

## LETTERS TO THE EDITOR

### Dubious Assumptions Underlying the Adjustment of Metabolic Rates for Changes in Fat-Free Mass

To the editor:

An article (1) with accompanying editorial (2) published recently in this journal provides new data and a comprehensive discussion of energy expenditure in dietary-restricted (DR) animals. The aim was to provide evidence bearing on the hypothesis that reduced oxygen consumption may lower the formation of reactive oxygen species (1), thereby reducing oxidative damage and extending lifespan. This hypothesis implies that oxygen consumption in DR animals is reduced beyond that expected on the basis of reduced body size or altered body composition. The resulting analysis found that after adjusting for the amount of fat-free mass (FFM), resting energy expenditure (REE) was 13% lower ( $-250$  kJ/d) in DR animals. These findings were interpreted to mean that DR lowers REE independent of DR-induced changes in body composition. The editorial (2) recommends regression-based approaches to adjusting metabolic data when concomitant changes in body composition occur.

It is quite certain that adjusting changes in energy expenditure for changes in FFM can provide no evidence of rate of oxygen flux at the cellular level, which is the level at which oxygen flux must decrease if exposure to free radicals is to be lessened. Although normalizing for FFM may be preferable to using body weight or body surface area, FFM is a construct that lumps together diverse fluids, organs, and tissues with different cellular oxidative requirements. Heterogeneity in heat-producing tissues that make up body mass and FFM has long been recognized (3–6), and the existence of large between-organ differences in the rates of energy flux is well established (3–6). Brain and visceral organs such as liver, heart, and kidney have high metabolic rates in the postabsorptive state, whereas adipose and skeletal muscle tissues have relatively low metabolic rates. Specifically, organs such as liver, brain, kidney, and heart account for only approximately 5% of total body weight (6–7% of FFM); in reference male and female, they collectively account for 58–59% of whole body REE (7). If the mass of one or more high-metabolic-rate organs were to decrease in greater proportion than the mass of low-metabolic-rate organs, REE normalized for FFM would be lower, although the energy flux (kilocalories per kilogram per day) of each organ remained unchanged. Therefore, in order for FFM-adjusted REE to provide evidence for reduced oxygen flux, data must be presented showing that the proportion of FFM represented by each organ/tissue/fluid is identical in DR and control animals.

The authors do not present or cite such evidence, and the proposition that all organs comprising FFM are changed in a constant proportion after DR is unlikely to be true. A number of animal studies (8–12) have reported that weight change is accompanied by disproportionate changes in the size of various organs. More recently, Mayer *et al.* (13) reported preliminary data that organs are reduced disproportionately in patients with anorexia nervosa compared with controls.

It is unfortunate that in this otherwise excellent study and discussion that the heterogeneity of FFM and its bearing on the oxidative flux hypothesis of DR and aging was ignored. Future investigations should consider the *in vivo* measurements of individual organs and tissues (14, 15) and, where possible, the measurement of tissue specific metabolic rates.

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### Authors' Response: Dubious Assumptions Underlying the Adjustment of Metabolic Rates for Changes in Fat-Free Mass

To the editor:

We appreciate the interest of Drs. Gallagher, Heshka, and Heymsfield in our recent report on the effect of long-term dietary restriction (DR) on energy expenditure in rhesus monkeys (1). These authors raise an important point regarding the heterogeneity of organs that make up fat free mass (FFM). As these authors know, we are well aware of the potential importance of this heterogeneity (2, 3). We agree that this is a critical point that will need to be tackled in future research. Gallagher and colleagues, however, erred on two important points.

The first point concerns the hypothesis being tested by our experiments. Although the general hypothesis that reduction in energy ex-

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penditure during DR may lower the formation of free radicals and extend lifespan as mentioned in the introduction, it was not our primary hypothesis as purported by these authors. Instead, the main objective was to test whether long-term DR induces changes in energy expenditure that are independent of the changes in body composition compartments we could readily assess. To test this hypothesis, we used a regression-based approach to linearly adjust metabolic rate for FFM. This approach takes into account the fact that FFM is a heterogeneous compartment represented by a high oxygen-consuming compartment that does not change much with FFM (represented by an intercept different from zero), and a lower oxygen-consuming compartment that does change with FFM (represented by the  $\beta$ -coefficient) (4). Although not as sophisticated, this is similar to the assumption made in the recent paper by Heymsfield *et al.* (5).

The second point seemingly missed is that the adjustment we used accounts for the FFM heterogeneity and is different from the normalization per kilogram that assumes homogeneity in FFM. Although we did not explicitly state that a more sophisticated compositional analysis should be undertaken to understand why the FFM adjusted resting metabolic rate was reduced in restricted animals, this was meant to be implicit when we said further research was warranted. Such studies, however, are still very impractical considering the accuracy and precision of current technologies for imaging of organs. As indicated in their letter, organs that comprise 6–7% of body mass account for nearly 60% of the REE. To determine whether the 13% reduction in REE that we observed was due to changes in the mass of these organs, we would require an accuracy and precision of 1–2% of body weight for the high energy expenditure organ mass. Unfortunately, even Heymsfield *et al.* (5) found that the FFM regression model yielded a higher correlation with resting metabolic rate than the four-compartment model using an assessment of high and low energy expenditure tissues. Given our results, however, such imaging studies are worth pursuing in the restricted animals. Indeed, one of us is pursuing this question and has found that liver mass is rapidly reduced after initiation of DR in rats (Ramsey, J., unpublished data). However, during long-term DR, total and lean body mass losses tend to catch up with the initial rapid drop in liver mass.

