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ABSTRACT

The respiration of uniformly labeled glucose-C^{14} by normal and virus infected mice was studied over an infection period of 10 days. The rate and extent of viral multiplication is without apparent effect on the rate and extent of glucose metabolism by the infected intact host.

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It is regularly observed that in a group of animals infected with mouse-adapted poliomyelitis virus, some mice, after a few days of infection, will manifest clinical symptoms while others will appear to be well. Yet, viral titrations of brains and spinal cords of paralytic animals and apparently healthy ones clearly demonstrate that inoculated mice are undergoing a well established infection irrespective of the time at which clinical disease or death may ensue.[1] It has been considered of interest to examine the role of the extent of altered metabolism induced in the infected host as a possible physiological explanation.[2] There might exist under conditions of infection, for example, altered degrees of oxidation and assimilation in the metabolic pathways of a given substrate. In the process of oxidative metabolism part of the foodstuff is oxidized completely to CO_2 while part is incorporated in the cells as such or in the form of its intermediate breakdown products;[3] the latter could vary widely depending on the mechanism of oxidation employed by the animal cells.[4] Perhaps, as a result of infection with virus, the degree of altered metabolism brought about in the host could be reflected in the temporal occurrence and gradation of clinical symptoms.

This paper describes an experiment which was designed to study the manner in which animals, normal and infected, handled a given substrate. The substrate employed was uniformly labeled glucose-C^{14}, and the outcome determined was respired $C^{14}O_2$.

MATERIALS AND METHODS

Webster strain white mice, 4 to 5 weeks of age, were inoculated intracerebrally with 0.03 cc. of a suspension containing 4 LD_{50} (50% lethal dose) of mouse-adapted MEF_1 (Type 2) poliomyelitis virus. On the same day,

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four uninfected mice were injected intraperitoneally with 0.1 cc. of a solution containing 1 mg. of uniformly labeled glucose-C^{14} with an activity of 6.6μc. per mg. They were then immediately placed in an apparatus designed to measure respiratory radioactivity excretion.[5] This apparatus consisted of a simple flow system carrying the air from a small glass animal cage through an ionization chamber. The potential of the chamber was amplified by a vibrating reed electrometer and charted on a continuous recording potentiometer. The $C^{14}O_2$ respired was measured for 7 hours and the resulting curves analyzed to give the percent of administered dose excreted as a function of time. Two days, 5 days, and 10 days following virus administration four infected mice were selected and similarly injected with carbon-14 labeled glucose and the respired $C^{14}O_2$ determined. At the same time four mice of a comparable period of infection and appearance were sacrificed and their brains and spinal cords harvested. These were then pooled, and the amount of virus in the material was determined by intracerebral injection of 0.03 cc. of a series of 10-fold dilutions in groups of eight mice. Titers are expressed as the LD_{50} calculated according to the method of Reed and Muench.[6]

RESULTS

The data obtained in this study are delineated in Figs. 1 and 2. Curves A, B and C represent mean values for the respiration of four mice, curve D of two mice, and curves E and F the respiration obtaining in each of two individual mice in their indicated states of paralysis. The LD_{50} values are those of the pooled brains and spinal cords of mice in the same period and appearance of infection. As can be noted from Fig. 1 the percent of the injected dose recovered as respired $C^{14}O_2$ over a 7-hour period was of the same order for controls, 2, 5 and 10 day-infected animals. It was only when the animal was in an advanced state of paralysis and approaching a moribund condition that a diminution of respiration was observed to take place. Likewise, the rate of excretion curves (Fig. 2) show little change until the 10th day of the disease. Then, in the animals showing an advanced state of paralysis, the peak excretion rate is depressed and occurs at a later time. This change is typical of the changes seen in such rate curves for starvation or advanced cancer states, and, as indicated above, is not unique to the virus infection.

