Sir David Cuthbertson Prize Medal Lecture

Metabolic abnormalities and wasting in human immunodeficiency virus infection

Derek C. Macallan

Division of Infectious Diseases, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK

The metabolic response to injury

It is largely to the work of Sir David Cuthbertson that we owe the concept of the common metabolic response to injury. He performed studies on patients with fractures in the 1930s and demonstrated that the metabolic response to such injury went far beyond the local effects of the fractures itself (Cuthbertson, 1930, 1932). Specifically, he demonstrated that localized fracture was accompanied by catabolism of protein in distant tissues, particularly muscle. It has subsequently been found that similar responses are evoked by a wide variety of injurious stimuli, including inflammatory injury, and the concept of a 'common metabolic response to injury', which encompasses the acute-phase response in inflammation and infection, has been widely accepted (Cuthbertson, 1942, 1954).

In the present paper, I would like to discuss the metabolic response to a specific injurious agent in man, the human immunodeficiency virus (HIV). I will describe features of the response to HIV infection which are common to 'the metabolic response to injury' as seen with other agents, but also demonstrate metabolic features that appear to be unique to HIV infection. I will extend this argument to propose that it is now possible to divide this 'common response' into sub-types and perhaps disease-specific patterns of response.

Wasting in human immunodeficiency virus infection

HIV wasting may be severe and dramatic in some cases whilst in others it may be quite subtle, being apparent only by relatively minor loss of lean body tissue. At the world-wide level, we need to remember that the brunt of the HIV pandemic has been borne by sub-Saharan Africa, and in this situation HIV wasting is of enormous clinical importance, to such an extent that HIV has become known as 'slim disease' (Serwadda *et al.* 1985). Whilst acknowledging the enormous importance of HIV-related wasting in the tropics, within the scope of the present article I will only be able to focus on HIV wasting as experienced in Western countries.

Natural history of acquired immune deficiency syndrome-related wasting

In our early investigations of HIV wasting, we were curious to know how people arrived at the wasted state, and we began our research studies against the background of a prevailing view that almost everyone with acquired immune deficiency syndrome (AIDS) would develop wasting and that, once HIV infection had progressed to AIDS, wasting would be progressive, inexorable and relentless. We tried to quantify the amount and timing of weight loss, and were struck, not so much by such chronic relentless wasting, but by the fact that such a pattern was actually a rather unusual sequence of events. What we found, much more commonly, was that wasting occurred in acute episodes and that these short episodes were associated with clinical opportunistic infections (Fig. 1; Macallan *et al.* 1993). Following treatment of such episodes we observed that patients with HIV infection commonly regained weight, often quite dramatically, and would then remain weight stable until another complication arose. We observed that many individuals with HIV infection, even those with late-stage disease, remained weight stable for prolonged periods of time.

We also observed that particular clinical events correlated with particular patterns of weight loss. With acute-weight-loss events, we found a preponderance of acute opportunistic infections, particularly pneumocystis carinii pneumonia, whilst with chronic weight loss, we observed a frequent association with gastrointestinal disease and such patients frequently gave a history of chronic diarrhoea (Macallan *et al.* 1993).

On the basis of these observations, we were able to reach three important conclusions: first, that wasting is not an inevitable consequence of HIV; second, that wasting is
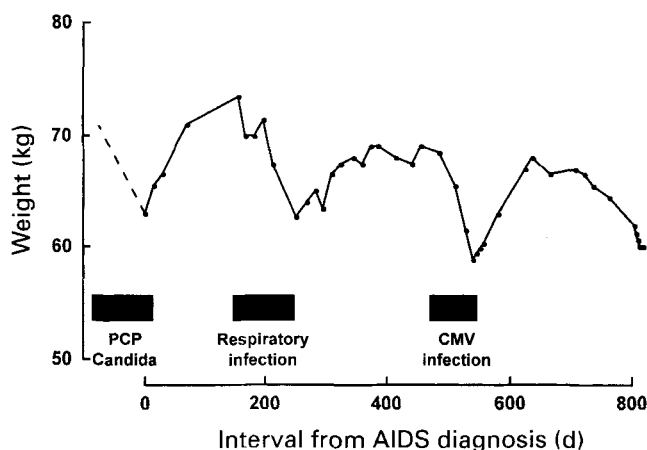

Fig. 1. Typical course of episodic weight loss in association with opportunistic infections in a patient with acquired immune deficiency syndrome (AIDS). PCP, pneumocystis carinii pneumonia; CMV, cytomegalovirus. (Based on Macallan *et al.* 1993.)

usually a consequence of a second insult in addition to underlying HIV infection; third, that HIV *per se*, does not block the potential for an anabolic response.