We agree that lean mass heterogeneity may play a role in energy expenditure changes with DR. However, until organ mass changes are characterized in rhesus monkeys, we believe that conclusions about the role organ mass alterations may play in the actions of DR are not yet possible. Given our results, such studies are needed once the precision of the technology can be demonstrated.

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## Regarding the Consensus Statement on 21-Hydroxylase Deficiency from the Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology

To the editor:

This consensus statement is a comprehensive review of a range of issues involving the management of 21-hydroxylase deficiency from before birth until adulthood. Many sections of this article are constructive and helpful, but the section on “surgical management and psychology” may be misleading and potentially detrimental to patient care.

The surgical management of ambiguous genitalia is controversial because few long-term follow-up data are available on the effects of surgery on sexual function and psychological outcome. There is increasing concern from intersex consumer groups about possible detrimental effects of genital surgery. Adult patients and parents of affected children should have a central role in this debate.

The authors list three goals of surgery (page 4050, first paragraph): 1) genital appearance compatible with gender; 2) unobstructed urinary emptying without incontinence or infections; and 3) good adult sexual and reproductive function.

1) The authors use the word gender but presumably mean sex of rearing as decided by the clinicians and parents. There is, to date, no evidence that surgery to render the genital appearance compatible with sex of rearing improves psychological or psychosexual outcome or promotes a stable gender identity.

2) Unobstructed urinary emptying without incontinence or infection is an important quality of life issue for the child. Until now clinical instinct that surgery is beneficial has led to early surgery, although there are no data to support this. Surgery itself can result in urinary infections and fistulae (1).

3) The final goal is good adult sexual and reproductive function. There is no evidence that reconstructive surgery gives a better outcome if performed in an infant rather than an adolescent. Clitoral surgery may not promote good sexual and reproductive function, and some studies suggest there may be damage to sexual function (2). Surgery performed in an infant may require revision in adolescence in a significant number of patients (3). An additional major advantage of surgery in an adolescent or adult is that informed consent can be obtained.

Early surgery may be the appropriate course of action and may or may not be supported by long-term outcome data in due course. For the moment, the apparently rigid guidelines in the consensus statement remove flexibility and potentially prejudice the possibility of constructive debate between specialties and with patient groups.

The only consensus attainable at the present time is that of a dedicated multidisciplinary team addressing an individual case including full participation of the affected family who will be responsible for the nurture of the child in the modern world.

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**Authors' Response: Regarding the Consensus Statement on 21-Hydroxylase Deficiency from the Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology**

To the editor:

We thank Dr. Sarah Creighton and her colleagues for their views concerning the consensus statement on 21-hydroxylase deficiency from the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology, which was published in the September 2002 issue of the *JCEM* (1). The consensus statement was prepared by a group of 40 endocrinologists, psychologists, and surgeons concerned with the management of congenital adrenal hyperplasia (CAH), representing 35 institutions in 12 countries on four continents. This highly qualified and diverse group, which included one of the signatories to Dr. Creighton's letter, represented a broad range of views and experience.

We disagree with the assertion that the guidelines concerning surgical management and psychology are misleading, and we strongly disagree that they might be detrimental to patient care. Dr. Creighton's letter refers to "increasing concern from Intersex consumer groups." These groups primarily represent the experience of women with disorders other than CAH, primarily androgen insensitivity; many of these women were subjected to ill-advised mutilating surgery by inexperienced surgeons. By contrast, the consensus statement deals only with 21-hydroxylase deficiency and emphasizes focusing surgical care in the hands of a small number of highly experienced surgeons. Whereas the care of patients with ambiguous genitalia who do not have CAH may be controversial, there should be little controversy regarding CAH patients who are 46,XX with normal female internal structures and variable masculinization of the external genitalia. Only a small number of these patients are extremely masculinized.

Although there are few studies of long-term outcome showing that improvement of genital appearance improves psychological or psychosexual outcome or promotes a stable gender identity, competent surgery can provide an excellent outcome in the most severely affected children (2) and is compatible with normal reproductive function (3). Therefore, we believe that it is cruel to leave children in a state of gender uncertainty until "they can participate in an informed consent," particularly in this disorder. While a third sex may be acceptable in some cultures, we believe that it is not so in either North America or Western Europe. Body image, while growing up, particularly through stormy adolescence, is very important to confidence and identity of self.

It is also true that surgery can result in urinary infections and fistula

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and that clitoral surgery may damage sexual function. The decision to reduce clitoral size is not taken lightly, and every precaution is made to preserve the nerve supply and, hence, sexual function (4). As emphasized in the consensus statement, if highly experienced surgeons do these procedures, the incidence of such complications is low.

The decision for surgery is made jointly among parents, surgeons, and endocrinologists. Most surgeons inform the parent that simple revision or introitoplasty will probably be needed at adolescence. However, revision surgery is far simpler than having to do the entire pull through at adolescence, because the distance from the urogenital sinus to the perineum has elongated with growth. We agree that a dedicated multidisciplinary team is needed to address each individual case and that the affected families should participate fully. This indeed was recommended in the consensus statement.

We agree that outcome data are exceedingly important, but they must be based on present, improved techniques, by experienced pediatric surgeons or urologists, not on those used three decades ago. We suggest careful follow-up of all surgically reconstructed patients and urge a National Institutes of Health-funded long-term outcomes study of CAH patients.

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