Are health and ill-health lessons from hunter-gatherers currently relevant?

Dear Sir:

In their Special Article in the March 2000 issue of the Journal, Cordain et al (1) discussed plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. They noted from the various reports on the societies of hunter-gatherers that these people were relatively free of many of the chronic degenerative diseases and symptoms that pervade modern societies. Accordingly, Cordain et al recommended that "the macronutrient characteristics of hunter-gatherer diets may provide insight into potentially therapeutic dietary recommendations for contemporary populations."

First, it must be stressed that relative freedom from degenerative disorders or diseases was, and still is, characteristic of all societies of hunter-gatherers. This prevailed whether the diets had a high fat content, supplying 28–58% of energy, as reported in the societies studied by Cordain et al (1), or a far lower fat content, as indicated in the societies of hunter-gatherer agriculturalists described by Milton (2) in her Editorial on the subject. Further, this relative freedom from degenerative diseases is equally characteristic of all of the numerous rural pastoral societies in Africa, which, until very recently, have been accustomed almost wholly to diets with a relatively low contribution to energy by fat of 15–20% (3). In such contexts, obesity and diabetes had a low prevalence (4); indeed, this is still the case in some rural areas. Coronary heart disease (CHD) is still virtually absent and is rarely seen in patients admitted to rural hospitals (5). Simultaneously, in rural contexts, the cancers of prosperity are uncommon, although, understandably, they are increasing in urban dwellers (6). Thus, with limited exceptions, the nutritional pattern of the diet of rural Africans could still serve as a model for possible implementation in Western populations. In support of the uncommonness of deaths from degenerative diseases, in South Africa, as recently as 1970, of Africans who reached the age of 50 y, even more reached an age ≥70 y than was the case with the white population (7). Elderly Africans died almost entirely from infections. Two features insufficiently stressed were their very high levels of everyday physical activity and low levels of smoking, especially among women.

Of much greater import to the situation at issue, this rarity of CHD in African patients in rural hospitals, is the similarity of the situation in the wards of Massachusetts General Hospital as late as 1910–1920, when CHD was considered rare (8). Hence, what were Americans, most of whom were very poor, doing in their lifestyle that made them different from subsequent generations among whom the disease became extremely common, and still remains so despite major decreases in mortality rate (9)? Instead of seeking nutritional lessons from primitive communities and from developing populations, it would be far more pragmatic to try to learn more from certain present-day Western populations who have much less CHD than do other populations. In this respect, the recent MONICA Study showed the CHD mortality rate in Spain to be only one-fifth of that in Poland (10). In the United States, the age-adjusted death rate from CHD in New Mexico is less than half of that in New York (11). To reiterate, which beneficial characteristics of these lesser prone but sophisticated populations lend themselves to adoption?

Crucially, however, even if highly apposite and practicable information were forthcoming, would it really be put into practice? Before we answer this question, it is imperative to keep in mind the current context of long life, namely, that despite high mortalities from degenerative diseases, expectations of life are now at their highest (≈75 y for men and 80 y for women). This implies the enjoyment of a long life even by individuals with unfavorable lifestyles (eg, in regard to CHD, about three-quarters of cases occur after age 65 y). There is near universal reluctance to make changes for the lengthening of life. Thus, concerning the risk factor obesity, probably all is known that needs to be known for its successful treatment. Yet, in the United States, with the present rate of increase in obesity, it has been predicted that all Americans will be obese by 2230 (12). In Australia it was noted that only 6% of articles about cardiovascular disease risk factors in a MEDLINE search and 5% of articles in a medical magazine search discussed exercise prescription or how to start and maintain an exercise program (13). As to combating other important risk factors, a recent study in the United States showed that cholesterol-lowering medications are underutilized, even according to the narrowest indications for use (14). Furthermore, it was stated that national guidelines on the treatment of hypertension had little effect on prescribing patterns of antihypertensive medications. It was emphasized that greater attention must be paid to educating health care providers, so that treatments of proven benefit are implemented. As related by *Minerva* (15) as an example of resistance to change, "Health educators have a tough time persuading people to eat broccoli when chocolate, pop tarts, and sticky buns are everywhere, so US researchers have tried recruiting teams of trusted workers to pester their friends and colleagues to eat better. A lengthy and expensive programme of peer education, which included some intrusive sales techniques, led to participants eating about half an extra portion of fruit and vegetables a day. The authors don't say how many friends the peer educators lost in the process." In brief, no matter what efficacious lifestyle changes are recommended, whether they be derived from past or from present

experiences of populations, they seem almost irrelevant because they will be very largely ignored.