Energy metabolism in human immunodeficiency virus infection

Despite having observed that HIV infection alone does not seem sufficient to induce weight loss, it can certainly be said that HIV infection does induce marked metabolic abnormalities. Perhaps the most reproduced of these is the observation of an increase in resting energy expenditure (REE). This has been found in individuals with asymptomatic stage II HIV infection (Hommes *et al.* 1991*a*; Sharpstone *et al.* 1996); it tends to be more marked in individuals with AIDS (Hommes *et al.* 1990; Melchior *et al.* 1991), and is more marked still in individuals with secondary infection (Grunfeld *et al.* 1992*b*; Melchior *et al.* 1993). Such increased REE is independent of changes in body composition, but does show marked inter-individual variation (Schwenk *et al.* 1996), such that some individuals are frankly hypometabolic (Kotler *et al.* 1990; Suttmann *et al.* 1993) whilst others are markedly hypermetabolic.

Such observations of increased REE lead authors to suggest that hypermetabolism might be a major contributor to the weight loss seen in HIV, by increasing the demand for energy intake. There are two problems with this suggestion, the first observational, the second theoretical. First, if we consider REE values in individuals during weight-losing, weight-gaining or weight-stable phases, we find no correlation between the change in REE and the rate of weight change (Macallan *et al.* 1995*b*). Second, at a theoretical level, it can readily be argued that, in terms of energy balance, REE is not the primary determinant of energy balance; the primary determinant of energy balance is, of course, total energy expenditure (TEE), which also includes components related to activity and diet-induced thermogenesis. We therefore set out to investigate TEE in HIV patients during weight-stable phases, weight-gaining phases and weight-

losing phases, and I would like to summarize the results of those investigations (Macallan *et al.* 1995*b*).

First, we asked the question: are HIV patients hypermetabolic in terms of TEE? The answer to this question was clearly, no. When we looked at the mean TEE in HIV-infected patients, we found values of 13·8 MJ/d in weight-stable HIV-positive individuals, and 11·5 MJ/d in the whole group of HIV-positive individuals; such values are no higher than values seen in comparable similarly-aged men in the literature (Macallan *et al.* 1995*b*). We could conclude, therefore, that HIV-infected men were not 'hypermetabolic' in terms of TEE. Second, we asked the question: is TEE related to whether patients lose weight or not? We found that indeed there was a correlation between TEE and weight loss, but the direction of this relationship was positive; in other words, those individuals that were losing weight had the lowest rates of TEE (Fig. 2(*a*)). We can deduce from this observation, without making any direct measurements of energy intake, that it must be reduced intake that drives wasting in these individuals. Indeed, when we did measure intake, we found that those individuals who were losing weight had profoundly depressed levels of food intake. Similarly, those individuals who were gaining weight, even though they had relatively high levels of TEE, had sufficiently high levels of energy intake to place them in positive energy balance (Fig. 2(*b*)). When we divided subjects into four groups on the basis of their rate of weight change, the relative contributors to negative energy balance in the weight-losing group became apparent (Table 1). In the acute-weight-loss group, negative energy balance was due to dramatically reduced energy intake rather than any increase in energy expenditure.

One might ask why TEE is lower in such weight-losing patients? The answer becomes apparent when we look at the relationship between activity-related energy expenditure and weight change in this group of subjects. It can be seen that those subjects who were losing weight rapidly were those with lowest levels of activity-related energy expenditure and, hence, the lowest levels of TEE, even though their REE values may have been relatively high (Fig. 3). At a real-life clinical level, these subjects represent those individuals who are clinically unwell and who, as a consequence of their illness, have become both inactive and also profoundly anorexic.

Another way of looking at the relationship between intake, expenditure and balance is to look at the relative contribution of different factors to variations in TEE and variations in energy balance. We have used this approach to produce linear structural models of the relationship between these two variables (Fig. 4; Sheehan *et al.* 1998). The correlation between energy intake and energy balance (r 0·80) is much stronger than that between TEE and energy balance (r 0·04) indicating that variation in intake is a far greater contributor to negative energy balance than is variation in expenditure.

