ROTHWELL AND STOCK REPLY—We need not go beyond Alpert's first paragraph to see that the paradox in the control of energy intake revealed in our paper and further discussed below (see reply to Mrovosky) has been confused with the question of why tube-fed rats gain more weight than control rats on identical energy intakes.

Our paper was not intended to explain this effect of 'meal-feeding' on energy metabolism; we simply took advantage of this well known effect so as to induce excessive weight gains and observe the effect on residual voluntary intake. We were concerned with how intake is related to the regulation of energy balance whereas Alpert is concerned with mechanisms responsible for the greater efficiency of energy utilisation in tube-fed rats.

Although Alpert's theoretical considerations are not pertinent to the paradox discussed in our paper we would, nevertheless, like to make the following points.

First, differences in body energy gain in animals on identical metabolisable energy intakes must be due to differences in energy expenditure. Apart from the 'basal' contribution, expenditure can vary due to changes in activity and/or the efficiency of energetic transformations within the body (that is, diet-induced thermogenesis or the heat increment of feeding). Alpert assumes that the efficiency of energy utilisation within the body is constant and therefore ascribes differences in total energy expenditure entirely to changes in activity. He states that this is logical and mathematically consistent but ignores the fact that it is just as logical and mathematically correct to fix activity at a constant level and ascribe the changes in total energy expenditure to differences in the efficiency of utilisation.

Second, there is evidence that metabolic efficiency is greater in meal-fed animals (see ref. 1 for review). Activity may also be affected but observations have not revealed any noticeable differences. Furthermore, we have calculated the difference in activity that would be required to explain the greater energy retention of our tube-fed rats. Parkes[2] has determined the energy cost of walking in the rat to be 0.105 kJ per km per g body weight. Applying this value to the rats which were tube-fed 74% of control intake, we estimate that control rats would have to walk 2,000 m per day more than tube-fed rats to explain the differences in energy retention. Note that these were adult rats housed in pairs in cages with floor dimensions of 40 cm × 30 cm, so that it is extremely unlikely, if not physically impossible, for two rats to each walk 2 km per day in these conditions—and even this assumes that tube-fed rats were completely inactive.

In conclusion, we are not convinced by Alpert's deductions concerning the cause of the greater energy retention in our tube-fed rats and he has not attempted to explain why these rats failed to depress voluntary intake to compensate for their excessive weight gain.

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Rothwell and Stock's paradox and multiple controls of feeding

ROTHWELL AND STOCK[1] reported recently that rats tube-fed a balanced diet intragastrically ingest overall (the tubed plus the voluntary intake) the same amount of energy as do control rats. However, the tube-fed rats gained more weight, presumably because of increased efficiency of energy utilisation associated with receiving intragastric loads in a few discrete meals. They considered it paradoxical that the total energy intake was not affected by the fate of the ingested energy.

These are interesting results, but how paradoxical they appear may depend on how strongly one considers energy content of the body to be the fundamental determinant of food intake. Most people, however, would probably accept that intake is under multiple controls, including such factors as palatability, previous conditioning and cost in obtaining food. Energy content of the body could be one factor in the control of food intake but is not necessarily the most important factor in every instance[2].

To determine if energy content of the body is one factor that affects food intake, or utilisation, in the intragastric tube-feeding situation, further analyses of the data might be useful. For instance, intake during the last few days of Rothwell and Stock's experiment, when the tube-fed rats were somewhat heavier than controls, could be compared with that during the first few days when the animals were similar in weight; if there were differences, energy content of the body would be implicated. If, on the other hand, it could be shown that intake and utilisation in the intragastric tube-feeding situation are independent of body weight, this would be much more surprising than the fact that tube-fed animals fail to control their intake in a way that maintains constant body weight. However, to show conclusively that intake is independent of weight might require longer experiments involving greater weight gains than those occurring in Rothwell and Stock's study.

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1. Rothwell, N. J. & Stock, M. J. *Nature* **273**, 146–147 (1978).
2. Mrosovsky, N. & Powley, T. L. *Behav. Biol.* **20**, 205–223 (1977).

ROTHWELL AND STOCK REPLY—Mrosovsky suggests further analyses of the data to see if intake and utilisation are independent of the changes in body weight occurring during the experiment. A comparison of the energy intake of tube-fed rats during the first 5 days of each experiment with the intake during the last 5 days shows that they are identical, in spite of weight gains equivalent to 20% of starting weight. Furthermore, the rate of weight gain was remarkably constant throughout each experiment, therefore suggesting that both intake and utilisation were independent of body weight. By his own admission, Mrosovsky will be surprised by these results but we would agree that a conclusive demonstration of this independence of intake and body weight probably requires longer experiments with greater weight gains.

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Is the benzodiazepine receptor coupled to a chloride anion channel?

FROM their observations on the ability of several anions to facilitate the binding of ^{3}H-diazepam to membrane fragments from rat cortical tissue, Costa, Rodbard and Pert[1] have inferred that this binding site is closely associated with a chloride ion channel. Their data are qualitatively similar to ours with regard to the rank order of potency of the anions and we can confirm that the bromide ion also causes a significant increase in the affinity of the benzodiazepine receptor for the ligand diazepam without significantly affecting the total number of sites available.

Costa *et al.*[1] have drawn a correlation between the ability of various anions to enhance ^{3}H-diazepam binding and their ability to penetrate the activated inhibitory postsynaptic membrane of cat motoneurones as reported by Eccles[2]. As the binding experiments were carried out in cortical tissue membrane fragments it is probably advisable to attempt correlations with electrophysiological data on chloride channels obtained in the same region of the central nervous system. Such data are available in the literature[3] and comparison of the electrophysiological data from Eccles[2] and Kelly *et al.*[3] immediately shows that the anion-size specificity in cortical tissue is considerably less than that in the spinal cord; this may

0028-0836/79/280172-02$01.00