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Reply to ARP Walker

Dear Sir:

We appreciated and enjoyed Walker's constructive comments and interesting insights and agree with many, but not all, of his conclusions. Numerous epidemiologic data support the notion that increasing Westernization and industrialization in human populations is associated with a greater incidence of chronic degenerative diseases. It is almost axiomatic that changes in diet and activity levels initiated by Westernization and industrialization are largely responsible for these health disorders. As human societies stray farther and farther from the original environmental conditions (both diet and exercise) for which our present genome was selected, it is not unexpected that ill-health effects should emerge (1, 2).

We have little doubt that some, but not all, lifestyle characteristics of rural Africans and many of the world's other less industrialized people could serve as a model to benefit the health and well-being of Western populations. However, the reason certain of these lifestyle variables are advantageous is that they are consistent with those of Stone Age hunter-gatherers that in turn represent the lifestyle characteristics for which our species is genetically adapted. High levels of physical activity are required of both hunter-gatherers (2) and rural Gambian subsistence farmers (3) and similarly may provide both of these groups with protection from degenerative disorders and disease. However, the proximate mechanisms of exercise's therapeutic effect are not specifically intrinsic to subsistence farming but, rather, stem ultimately from the rigors and selective pressures dictated by the physical requirements of the hunter-gatherer lifestyle that shaped the present human genome over >2 million years of evolutionary experience. Similarly, it was found that increased dietary intakes of n−3 fatty acids may provide protection from chronic disease in highly industrialized societies such as Japan (4) and in partially Westernized hunter-gatherers such as the Inuit (5). The ultimate evolutionary reason these fatty acids afford protection for these diverse populations is based on our species' genetically determined requirement for them, which in turn was shaped by the environmental selective pressures that fashioned the present human genome. By examining the original environmental conditions for which our present genome was selected during the Paleolithic Era (the Old Stone Age, lasting from 2.6 million y ago until the agricultural revolution 10 000 y ago), it is possible to gain insight into optimal lifestyle characteristics that may be of therapeutic value for modern populations experiencing degenerative disorders.

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Reply to ARP Walker

Dear Sir:

It is gratifying to see that Walker's letter supports my recent Editorial (1), which pointed out that hunter-gatherer societies are largely free of chronic degenerative diseases despite notable differences in plant-animal subsistence ratios and macronutrient energy patterns. Walker, whose expertise on this topic is widely recognized, expands on this point, discussing the relative freedom from degenerative disease that is characteristic of all pastoral societies in Africa (who consume low-fat diets) and of other rural African populations.

In keeping with his letter's title, Walker then suggests that, rather than seek health and ill-health lessons from hunter-gatherers, it might be more relevant to study present-day Western populations that vary in their incidence of degenerative disease. I assume that he suggests this because, in the near future, most or all human populations worldwide will probably be Westernized. Thus, regardless of how healthful the hunter-gatherer lifestyle and diet may be, no one will live under such conditions. But, as Walker suggests, if we could determine why some Western populations show less evidence of certain degenerative diseases than do others, we could emulate the more healthful patterns. Walker concludes his letter somewhat pessimistically, noting that, even if such recommendations were forthcoming, current evidence suggests that they would largely be ignored.

The comparative studies that Walker advocates are of considerable value and importance. However, because human biology appears to have altered little over the course of human evolution (most human adaptations having been cultural rather than biological), it seems that casting a wide net would produce a more complete picture. We need to bear in mind that the contemporary Western lifestyle is only an experiment in progress. In contrast, the hunter-gatherer way of life has been time-tested and proven for >2 million y.

