Sir David Cuthbertson Prize Medal Lecture

Metabolic abnormalities and wasting in human immunodeficiency virus infection

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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 subtypes 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

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus; REE, resting energy expenditure; TB, tuberculosis; TEE, total energy expenditure.

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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. 1991a; 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. 1992b; 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. 1995b). 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. 1995b).

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. 1995b). 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
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. 1991b) 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. 1989).
Table 1. Energy expenditure, intake and balance according to weight change in men with human immunodeficiency virus infection (from Macallan et al. 1995b)

(Values are means and one standard deviation)

<table>
<thead>
<tr>
<th>Study group . . .</th>
<th>Rapid weight loss (&gt; 3 kg/month)</th>
<th>Slow weight loss (&lt; 3 kg/month)</th>
<th>Weight stable</th>
<th>Weight gaining (&gt; 0.25 kg/month)</th>
<th>Statistical significance (ANOVA F test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects . .</td>
<td>6</td>
<td>15</td>
<td>12</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>No. of studies . .</td>
<td>7</td>
<td>21</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Energy expenditure per unit weight (kJ/kg per d)</th>
<th>Mean 1 SD</th>
<th>Mean 1 SD</th>
<th>Mean 1 SD</th>
<th>Mean 1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting</td>
<td>109.6</td>
<td>14.1</td>
<td>107.4††</td>
<td>10.5</td>
</tr>
<tr>
<td>Total</td>
<td>139.9***††</td>
<td>16.8</td>
<td>173.7</td>
<td>22.6</td>
</tr>
<tr>
<td>Activity-related</td>
<td>30.3</td>
<td>15.3</td>
<td>66.3</td>
<td>23.4</td>
</tr>
<tr>
<td>Energy intake and balance per unit weight (kJ/kg per d)</td>
<td>Mean 1 SD</td>
<td>Mean 1 SD</td>
<td>Mean 1 SD</td>
<td>Mean 1 SD</td>
</tr>
<tr>
<td>Intake</td>
<td>84.0***†††</td>
<td>34.5</td>
<td>142.3***††</td>
<td>22.6</td>
</tr>
<tr>
<td>Balance</td>
<td>-55.8***††</td>
<td>36.4</td>
<td>-33.9††</td>
<td>31.8</td>
</tr>
</tbody>
</table>

Mean values were significantly different from those for weight-stable subjects (ANOVA and Sheffe's post hoc test): †P < 0.01, ††P < 0.001. Mean values were significantly different from those for weight-gaining subjects (ANOVA and Sheffe's post hoc test): †††P < 0.001. Mean values were significantly different from those for slow-weight-losing subjects (ANOVA and Sheffe'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. 1995a). Several other studies have found similar results with increased whole-body protein turnover (Lieberman et al. 1994; Rakotoambinina et al. 1996; Bermeis 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. 6a; Macallan et al. 1995a). Thus, the pattern of abnormal protein metabolism in HIV infection 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. 1997a). 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-

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,

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. 1992c). 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 (Schanbelan 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.

**Acknowledgements**

The present review, by its very nature, has focused on work performed by our own department and has neglected a vast relevant literature from other centres; I apologize for this omission. The work I have presented owes a great deal to many collaborative endeavours, particularly with the Dunn Clinical Nutrition Unit in Cambridge, UK and with Peter Garlick and Margaret McNurlan at the Rowett Research Institute in Aberdeen, UK, and more recently at the State University of New York, NY, USA. I have learnt much from many other colleagues, particularly Marc Hellerstein in Berkeley CA, USA, and colleagues in San Francisco CA, USA, as well as Professor Griffin who has guided much of this work.

**References**


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