The question of what drives the profound anorexia that produces such negative energy balance still remains unanswered. Leptin was clearly a prime suspect for such a role when its place in normal appetite regulation was first demonstrated. However, studies of leptin levels in AIDS patients suggest that leptin is not directly involved in the anorexia of
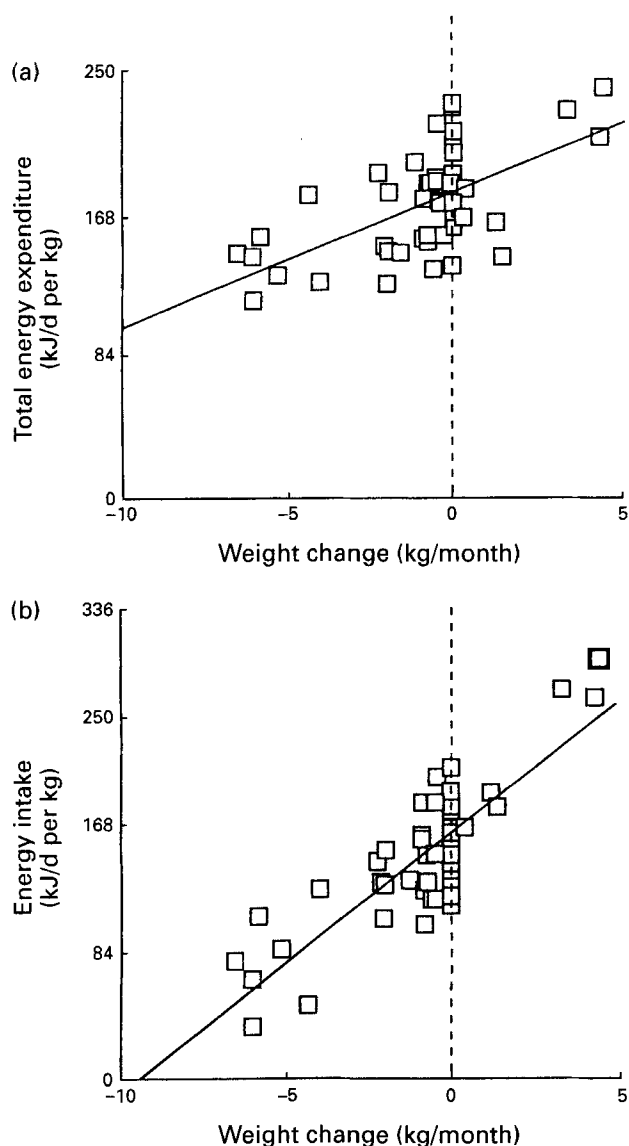
Fig. 2. Total energy expenditure (a) and energy intake (b) related to rate of weight change in men with human immunodeficiency virus. (a) r 0·60, P < 0·001; (b) r 0·84, P < 0·001. (From Macallan *et al.* 1995*b*.)

Fig. 3. Activity-related energy expenditure (including diet-induced thermogenesis) related to rate of weight change in men with human immunodeficiency virus. r 0·54, P < 0·001. (From Macallan *et al.* 1995*b*.)

Fig. 4. Linear structural model of determinants of energy balance and weight change in patients with human immunodeficiency virus infection and acquired immune deficiency syndrome. Values represent path coefficients. TEE, total energy expenditure.

HIV-related wasting (Grunfeld *et al.* 1996). The search for the biochemical or neuro–hormonal mediators of such anorexia thus continues.

We can summarize our observations of energy metabolism in HIV infection, therefore, by concluding that, although REE is elevated by the presence of HIV and is further elevated by the occurrence of secondary infections, it is really the reduction in intake which accompanies secondary infections that drives acute-weight-loss episodes.

Metabolic abnormalities: more than starvation

If reduced intake is the primary driving force behind HIV-related wasting, is the solution to this problem simply to provide more nutrition? The answer to this question is partly to be found in the observation that simple starvation is not an
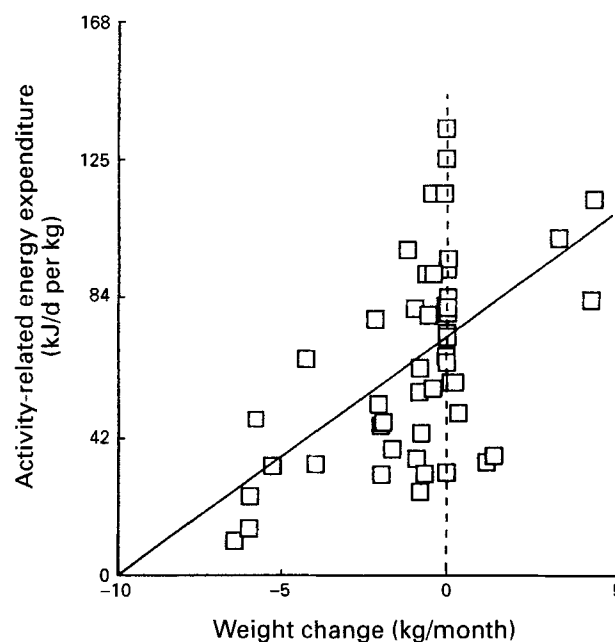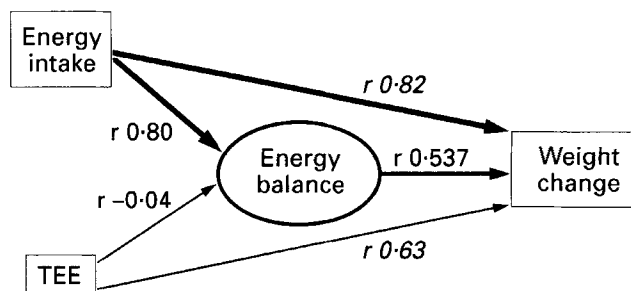
adequate explanation of the range and extent of metabolic abnormalities observed during HIV wasting. These abnormalities affect several pathways of intermediary metabolism. First, glucose metabolism is affected by HIV infection; insulin clamp studies by Sauerwein's group (Hommes *et al.* 1991*b*) have demonstrated that both insulin clearance rate and insulin sensitivity are increased in HIV-infected individuals. Such an observation contrasts with the relative insulin resistance seen in septic individuals, and perhaps begins to make one wonder if the features of the 'common response to injury and inflammation' are necessarily applicable to HIV.