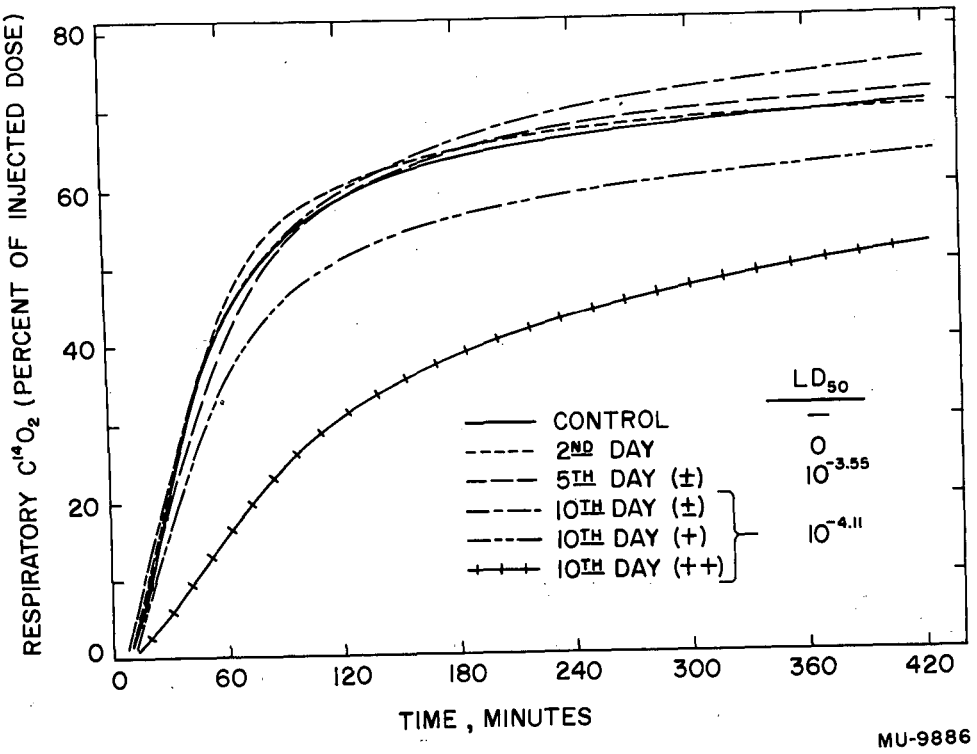

Fig. 1 Cumulative excretion of $C^{14}O_2$ in expired air over a period of 420 minutes following injection of uniformly labeled glucose-C^{14}. Legend. ±, animals commending to show signs of CNS infection, such as excessive irritability and some weakness in one or more limbs; +, animals paralyzed in one or more limbs, some difficulty in breathing but otherwise alert; ++, animals very sick and practically prostrate. See text for further details.

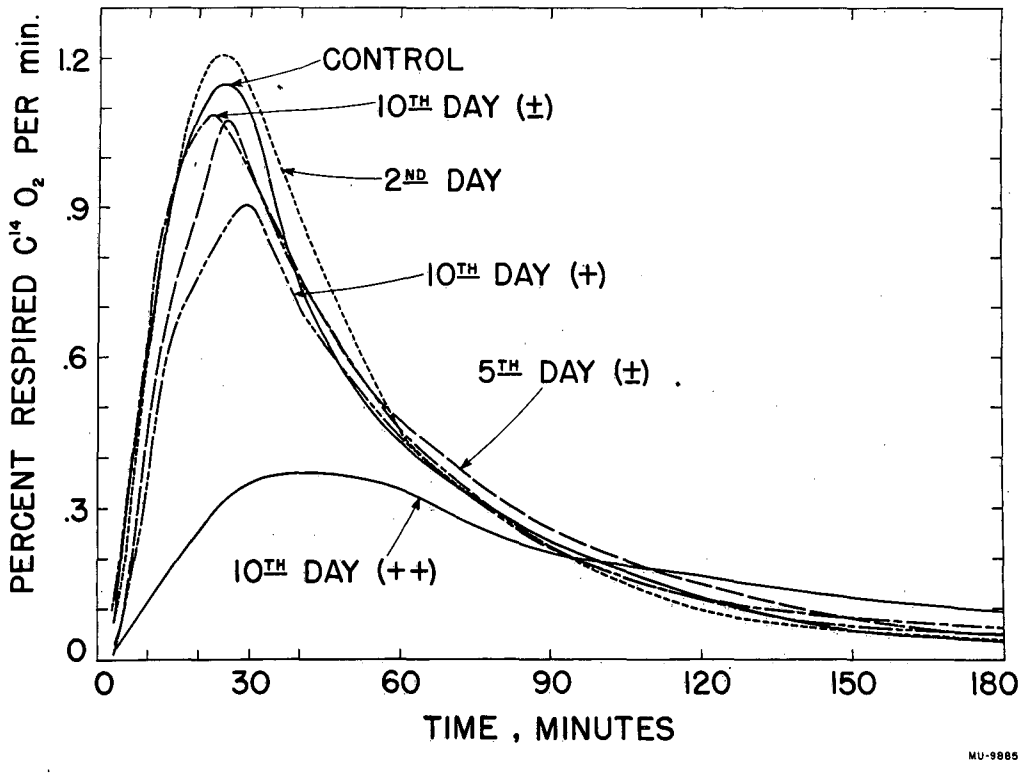

Fig. 2 Rate of excretion of $C^{14}O_2$ in expired air shown for a period of 180 minutes following injection of uniformly labeled glucose-C^{14}. Legend the same as in Fig. 1. See text for details.

DISCUSSION

The curtailed respiration of glucose under conditions of paralysis and morbidity cannot be ascribed uniquely to the effect of infection with the poliomyelitis virus, since such a diminution could be anticipated in similar physiological situations where impaired circulation or reduced metabolic rate might be brough about by a variety of debilitating factors. It would seem that the rate and extent of poliomyelitis multiplication, as indicated by the titers over a 10-day period, is without apparent effect on the rate and extent of substrate, specifically glucose, oxidation by the infected host.

Cohen and Anderson[7] working with the T2-Escherichia coli system found that infection of the bacterium by the bacteriophage and the subsequent replication of the latter did not alter the rate of cellular respiration. Similarly, Takahashi[8] found the respiration of normal and tobacco mosaic virus-infected Turkish tobacco leaves to be essentially the same, although the production of virus in the diseased host was considerable. The present experiments would indicate that in animal infections with poliomyelitis, just as in the case of plant and bacterial virus infections, the respiration of the host is unaffected, at least until morbidity and death ensue.

With as small an initial inoculum as 4 LD_{50} no virus was indicated in the central nervous system of infected mice up to 48 hours. Evidently the lag period of growth was much prolonged and/or the mouse titration technique employed was not sufficiently sensitive to detect the small number of viral particles present.

SUMMARY

The respiration of uniformly labeled glucose-C^{14} by normal mice and by mice infected with mouse-adapted MEF_1 poliomyelitis virus was studied over an infection period of 10 days. During this 10-day period of infection accompanied by viral multiplication, there were no significant differences observed in the oxidation of substrate by infected mice as compared to normal mice, except in instances of advanced paralysis and prostration. Such marked diminutions in respiration as occurred could likewise be anticipated under circumstances where the physiological processes of the animal were impaired, and thus could not be imputed uniquely to the presence and proliferation of poliomyelitis virus. It is concluded, on the basis of these findings, that the rate and extent of viral multiplication in poliomyelitis is without apparent effect on the rate and extend of glucose metabolism by the infected intact host.

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