 days after infection. These assays were performed with 5% tissue homogenates and replication might have been detectable even earlier had more concentrated homogenates been used. It is therefore conceivable that infection of the thoracic cord requires little or no preceding extraneural replication and occurs as soon as 263K has been transported there from an initial site of infection in the peritoneum. Possible sites of infection include pre-vertebral ganglia some of which are permeable to horseradish peroxidase in some species (Al-Khafazi et al., 1983) or even nerve endings in the peritoneal wall. However, both explanations assume that these routes are more accessible to scrapie in hamsters than in mice. If direct infection of peripheral nerve tissue can occur then it might render 263K in hamsters unresponsive to the suppressive effects of dextran sulphate which is believed to act on the extraneural stages of pathogenesis (Ehlers et al., 1984; Ehlers & Diringer, 1984). Furthermore, the high neuroinvasiveness of 263K scrapie in hamsters suggests that scarification at sites containing a high density of nerve terminals might be an efficient route of infection.

Two important findings were made using the i.o. route. First, scrapie infection can spread within nerves. This supports the conclusions drawn from studies of several models of mouse scrapie (Fraser, 1982; Kimberlin et al., 1983b; Fraser & Dickinson, 1985) and also of hamster
scrapie (Buyukmihci et al., 1983). Secondly, it is likely that scrapie can be transported intraaxonally as has been indicated in mice, both indirectly by the contralateral targeting of early vacuolar lesions (Fraser, 1982) and directly by infectivity studies (Fraser & Dickinson, 1985).

When hamsters were injected i.o. with 263K scrapie, the apparent spread of infectivity was in the expected sequence, from eye to optic nerve and to the superior colliculus in brain (Fig. 4 and Buyukmihci et al., 1983). However, studies of ME7 in C3H mice (Fraser & Dickinson, 1985) showed that replication in the ipsilateral optic nerve occurred after replication had started in the contralateral superior colliculus. This discrepancy raises an interesting possibility: replication of scrapie in neurons after i.o. infection may be more active in the cell body than in the axon with the result that transport occurs undetected by present methods until the infectivity reaches axon terminals, and either replicates there or in the cell bodies of the next neurons to become infected. The apparent replication in axons could be due entirely to the accumulation of infectivity transported centrifugally or even centripetally. On this hypothesis, the rapid replication rate of 263K scrapie in hamsters would lead to the centrifugal accumulation of infectivity in the optic nerve before replication becomes detectable in the contralateral colliculus, but with ME7 in C3H mice, a slower scrapie model, the accumulation of infectivity in the optic nerve would occur afterwards.

Earlier studies of 139A scrapie in CW mice indicated that agent replicated faster in whole brain after infection by a peripheral route than after i.c. infection (Kimberlin & Walker, 1979). A comparison of Fig. 2 with Fig. 3(b) shows a similar difference between routes of infection with 263K in hamsters. The observed replication rate in whole brain would be the sum of at least three processes: the replication rate at each site in brain to which infection has spread, plus the rates of transport within infected cells (neurons) and of spread to other cells. The difference between routes implies that infectivity does not spread with equal efficiency to all parts of the brain. Compared to i.c. infection of anterior brain, it appears that agent entering from the spinal cord has better access to certain neural tracts along which it can spread rapidly and widely so that the overall rate of agent replication in brain is faster.

It has been postulated that the development of scrapie depends on infection spreading to and replicating in certain clinical target areas in the brain and that agent entering from the thoracic cord (after peripheral infection) is transported more directly to these target areas than agent injected i.c. (Kimberlin & Walker, 1983). This difference between routes is regarded in terms of the number of cells (neurons) forming the pathways between points of entry and the clinical target areas, and also in terms of the relative difficulty of infection spreading from one cell (neuron) to another. The concept is based on the repeated observation that the duration of 139A scrapie replication in mouse brain is always longer after i.c. infection than after infection by any of the non-neural, peripheral routes tested (Kimberlin & Walker, 1983). It is of great interest that the present study shows a similar difference in the duration of agent replication in brain after i.c. and i.p. infection in a different scrapie model. In addition, the duration of replication in hamster brain was even greater after i.o. infection than after i.c. infection. This observation strengthens the view (Kimberlin & Walker, 1983) that measurement of incubation period after stereotaxic infection in different parts of the brain could be used to suggest the location of the clinical target areas.

REFERENCES


Pathogenesis of scrapie in hamsters


(Received 9 July 1985)