Second, lipid metabolism is deranged by HIV infection. Triacylglycerol levels are increased (Grunfeld *et al.* 1989), cholesterol levels are reduced (Grunfeld *et al.* 1989), and *de novo* lipogenesis is markedly stimulated (Hellerstein *et al.*

Table 1. Energy expenditure, intake and balance according to weight change in men with human immunodeficiency virus infection (from Macallan *et al.* 1995*b*)

(Values are means and one standard deviation)

Study group . . .	Rapid weight loss (> 3 kg/month)		Slow weight loss (< 3 kg/month)		Weight stable		Weight gaining (> 0·25 kg/month)		Statistical significance (ANOVA F test)
No. of subjects . . .	6		15		12		7		
No. of studies . . .	7		21		16		7		
	Mean	1 SD	Mean	1 SD	Mean	1 SD	Mean	1 SD	
Energy expenditure per unit weight (kJ/kg per d)									
Resting	109·6	14·1	107·4††	10·5	104·5	7·7	125·9**	11·8	$P = 0·001$
Total	139·9**††	16·8	173·7	22·6	193·8	22·8	192·9	37·8	$P < 0·001$
Activity-related	30·3	15·3	66·3	23·4	88·7	22·4	67·0	31·1	$P < 0·001$
Energy intake and balance per unit weight (kJ/kg per d)									
Intake	84·0***††††‡	34·5	142·3†††	22·6	165·2	25·9	230·7**	49·5	$P < 0·001$
Balance	−55·8†††	36·4	−33·9††	31·8	−27·8	33·6	+33·4**	21·8	$P < 0·001$

Mean values were significantly different from those for weight-stable subjects (ANOVA and Sheffé's post hoc test): **$P < 0·01$, ***$P < 0·001$.
Mean values were significantly different from those for weight-gaining subjects (ANOVA and Sheffé's post hoc test): ††$P < 0·01$, †††$P < 0·001$.
Mean values were significantly different from those for slow-weight-losing subjects (ANOVA and Sheffé's post hoc test): ‡$P < 0·05$.

1993). Such increased lipid synthesis may represent the diversion of substrates, particularly the C skeleton of amino acids released from protein degradation, away from anabolism into lipogenesis and, hence, oxidation as fuel. As such, this may represent the mirror-image for lipid metabolism of the 'anabolic block' for proteins, which is discussed later (see p. 376).

Third, protein synthesis is perturbed by the presence of HIV infection. Our own studies have demonstrated that protein turnover is accelerated, particularly in stage IV HIV infection, where levels of whole-body protein turnover, reflected by leucine flux, are about 25 % higher than comparable controls (Fig. 5; Macallan *et al.* 1995*a*). Several other studies have found similar results with increased whole-body protein turnover (Lieberman *et al.* 1994; Rakotoambinina *et al.* 1996; Berneis *et al.* 1997), although in one study, protein turnover was reduced (Stein *et al.* 1990).

Protein metabolism and anabolic block

One thing we were particularly interested in was whether we could demonstrate that HIV-induced a 'block' in the anabolic response to nutrition. Normally, the provision of nutrition stimulates a switch from net whole-body protein breakdown to net synthesis (Garlick *et al.* 1980; Melville *et al.* 1989). The excess of protein intake over net protein synthesis is lost to the body as an increase in oxidation. Several studies in other catabolic states have suggested that the normal anabolic response is inhibited or completely blocked by mediators of inflammation. Thus, for example, severely-septic intensive care patients fail to accrue lean tissue, even when supplied with a more-than-adequate input of amino acids and energy (Streat *et al.* 1987). By contrast, in HIV-infected patients, we found a quantitatively similar change in protein metabolism, as reflected by leucine kinetics, as we found in healthy controls (Fig. 6(*a*); Macallan *et al.* 1995*a*). Thus, the pattern of abnormal protein metabolism in HIV infection
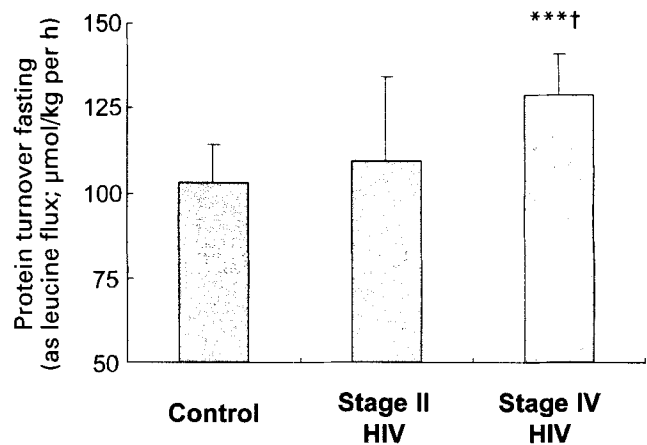

Fig. 5. Whole-body protein turnover in stage II human immunodeficiency virus (HIV) infection and stage IV HIV infection (acquired immune deficiency syndrome). Values are means and standard deviations represented by vertical bars. Mean value was significantly different from that for the control group: ***$P < 0·001$. Mean value was significantly different from that for stage II HIV group: †$P < 0·05$. (From Macallan *et al.* 1995*a*.)

appears to be one of increased whole-body turnover, but this disturbance does not appear to block the normal anabolic response to nutrition.

