regard documents on the Internet as too impermanent to play the essential role of being the fixed public record of science.

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Antiscrapie Drug Action

In their report "Porphyrin and phthalocyanine antiscrapie compounds" (25 Feb., p. 1503), Priola *et al.* present data showing that pthalocyanine tetrasulfonate (PcTS) and related compounds prolong scrapie incubation. They suggest that these compounds interact with host prion protein (PrP), or with the infectious agent, to directly reduce the accumulation of pathologic PrP and thereby slow the onset of disease. Although this is one possibility, their data could be explained by a drug effect on recipient cells that normally take up the infectious agent in brain homogenates.

First, there is an unusually large range of incubation times in the drug-treated group but not in the control groups (for example, a scatter of points between ~85 and 380 days as compared with ~75 to 95 days, respectively). The incubation time was measured as the time from scrapie infection until death, and in these experiments drug treatment began on the same day as infection. Additionally, if a drug interacts directly with the infectious agent, as it should have in the subsequent direct-mixing experiment in figure 3 of Priola *et al.*, more uniform incubation times would be expected than were found. In contrast, drug effects on heterogeneous peritoneal cells could have more variable outcomes.

Second, the colored PcTS was taken up by many peritoneal cells (detected visually by Priola *et al.*), and its effects were more profound as drug accumulation approached saturating levels (judged by the intense color of the peritoneal tissues). These findings also indicate cellular effects not necessarily confined to either agent or PrP interactions.

Third, the drugs were effective when given 14 or 28 days before infection. This again suggests an inhibitory effect on pretreated cells rather than a specific interaction with PrP or the infectious agent. Although it is tempting to study drug candidates for scrapie and Creutzfeldt-Jakob disease in terms of PrP conversion, many different drugs that affect macrophage function but have no obvious PrP interaction can significantly alter incubation times (*1,*

2). Macrophages can also incorporate complex mixtures containing the infectious agent and retain or sequester infectivity.

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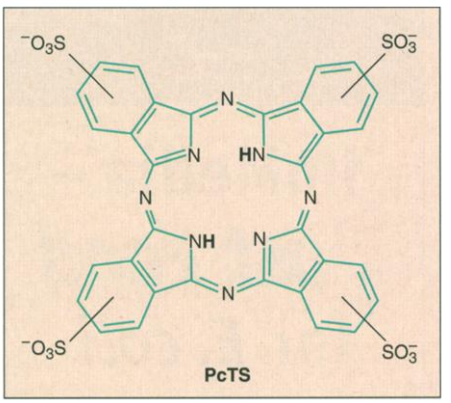
Response

In general, regardless of the mechanism whereby infectivity is lost, incubation periods become less uniform as the amount of infectivity approaches its end point. Therefore, we cannot differentiate the killing of agent by direct interaction with PcTS from other effects of PcTS. For example, expecting the direct mixing of PcTS with infectivity to produce a more uniform incubation time assumes that the sole effect of PcTS is to inactivate the agent. It does not take into account any additional effects of PcTS persistence on further agent replication, cell-mediated or not. The longer incubation period of PcTS-treated mice indicates that very little agent persists at this point and suggests nothing specific about the mechanism.

Mechanistically, we do know that PcTS and the other cyclic tetrapyrroles we tested that inhibited scrapie in vivo also prevented abnormal PrP formation in vitro (*1*). Furthermore, we have shown that there is a very good correlation between in vitro inhibition of abnormal PrP formation and inhibition of disease in vivo (*2*). Thus, although we have no evidence that PcTS has an effect at the cellular level, all of the evidence presently available provides firm support for the mechanism of action of PcTS proceeding via PrP interactions.

Although it is possible, as Manuelidis suggests, that PcTS and the other compounds we tested could affect cells such as macrophages that might take up infectivity, this is not necessarily a better explanation for our data. There is no direct evidence that macrophages play a major role in scrapie. Recent data have shown that agent replication is dependent on PrP-expressing follicular dendritic cells in the spleen (*3*) and not on PrP-expressing lymphocytes or myeloid cells such as macrophages. PcTS is present in the spleens of treated animals and could either be toxic to follicular dendritic cells or could interact with them via PrP to prevent agent uptake or inhibit abnormal PrP formation. This latter hypothesis is consistent with the mechanism of action of PcTS involving PrP interactions. However, further experiments are necessary before any conclusions can be drawn about the potential effect of PcTS on cells involved in scrapie pathogenesis.



PcTS was the most effective of three cyclic tetrapyrroles that inhibited scrapie.

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