True, we can only speculate about dietary proportions of ancestral hunter-gatherers. But other relevant dietary information can be determined from the fossil record, and our ability to recover such information is constantly improving (2). Archaeological and skeletal remains permit us to trace the changes in human health that accompanied the dietary transition to agriculture and estimate the length of time a population may have used a given plant or animal staple (3). Detailed information about nutrient characteristics of wild foods shows important ways in which hunter-gatherer diets differ from contemporary Western diets (4–6)—and here I am referring not to processed modern foods but to differences in the nutrient content of fresh cultivated compared with wild plant foods and domesticated compared with wild animal foods. Study of hunter-gatherer behavior shows that most hunter-gatherers have a very active, physically demanding lifestyle. In addition, our investigation dose not have to be restricted to humans. For example, examination of the natural diets of wild apes and monkeys shows interesting differences between the nutrient patterns of their diets and those of contemporary Westerners (6).

Walker is justly concerned because many people appear to ignore diet-related suggestions that could improve their health and longevity. Research with hunter-gatherers may provide clues as to why people behave in this manner. Although considerable material has been published on the dietary behaviors of some hunter-gatherer societies, quantitative data are generally scant and there is a strong need for more detailed study of this topic while time permits.

It seems that many hunter-gatherer diets consist largely of the same foods each day. Most wild foods are low in energy, and it often requires tremendous effort to secure a sufficiency. For example, indigenous Amazonians, both men and woman, typically devote ≥8 h/d to subsistence activities (7). Rare, energy-rich wild foods seem particularly critical for children and women because of the costs of growth and reproduction, respectively. Fat reserves are also necessary to survive seasonal low points in overall food availability (8, 9).

In contemporary Western nations, it makes perfect sense that a well-nourished person who has already consumed sufficient energy for a 24-h period does not need to eat a piece of cake. Why do most of us reach for that cake more or less automatically? Perhaps it is because we are "programmed" through our common evolutionary heritage as hunter-gatherers to be particularly responsive to foods that appear rich in energy (8, 9).

For similar reasons, we can predict that people might show resistance to changing the features of their customary diet, even when such changes would prove beneficial. Smith and Smith (10) compared 3 diets of northwestern Australian Aborigines over the period 1890–1970: their diet as hunter-gatherers, their diet when they lived on cattle stations where some Western staples were available, and their diet in contemporary Aboriginal communities in which Western foods could be self-selected.

Comparison of the 3 diets with a modern recommended diet supported the nutritional adequacy of the hunter-gatherer diet (wild cereal and fresh plus dried fruit with a moderate amount of meat). However, there was a common link among the 3 diets in that they all represented a relatively unchanging Aboriginal evaluation of the worth of several major kinds of food despite the radically changing availability of these foods. Such traditional evaluations in the context of Western rather than wild foods resulted, for example, in a dramatic increase in the proportion of dietary energy from fat and lower intakes of some vitamins (10). Dietary changes were accompanied by altered patterns of disease, including well-documented increases in hypertension, diabetes, and heart disease (10). Similar observations were made of the Maori—"in spite of increasing use of Westernized foods the Maori will favor fatty foods and traditional seafoods if available" (11).

Such examples suggest that certain contemporary behaviors of humans with respect to foods may relate, at least in part, to non-immediate dietary circumstances. Obesity and its associated health problems and some other current diet-associated conditions (eg, lactose intolerance and celiac disease) seem inextricably bound up in past interactions between humans and their foods. Comparative study of only contemporary Western populations would not provide the temporal depth needed to understand the full etiology of these conditions. Also, for humans, food often is not consumed for its nutritional content but for its relation to the social context and cultural meanings that different

human societies attach to it. As biocultural beings, humans have and will continue to evolve largely in response to their own self-created environment. For this reason, it seems prudent to try to understand features of human dietary behavior and health in as broad a context as possible.

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Use of compartmental analysis as a gold standard to compare against other methods for assessing fractional zinc absorption

Dear Sir:

In the article by Lowe et al (1), several experimental methods for assessing fractional zinc absorption (FZA) were compared in 6 women. A rigorous evaluation of the validity of the different experimental techniques is long overdue and we congratulate the authors for their attempt to clarify the issues concerning the various methods being used in different laboratories. The performance of each method was analyzed in relation to the results of a compartmental model, developed and reported on previously (2), that used the same experimental data. Although we read Lowe et al's article with interest, several issues need clarification.