Patterns of protein metabolism

Is this pattern of protein metabolism common to all infectious states? Studies in melioidosis, a severe systemic infection common in South-east Asia, have demonstrated a very similar pattern, i.e. high turnover, normal anabolic response, except that in melioidosis the increase in turnover was even more marked at 37 % (Paton *et al.* 1997*a*). However, such increased turnover does not appear to occur in all infections. We recently completed a study of protein

metabolism in subjects with tuberculosis (TB) in South India. Here we used two control groups: one group of well-nourished subjects and one group with wasting secondary to chronic energy deficiency. The latter group were recruited in order to separate those effects due to altered body com-
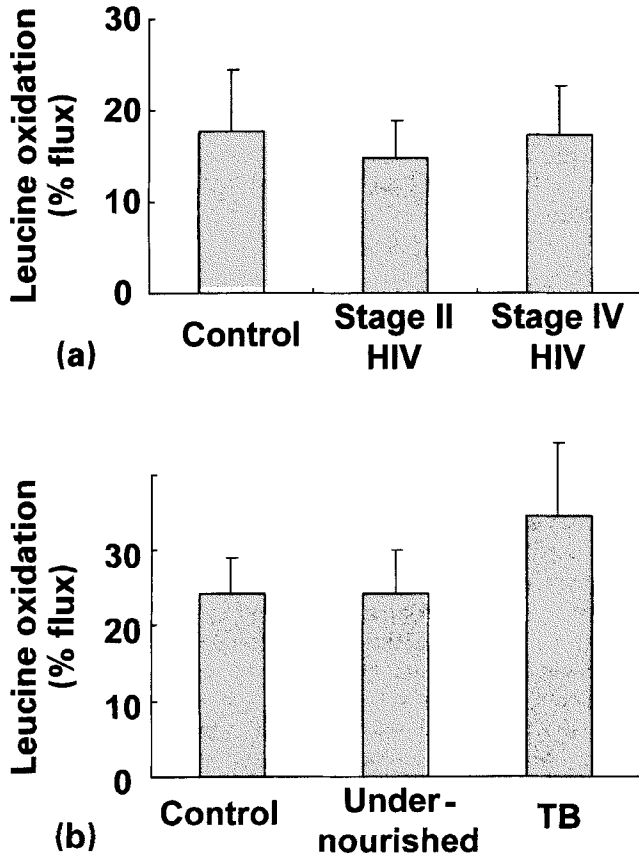

Fig. 6. Anabolic block in response to nutrition. Values represent the proportion of leucine flux diverted towards oxidation in the fed state. (There were no differences between groups in the fasted state.) In human immunodeficiency virus (HIV) infection (a), no difference was observed (from Macallan et al. 1995a), whilst in tuberculosis (TB; b), increased oxidation was seen in the TB group (ANOVA; $P = 0.019$; from Macallan et al. 1998). Values are means and standard deviations represented by vertical bars.
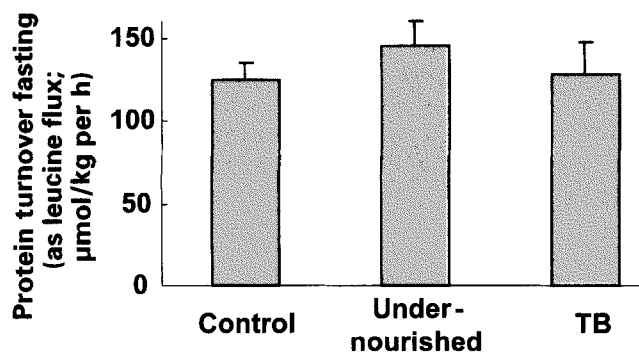

Fig. 7. Whole-body protein turnover in undernutrition and tuberculosis (TB). Mean value for undernourished group was significantly different from that for the control group (ANOVA): $P = 0.014$. (From Macallan et al. 1998.)

position and chronic reduced energy intake from those due to TB infection itself. We found no increase in whole-body protein turnover when expressed per unit lean body mass (Fig. 7; Macallan et al. 1998). However, we did find that, on feeding, a greater proportion of food intake was oxidized in the TB group than in either control group (Fig. 6(b); Macallan et al. 1998). There did appear, therefore, to be evidence of so-called 'anabolic block' in TB. This observation, at the level of amino acid metabolism, is consistent with other observations of the effect of TB on body composition. In a comparison of body composition in Brazilian patients with HIV and TB infection, it was found that TB caused a much greater loss of lean tissue than did HIV infection (NIJ Paton, MBO de Sampaio, G Jennings, LRR Castello-Branco, M Elia, S Costa and GE Griffin, unpublished results), and this supports the notion of induction of anabolic block by TB but not by HIV.

