news and views

Protein turnover in the whole body

from J. C. Waterlow

IN this issue of *Nature* (page 192) Young and co-workers at the Massachusetts Institute of Technology report measurements of the rate of protein synthesis in the whole body in human subjects from birth to old age. This is a timely contribution to a topic which is attracting increasing attention, and which has lain fallow for some time. It is 35 years since Schoenheimer, Ratner and Rittenberg (*J. biol. Chem.*, **127**, 333; 1939) reported "the first experiment in which one amino acid of a normal diet, tyrosine, has been labelled by the nitrogen isotope". In subsequent papers the concept of protein turnover was firmly established, but it was not for another 10 years that attempts were made by two groups, that of Rittenberg at Columbia and of Wu in Alabama, to measure the overall rate of this process in the whole body (Sprinson and Rittenberg, *J. biol. Chem.*, **180**, 715; 1949; Wu and Snyderman, *J. gen. Physiol.*, **34**, 339; 1950). In these early studies the method used was to give a single dose of an amino acid labelled with ^{15}N and to calculate the rate of turnover from the curve of ^{15}N excretion over the next 48 hours or so. It was soon realised that such a calculation is erroneous: the shape of the early part of the excretion curve is the resultant of a large number of processes, and cannot be analysed in a meaningful way. After the first few hours the slope is determined largely by the turnover rate of urea and not by that of protein.

From this point development occurred in two directions. Olesen *et al.* (Olesen, Heilskor and Schønheyder, *Biochim. biophys. Acta*, **15**, 95; 1954) measured ^{15}N excretion in urine for 15 days after a single dose of ^{15}N -glycine, and calculated the rate of protein synthesis by multi-compartmental analysis. Theoretically this method is an improvement on the earlier ones; in practice it has not been followed up, presumably because of the difficulty of maintaining a constant nitrogen intake and a steady state in subjects other than healthy volunteers. San Pietro and Rittenberg (*J. biol. Chem.*, **201**, 457; 1953) took an opposite line. They devised a method which depends on measuring the maximum ^{15}N abundance in urinary urea after a single dose of ^{15}N . Peak labelling occurs about 3 hours after the dose, and the calculation of

protein turnover depends upon this interval being accurately timed. In fact it is impossible, from measurements on urine, to know precisely the time at which maximally labelled urea was synthesised. The method is therefore unsound. In spite of this it was quite widely adopted in subsequent years to study protein turnover in various pathological states such as pituitary and thyroid disease. But the results in normal subjects showed a wide scatter, and nothing of interest was revealed in patients with metabolic disease. Probably for this reason interest in the subject waned. It is unfortunate that the method most widely used was the least reliable.

Nothing more seems to have been attempted for about 10 years until Picou and Taylor-Roberts (*Clin. Sci.*, **36**, 283; 1969) working on malnourished infants in Jamaica, used a continuous infusion of ^{15}N -glycine to produce an isotopic steady state. If nitrogen balance is measured as well, total rates of both synthesis and breakdown can be calculated. This is the method which six years later has been used to good effect by the workers at MIT. It probably gives more accurate estimates of total protein turnover than the older methods, but problems remain. On theoretical grounds a likely source of error is that even in the steady state the labelling of amino acids in the precursor pool for urea synthesis may not be the same as that of amino acids for protein synthesis. The report of Young *et al.* suggests however that the method gives results which at least have comparative meaning. Moreover, the value for protein turnover in normal adults, of $3 \text{ g kg}^{-1} \text{ d}^{-1}$ agrees well with results obtained by infusion of radioactive amino acids, whereby the special problems associated with urea formation are avoided (James, Sender, Garlick and Waterlow, unpublished).

It seems reasonable to suppose that

the difference in turnover rate in infants and adults is related at least in part to growth. A major contributor to whole body turnover is the turnover rate of muscle protein. Table 1, from unpublished results of D. J. Millward, shows the rates of synthesis and breakdown of muscle protein in rats of various ages. The difference represents net growth of muscle protein. Rapid rates of growth are accompanied by rapid rates of turnover. From the energetic point of view this is a costly process. The energy cost of protein synthesis is not negligible; estimates range from about 4 kJ per gram, based on the requirement of 4 moles ATP + GTP per mole peptide bond, to about 30 kJ per gram, derived from nutritional measurements. Whatever the true figure *in vivo*, it looks as if protein turnover must account for a considerable part of the basal energy expenditure. A general relationship was suggested between rates of protein turnover and of basal metabolism (Waterlow, *Lancet*, **ii**, 1091; 1968) and Young's work confirms this.

There remains a substantial gap between rates of protein synthesis at the subcellular level and in the whole animal. The information that is becoming available about synthesis rates *in vivo* shows that the efficiency of synthesis (g protein synthesised per g ribosomal RNA) in subcellular systems is perhaps 100 times less than the efficiency in the whole animal (Henshaw *et al.*, *J. biol. Chem.*, **246**, 436; 1971; Millward *et al.*, *Nature*, **241**, 204; 1973). Until this difference is reduced, we can rely on subcellular systems for information about mechanisms but not about rates. A major problem for the future is to understand the means by which rates of protein turnover are controlled. It is perhaps provocative to suggest that, in spite of all the difficulties, a solution is most likely to come from studies on the whole animal.

Table 1 Rates of muscle protein synthesis, breakdown and net growth in normal hooded rats at different ages

Age (d)	Fractional rate (% d^{-1})			Efficiency of synthesis (g protein/g RNA/d)
	Synthesis	Breakdown	Net growth	
23	28.6	22.4	6.2	19.2
46	16.1	13.1	3.0	14.2
65	11.5	9.8	1.7	13.8
130	5.3	4.6	0.7	10.1
330	4.9	4.6	0.3	11.5