The incorporation of 3 types of data (fecal, urinary, and plasma) was used as the justification for choosing the compartmental model as the gold standard to compare against other methods that used only one set of data (fecal, urinary, or plasma). We suggest that both the quantity and the quality of the data used should be the main criteria, but there is no information on quality, other than the fact that a constant fractional SD of 0.1 was used by the CONSAM program (3) when the tracer data sets were fit in the compartmental model. Are we to assume that the fecal, urinary, and plasma data all had the same uncertainty associated with them? This seems unlikely given that the sample preparations were all different and that the quantity of zinc in each sample varied widely. The precision of the parameter estimates from an earlier report by Lowe et al (2) was generally good, reflecting the excellent structure and design of the model. However, in 5 of the 6 subjects, the CV for the parameter associated with urinary excretion was >60%. On the basis of these results, we estimated that the removal of the urinary data from the model would not weaken it.

A criticism of any model is that it is just that: a model. The modeling process makes gross simplifications of the way the body works and any results from it should be scrutinized for false assumptions, unjustified complexity, and unsubstantiated claims of parameter precision. In Lowe et al's (1) discussion, there was plenty of excellent, well-argued criticism of the other methods used to calculate FZA but no criticism of the compartmental model against which these other methods were compared. Attention should have been drawn to the shortcomings of using modeling in nutritional studies so that other investigators would not be left with the impression that the results from a compartmental model are beyond contradiction.

Another weakness of Lowe et al's study (1) was the small number of data sets used. Detailed metabolic studies are often constrained by the resources available, thus limiting the number of subjects studied, the procedures that can be undertaken, or both. Although the results obtained from the different methods reviewed was interesting, the method of comparison used was not appropriate. The FZA calculated from the compartmental model is based on an equation containing 2 of the rate constants ($k_{1,5}$ and $k_{6,5}$), which are simultaneously fitted with the other rate constants to the data set provided. There are uncertainties associated with these parameters that were not stated in Lowe et al's (1) article, although these uncertainties were addressed in their previous study (2) in which the compartmental model was developed. In their more recent article, Lowe et al (1) used the mean and SD of the FZA calculated from the compartmental model, generated from the 6 subjects, as their reference point. Calculation of the SD of the 6 results could give a misleading picture of how good the estimate of the reference FZA is. For instance, if the uncertainties concerning the rate constants $k_{1,5}$ and $k_{6,5}$ are large for each individual subject's data, the corresponding uncertainty concerning each calculated FZA will be large. If, however, the difference between each of the 6 calculated FZAs is, by chance, small, the SD of the mean FZA will be small. This is the drawback to having only 6 data sets and it applies equally to other methods used to calculate FZA. The conclusion that "We therefore recommend the DITR technique

with use of a spot urine sample collected ≥2 d after tracer administration. . .” cannot, therefore, be justified from the data provided in Lowe et al’s (1) article.

Because of the limited number of subjects in Lowe et al’s (1) study, it would have been more worthwhile to analyze each subject’s data separately and to examine the random and systematic errors associated with both the collection of that data and the calculation of the FZA. The different methods could then have been assessed genuinely within each individual. Although this type of analysis would not make clear which absorption value is the most accurate, it would enable investigators to gauge which method produces a value for FZA with the lowest associated uncertainty.

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Reply to JR Dainty et al

Dear Sir:

Dainty et al make some good points in their letter about our article (1). They suggest that the comparison of the fractional zinc absorption (FZA) data of each subject obtained by using the compartmental model with the same data obtained by using simpler measures is not the best technique for determining the accuracy of the simpler techniques. They point out that random fluctuations in the data may be propagated in the simple estimates of FZA in unpredictable ways, possibly resulting in a spurious comparison. We agree and are currently studying a theoretical data set generated from the compartmental model with a precision much greater than what could be expected in an in vivo tracer study of zinc metabolism; we will use this data set to determine how accurately FZA values obtained with the simple measures compare with FZA values obtained with the compartmental model. With use of this strategy, only logical deficiencies associated with each of the simple techniques relative to the compartmental model would be elucidated.