We therefore begin to see differing patterns of protein metabolism emerging as different disease states are investigated. One might propose a division of these different patterns of response as follows:

type I	high turnover;	no block;	e.g. HIV, melioidosis;
type II	normal turnover;	anabolic block;	e.g. TB;
type III	high turnover;	anabolic block;	e.g. severe sepsis.

Such a classification may be useful in investigating the protein metabolic response to other inflammatory states.

It is tempting to suggest that particular patterns of response may be associated with specific mediators. Thus, we found that TB seemed to be associated with elevation of interleukin-6 but not tumour necrosis factor (TNF)-α, whereas in our HIV patients increased tumour necrosis factor levels were found (Macallan et al. 1995a, 1998). It is possible, therefore, that high levels of interleukin-6 tend to promote anabolic block, or a type III response, whereas TNF tends to induce a type I high-turnover response. Others have suggested a key role for interferon-α (Grunfeld et al. 1992a). It is unlikely, however, that one cytokine is associated with one pattern of response, but is possible that particular patterns of cytokine response are associated with particular patterns of metabolic response, perhaps in an analogous way to the Th1 : Th2 (subsets of T-lymphocytes characterized by their profile of cytokine production) split in patterns of immune response.

Reversal of metabolic abnormalities and therapeutic approaches

One more piece in the protein metabolism puzzle may be contributed by recent literature on the effects of human growth hormone in HIV wasting. The efficacy of growth hormone at a whole-body level is impressive, resulting in accrual of lean tissue and improvements in function and well-being when given for periods of 12 weeks (Schambelan et al. 1996), or in terms of indices of protein breakdown when given for 2 weeks, in the context of acute opportunistic infection (Paton et al. 1997b, 1998). Some of the data on

tissue-specific effects have been more difficult to interpret (McNurlan *et al*. 1997), but the particularly striking observation regarding growth hormone is that the anabolic effects are achieved without reversal of the metabolic abnormalities in HIV infection. Protein turnover and energy expenditure remain high and abnormalities in carbohydrate and lipid metabolism persist, or in fact may be exacerbated (Schambelan *et al*. 1996). Reversal of such metabolic abnormalities is not, therefore, a prerequisite for a positive anabolic *response*. This makes one consider to what extent these abnormalities are mediators of wasting and to what extent they are 'bystander phenomena'.

Protein metabolism: unanswered questions

There appear to be, therefore, several key questions regarding protein metabolism in HIV infection which remain unanswered:
when and how fast does protein breakdown occur?
what drives protein breakdown?
can we modify the catabolic response?
is nutrition support sufficient; if so, when?
what is the place of anabolic agents?

The impact of anti-retroviral therapy

Finally, I would like to allude to a more recent development in HIV medicine, the impact of highly-active anti-retroviral therapy. One of the major areas of impact of such treatment has been to reduce the incidence of HIV-associated wasting. Opinion remains divided as to whether wasting will remain a problem. Personally, I feel that wasting is not a problem that has been resolved, for several reasons. First, studies of the impact of highly-active anti-retroviral combination therapy, usually including the use of a protease inhibitor, have all demonstrated that some patients continue to lose weight despite effective anti-retroviral therapy. For example, in one study of seventy-nine patients treated for 160 d (Teixeira *et al*. 1997), although the mean weight change was positive, 26 % of subjects lost weight despite effective therapy. Furthermore, no correlation was found between reduction in viral load and body-weight change. Less-encouraging results have been found by other groups. In a detailed examination of body-weight change in a group of German patients starting protease inhibitor-based regimens, no weight increase was found in the group as a whole, and, once again, no correlation between weight change and viral load reduction was seen, even in the subgroup who started the study with significant wasting (A Schwenk, personal communication).

Thus, not all patients who lose circulating virus with therapy regain their lost weight. The reasons for this are complex, but include factors such as drug side effects and dosing requirements. We await the results of several further studies by other groups which are ongoing, particularly in terms of the impact on body composition; one group measuring body composition indices has suggested that the tissue gain with protease inhibitors may consist largely of fat rather than lean tissue (S Gorbach, personal communication).

In addition to this failure of virologically-effective therapy to counteract wasting in some individuals, not all

patients can be established on an effective regimen. Side effects, tolerance, compliance and financial issues mean that a substantial proportion of patients, perhaps up to one-quarter, may not be able to take a virologically-effective treatment regimen. Furthermore, the emergence of viral resistance means that with time even some effective regimens may still fail. Thus, a proportion of patients will still require active management of persistent or recurrent wasting despite the availability of highly-potent drugs. What is likely to occur though is a change in the pattern of wasting observed. One phenomenon that has been observed with protease inhibitors is a disturbance of the axial *v*. appendicular distribution of fat known as lipodystrophy. The mechanism and significance of such changes are as yet poorly understood.

Conclusion

In conclusion, in HIV infection we see an array of metabolic abnormalities. Which of these are directly involved in the wasting process, and which are incidental, and thus of no real clinical significance, remains unclear. What is clear, however, is that reduced energy intake will inevitably lead to wasting, and this is important because it is a potential avenue for active intervention.