Although we agree in part with the comments of Dainty et al, we disagree with their comments on the nature and usefulness of compartmental modeling. It is true that a compartmental model of a metabolic system is a kinetic hypothesis describing how that metabolic system functions dynamically and, therefore, it is open to criticism and further testing, as is any other hypothesis. Nevertheless, because a compartmental model (the parameters of which are estimable from the data) must be consistent with all of the data to which it is applied (ie, zinc tracer and tracee measurements in plasma, urine, and feces in our study), it is a more robust description of the physiology than is a simple measure or model of a limited portion of the entire data set. Thus, the compartmental model should serve as the gold standard against which other simpler measures of the data can be compared (the problem of “noisy” data mentioned above notwithstanding). In fact, if a simple measure of the data is a good estimate of a particular physiologic parameter or combination of parameters (eg, FZA) and is also estimable in the compartmental model, such a measure could be derived within the logical context of the compartmental model.

Dainty et al suggest that any model makes “gross simplifications of the way the body works.” We agree. Nevertheless, however gross such simplifications may be in compartmental models, they are even more gross for simple measures of the data. Dainty et al mention the possibility of “false assumptions” in compartmental models, which is always a possibility, but they do not mention what these false assumptions might be in our model of zinc metabolism. They also criticize the “unjustified complexity” of our model. However, our model (2) is the simplest compartmental structure that fits all of our data. As is true with many mechanisms in nature, metabolic systems are complex and our “gross oversimplifications” (compartmental models) are often more complex than we would like. However, such complexity should not push us to retreat to gross oversimplifications and the use of simple unproven approaches for estimating various parameters (ie, FZA).

Dainty et al also refer to our “unsubstantiated claims of parameter precision.” The precision of our parameter estimates from the SAAM II computer program (SAAM Institute, Seattle) uses relative data weighting of the highest quality, and the algorithms used are well documented (3). In brief, the fractional SDs for a data array are entered as input estimates of 0.1 (relative weights) into the SAAM II program. The program then adjusts this value up or down for each data set, depending on the quality of the least-squares fit of the model to the data. The uncertainty estimates for each parameter are then scaled accordingly. We apologize for a misprint in footnote 1 to Table 2 in our original article (2), which apparently has generated concern about the precision of our estimates. The uncertainty estimates for each parameter in that table are fractional SDs, not SDs, as indicated in the footnote. Thus, the average fractional SD of the rate constant $k_{0,1}$, which describes the fractional movement of zinc tracer and tracee from the plasma to the urine per unit time, is ≈13%, not >60%.

In conclusion, we agree with Dainty et al that comparison of the adequacy of simple measures of FZA from a particular data set cannot be compared easily with the estimation of FZA from the compartmental model because of the uncertain way in which the random fluctuations in the data get propagated in the

simple estimates of FZA. A more rigorous theoretical comparison of simple with compartmental modeling techniques is currently under way. Nevertheless, we believe that the comments made by Dainty et al about compartmental modeling are misguided. The more robust the hypothesis, ie, the more extensive and more different the data set explained by a model (in our case zinc tracer and tracee data in plasma, urine, and feces over 6 d after administration of oral and intravenous tracers), the more accurate a particular measure of a model (ie, FZA) is likely to be. Under such conditions, we believe it is appropriate to use a well-documented compartmental model as the gold standard for evaluating the accuracy of simple estimates of a parameter such as FZA.

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Relation between basal metabolic rate and body composition in subjects with anorexia nervosa

Dear Sir:

The cross-sectional study of Polito et al (1) examined the relation between basal metabolic rate (BMR) and anorexia nervosa. In the introduction to their article, Polito et al state that many studies showed a reduced BMR in subjects with anorexia nervosa and that "the main controversy remains whether the decrease in BMR is due to a change in body composition or whether it represents a down-regulation of cellular metabolism." These authors conclude from their findings that BMR is depressed in subjects with anorexia nervosa and that this is not explained by changes in body composition. This suggests that ". . . the metabolic activity of the active tissue mass may have been reduced" in subjects with anorexia nervosa.