Finally, Sir David Cuthbertson left us with an enormous heritage. One aspect of this was the concept of a 'common response to injury'. We need to continue to build our understanding on the basis of this concept, but perhaps the time has now come when we can become more sophisticated in our approach, and begin to recognize subsets or patterns of response within the overall 'common' response. The importance of this lies in the observation that differing patterns of response are likely to be amenable to differing therapeutic approaches.

References

Berneis K, Leisibach A, Tietz A, Bassatti S, Battegay M & Keller U (1997) Whole body protein turnover in HIV-infected patients. *Nutrition* **13**, 269 Abstr.
Cuthbertson DP (1930) The disturbance of metabolism produced by bony and non-bony injury, with notes on certain abnormal conditions of bone. *Biochemical Journal* **24**, 1244–1263.

Cuthbertson DP (1932) Observations on disturbance of metabolism produced by injury to the limbs. *Quarterly Journal of Medicine* **1**, 233–246.

Cuthbertson DP (1942) Post-shock metabolic response. *Lancet* **i**, 433–436.

Cuthbertson DP (1954) Interrelationship of metabolic changes consequent to injury. *British Medical Bulletin* **10**, 33–37.

Garlick PJ, Clugston GA, Swick RW & Waterlow JC (1980) Diurnal pattern of protein and energy metabolism in man. *American Journal of Clinical Nutrition* **33**, 1983–1986.

Grunfeld C, Kotler DP, Hamadeh R, Tierney AR, Wang J & Pierson RN (1989) Hypertriglyceridemia in the Acquired Immunodeficiency Syndrome. *American Journal of Medicine* **86**, 27–31.

Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P & Feingold KR (1992a) Lipids, lipoproteins, triglyceride clearance, and cytokines in Human Immunodeficiency Virus infection and the Acquired Immunodeficiency Syndrome. *Journal of Clinical Endocrinology and Metabolism* **74**, 1045–1052.

Grunfeld C, Pang M, Shigenaga JK, Jensen P, Lallone R, Friedman J & Feingold KR (1996) Serum leptin levels in the Acquired Immunodeficiency Syndrome. *Journal of Clinical Endocrinology and Metabolism* **81**, 4342–4346.

Grunfeld C, Pang M, Shimizu L, Shigenaga JK, Jensen P & Feingold KR (1992b) Resting energy expenditure, caloric intake, and short-term weight change in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *American Journal of Clinical Nutrition* **55**, 455–460.

Hellerstein MK, Grunfeld C, Wu K, Christiansen M, Kaempfer S, Kletke C & Shackleton CHL (1993) Increased de novo hepatic lipogenesis in human immunodeficiency virus infection. *Journal of Clinical Endocrinology and Metabolism* **76**, 559–565.

Hommes MJT, Romijn JA, Endert E & Sauerwein HP (1991a) Resting energy expenditure and substrate oxidation in human immunodeficiency virus (HIV)-infected asymptomatic men: HIV affects host metabolism in the early asymptomatic stage. *American Journal of Clinical Nutrition* **54**, 311–315.

Hommes MJT, Romijn JA, Endert E, Schattenkerk JKME & Sauerwein HP (1991b) Insulin sensitivity and insulin clearance in Human Immunodeficiency Virus-infected men. *Metabolism* **40**, 651–656.

Hommes MJT, Romijn JA, Godfried MH, Schattenkerk JKME, Buurman WA, Endert E & Sauerwein HP (1990) Increased resting energy expenditure in human immunodeficiency virus-infected men. *Metabolism* **39**, 1186–1190.

Kotler DP, Tierney AR, Brenner SK, Couture S, Wang J & Pierson RN (1990) Preservation of short-term energy balance in clinically stable patients with AIDS. *American Journal of Clinical Nutrition* **51**, 7–13.

Lieberman SA, Butterfield GE, Harrison D & Hoffman AR (1994) Anabolic effects of recombinant Insulin-like Growth Factor-I in cachectic patients with the Acquired Immunodeficiency Syndrome. *Journal of Clinical Endocrinology and Metabolism* **78**, 404–410.

Macallan DC, McNurlan MA, Kurpad AV, De Souza G, Shetty PS, Calder AG & Griffin GE (1998) Whole body protein metabolism in human pulmonary tuberculosis and undernutrition: Evidence for anabolic block in tuberculosis. *Clinical Science* **94**, 321–331.

Macallan DC, McNurlan MA, Milne E, Calder AG, Garlick PJ & Griffin GE (1995a) Whole body protein turnover from leucine kinetics and the response to nutrition in Human Immunodeficiency Virus infection. *American Journal of Clinical Nutrition* **61**, 818–826.

Macallan DC, Noble C, Baldwin C, Foskett M, McManus T & Griffin GE (1993) Prospective analysis of patterns of weight change in stage IV human immunodeficiency virus infection. *American Journal of Clinical Nutrition* **58**, 417–424.

Macallan DC, Noble C, Baldwin C, Jebb SA, Prentice AM, Coward WA, Sawyer MB, McManus TJ & Griffin GE (1995b) Energy expenditure and wasting in Human Immunodeficiency Virus infection. *New England Journal of Medicine* **333**, 83–88.