I am not sure that the conclusions of Polito et al are justified because these authors did not adequately control for differences in body composition. Although they did control appropriately for fat-free mass by using analysis of covariance, their data (Table 1 of the article) show that the biggest difference in body composition between subjects with anorexia nervosa and control subjects is in fat mass and not fat-free mass. Fat mass was 57% lower in patients with anorexia nervosa than in control subjects (6.8 compared with 15.7 kg, respectively), whereas fat-free mass was only 16% lower (34.7 compared with 41.2 kg). It is now recognized that fat mass also makes a contribution to BMR (2) and recent studies controlled for both fat mass and fat-free mass when comparing BMR between groups (3–6).

If Polito et al had used fat mass and fat-free mass as covariates when comparing BMR, it is possible that group differences would have been eliminated, which would suggest that body composition differences were responsible for the reduced BMR values in subjects with anorexia nervosa. Such a contention is supported by the fact that when Polito et al used body weight as a covariate instead of fat-free mass they found no difference in BMR between subjects with anorexia nervosa and control subjects. In fact, if a single covariate is to be used for the data of Polito et al, it would be more appropriate to use body weight than to use fat-free mass. The rationale for using fat-free mass as a single covariate is that it is the best predictor of BMR (7). However, the data of Polito et al show that, for their subjects, body weight and not fat-free mass was the best BMR predictor (r^2 = 0.62 and 0.48 for body weight and fat-free mass, respectively; Figure 1 of the article).

Thus, a plausible explanation for the lower BMRs in subjects with anorexia nervosa after control for fat-free mass is their greatly reduced fat mass. To eliminate this possibility, Polito et al could reanalyze their data using analysis of covariance to control for both fat mass and fat-free mass. This would either strengthen their conclusion that reductions in BMR with anorexia nervosa are not due to body composition changes or invalidate that conclusion.

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Reply to DJ Stensel

Dear Sir:

We appreciate Stensel's comments on our article (1). He questions our conclusion that "BMR is depressed in anorexia nervosa . . . suggesting that the metabolic activity of the active tissue mass may been reduced." Stensel points out that "a plausible explanation for the lower BMR values in subjects with anorexia nervosa after control for fat-free mass is their greatly reduced fat mass."

We agree that differences in fat mass (FM) can explain part of the interindividual variability in basal metabolic rate (BMR), but only to a very limited extent, and we maintain that the mechanism of this effect does not invalidate our conclusions. FM consists of ether-soluble lipids and, as such, is to be considered metabolically inert. The contribution to BMR that has been attributed to FM by some authors (2–4), especially in obese women, is still the subject of controversy; a plausible explanation can be found only by equating FM with adipose tissue (2). Lipids are deposited in the body as adipose tissue, which requires a cellular matrix that, in healthy subjects, represents ≈20% of this tissue. This cellular matrix is metabolically active and therefore can contribute to BMR. The proportion of cellular matrix in adipose tissue is inversely associated with FM, and it has been calculated that in obese subjects—whose fat cells are more tightly packed with lipids than are those of lean subjects—it would represent no more than 16%; in anorectic individuals—whose adipocytes have lost most of their lipid deposit—it might increase to ≥21% (5). Therefore, we can expect that the relatively larger cellular matrix and the smaller fat deposit of the anorectic patients might result in an increase in BMR after control for FM.

Stensel suggests performing an analysis of covariance (ANCOVA) with simultaneous inclusion of FM and fat-free mass (FFM). This analysis is inappropriate statistically for our data because the regression slopes of BMR versus FM of the 2 groups were significantly different ($P < 0.01$), whereas the regression slopes of BMR versus body weight and FFM were parallel. The key assumption of homogeneity of the regression slopes is required for performing ANCOVA and the violation of this assumption would lead to gross misinterpretation of results and introduce serious biases (6, 7). Because of this limitation, we had performed an extension of ANCOVA suitable for use with heterogeneous regression slopes (Johnson-Neyman procedure; 8). This statistical technique computes "regions of significant differences" and was applied by other authors for a similar problem (7). The results confirm that FM does not represent a significant covariate in the model ($P = 0.94$) and that FFM and FM are not unique estimators of BMR. When the 95% CI of nonsignificance was calculated, BMR controlled for both FFM and FM was significantly lower in subjects with FM <10 kg. For these reasons, we maintain our conclusions that BMR is reduced in anorexia nervosa and that this observation suggests a reduction in the metabolic activity of the active tissue mass in anorexia nervosa.

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