McNurlan MA, Garlick PJ, Steigbigel RT, DeCristofaro KA, Frost RA, Lang CH, Johnson RW, Santasier AM, Cabahug CJ, Fuhrer J & Gelato MC (1997) Responsiveness of muscle protein synthesis to growth hormone administration in HIV-infected individuals declines with severity of disease. *Journal of Clinical Investigation* **100**, 2125–2132.

Melchior JC, Raguin G, Boulier A, Bouvet E, Rigaud D, Matheron S, Casalino E, Vilde JL, Vachon F, Couland JP & Apfelbaum M (1993) Resting energy expenditure in human immunodeficiency virus-infected patients: comparison between patients with and without secondary infections. *American Journal of Clinical Nutrition* **57**, 614–619.

Melchior JC, Salmon D, Rigaud D, Leport C, Bouvet E, Detruchis P, Vilde J, Vachon F, Couland J & Apfelbaum M (1991) Resting energy expenditure is increased in stable, malnourished HIV-infected patients. *American Journal of Clinical Nutrition* **53**, 437–441.

Melville S, McNurlan MA, McHardy KC, Broom J, Milne E, Calder AG & Garlick PJ (1989) The role of degradation in the acute control of protein balance in adult man; Failure of feeding to stimulate protein synthesis as assessed by 1-13C leucine infusion. *Metabolism* **38**, 248–255.

Paton NIJ, Angus B, Simpson A, Calder AG, Milne E, Chaowagul W, Newton P, Suputtamongkol Y, White NJ & Griffin GE (1997a) Protein metabolism in melioidosis. *Transactions of the Royal Society for Tropical Medicine and Hygiene* **91**, 500 Abstr.

Paton NIJ, Newton P, Ross H, Cotton J, Calder AG, Milne E, Sharpstone D, Macallan DC, Gazzard B & Griffin GE (1997b) Growth hormone therapy during acute opportunistic infections in AIDS has a protein-sparing effect. *Proceedings of 37th Interscience Conference on Antimicrobial Agents and Chemotherapy*, vol. 1, p. 246 Abstr.

Paton NIJ, Newton PJ, Sharpstone DR, Ross HM, Cotton J, Calder AG, Milne E, Elia M, Shah S, Macallan DC, Gazzard BG & Griffin GE (1998) Short-term growth hormone administration at the time of opportunistic infections in HIV-positive patients. *New England Journal of Medicine* (In the Press).

Rakotoambinia B, Raynaud JJ, Melchior JC, Crenn P, Thuillier F & Messing B (1996) Whole body protein turnover assessed with leucine and glutamine kinetics in vivo at an early stage of human immunodeficiency virus infection. *Clinical Nutrition* **15**, Suppl. 1, 13 Abstr.

Schambelan M, Mulligan K, Grunfeld C, Daar ES, LaMarca A, Kotler DP, Wang J, Bozzette SA & Breitmeyer JB (1996) Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. *Annals of Internal Medicine* **125**, 873–882.

Schwenk A, Hoffer-Belitz E, Jung B, Kremer G, Burger B, Salzberger B, Diehl V & Schrappe M (1996) Resting energy expenditure, weight loss and altered body composition in HIV infection. *Nutrition* **12**, 595–601.

Serwadda D, Sewankambo NK, Carswell JW, Bayley AC, Tedder RS, Weiss RA, Mugerwa RD, Lwegaba A, Kirya GB, Downing RG, Clayden SA & Dalgleish AG (1985) Slim disease: a new disease in Uganda and its association with HTLV-III infection. *Lancet* **ii**, 849–852.

Sharpstone DR, Murray CP, Ross HM, Hancock MR, Phelan MS, Crane RC, Menzies IS, Reaveley DA, Lepri AC, Nelson MR & Gazzard BG (1996) Energy balance in asymptomatic HIV infection. *AIDS* **10**, 1377–1384.

Sheehan LA, Macallan DC & Griffin GE (1998) Determinants of energy intake and energy expenditure in HIV and AIDS. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology* (In the Press).

Stein TP, Nutinsky C, Condoluci D, Schluter MD & Leskiw MJ (1990) Protein and energy substrate metabolism in AIDS patients. *Metabolism* **39**, 876–881.

Streat SJ, Beddoe AH & Hill GL (1987) Aggressive nutritional support does not prevent protein loss despite *fat gain in septic* intensive care patients. *Journal of Trauma* **27**, 262–266.

Suttmann U, Ockenga J, Hoogestraat L, Selberg O, Schedel I, Deicher H & Muller MJ (1993) Resting energy expenditure and weight loss in human immunodeficiency virus-infected patients. *Metabolism* **42**, 1173–1179.

Teixeira A, Leu JC, Honderlick P, Trylesinski A & Zucman D (1997) Variation in body weight and plasma viral load in HIV patients treated with tritherapy including a protease inhibitor. *Nutrition* **13**, 269 Abstr.