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Papers

Elevated Energy Expenditure in Cancer Patients with Solid Tumours

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Cancer patients (n = 106) and non-cancer subjects (n = 96) were classified as weight stable (n = 70) or weight-losing (n = 132). Cancer patients had elevated resting energy expenditure (REE) compared with either weight-losing (23.6 [0.4] vs. 20.5 [0.5] kcal/kg per day, $P < 0.001$) or weight-stable controls (22.0 [0.6] vs. 17.9 [0.4], $P < 0.001$). Cancer patients had increased fat oxidation irrespective of weight loss (1.24 [0.07] vs. 0.87 [0.04] mg/kg per min; 1.07 [0.04] vs. 0.78 [0.04], $P < 0.001$). Elevated energy expenditure was counter-regulated by a decrease in thyroid hormones. Abnormal liver function had no impact on REE in either group. Heart rate was the most powerful factor for prediction of high energy expenditure in both patients and controls. Elevated energy expenditure was related to the increased heart rate in cancer patients in a significantly higher proportion than that in controls. Increased metabolic rate is a significant component behind weight loss in cancer disease, independent of malnutrition and an elevated adrenergic state may be a likely explanation.
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INTRODUCTION

WHETHER CANCER patients lose weight primarily because of elevated energy expenditure or anorexia is controversial. Many cancer patients have elevated energy expenditure [1–5], which contributes significantly to weight loss with anorexia [6, 7]. However, the mechanisms behind elevated metabolism are unclear, although alterations in intermediary metabolism are involved. Such metabolic changes include increased glucose–carbon cycling [8–10], elevated protein turnover in some organ or tissue compartments [11–13] and possibly increased fat oxidation [14]. Altered tumour–host metabolism may represent normal adaption to partial starvation [15], although the higher resting energy expenditure in many cancer patients is a metabolic feature which undernutrition in itself cannot account for [4].

Our aim was to identify and weigh mathematically various factors that may either induce or promote elevated metabolism in weight-losing patients with solid tumours.

SUBJECTS AND METHODS

Our 202 subjects were studied between 1981 and 1987. Cancer patients and controls were included, based on chance when referred to our surgical ward. All patients who were treated in one of six surgical wards were considered. Our patients were allocated to the different wards consecutively. Control patients were included by the same procedure. Thus, study and control groups were recruited from the same large population, except for some healthy volunteers who acted as controls. Inclusion in the cancer group was based on a malignant diagnosis with or without nutritional disturbances. Tumour diagnosis and stage were confirmed by biopsy, computerised tomography, angiography, biochemical tests and clinical examination. None of the patients had received any medical treatment of known importance for the study within 6 months before our measurements, and none had received chemotherapy or radiotherapy. Non-cancer patients with or without malnutrition were used as controls. They were included from the same ward based on diagnoses associated with a high risk of nutritional disturbances superficially similar to those found in cancer patients. In addition, patients with no obvious risk for undernutrition were included (e.g. uncomplicated varicose veins, inguinal hernia). All patients had spent at least 3 days in the ward before measurements and they had been on a regular hospital diet of 34% fat, 48% carbohydrates and 18% protein. None of the patients had spent more than 6 days in the ward before investigation. Duration of inpatient stay did not differ among the groups. Food intake was not measured systematically. Estimates of food intake in subgroups of both study patients and controls revealed as expected a large variation between a normal and lowered intake, down to 400–500 kcal per day. Cancer patients and controls were divided into subgroups based on weight loss exceeding 4% of their normal weight during a recent 6 month period. 4% weight loss is at least ten times the sensitivity of the weighing procedure. The clinical and nutritional measures are shown in Table 1.

Weight-losing cancer patients. 81 patients with a mean weight loss of 16 (S.E.) 1%. All patients had clinical or biochemical signs of undernutrition in addition to weight loss. None was totally bedridden. The carcinomas included testicular (6), hepatic (18), colonic (16), gastric (9), oesophageal (8), pancreatic (5), salivary gland (3), prostatic (3), gallbladder (2), ovarian (2) and renal (1). There were 3 patients with retroperitoneal

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Table 1. *Nutritional status (mean, S.E.)*

	Cancer patients		Controls		
	Weight-losing (n=81)	Weight-stable (n=25)	Weight-losing (n=51)	Weight-stable (n=45)	P
Age (yr)	59 (2)	44 (3)‡	59 (2)	60 (2)	<0.01
Weight (kg)	58.1 (1.4)	72.6 (2.3)	58.5 (1.9)	72.4 (2.0)	<0.01
Height (cm)	171 (1)	176 (2)	169 (2)	172 (1)	NS
Body surface (m^2)	1.66 (0.02)	1.91 (0.04)	1.66 (0.03)	1.86 (0.03)	<0.01
Weight loss (kg)	16 (1)	0	13 (1)	0	<0.01
TBK (mmol)	2719 (118) (n=45)	3736 (267) (n=13)	2736 (146) (n=27)	3256 (162) (n=25)	<0.01
TBK index	0.92 (0.02)	0.99 (0.03)	0.96 (0.02)	1.0 (0.02)	<0.07
Albumin (g/l)*	31.2 (0.6)	36.0 (1.3)‡	33.9 (0.9)	39.0 (0.9)	<0.01
TSF (mm)	8.7 (0.5)†	13.9 (1.0)	11.3 (1.0)	15.0 (1.2)	<0.01
AMC (cm)	21.6 (0.4)	24.9 (0.5)	21.6 (0.5)	24.4 (0.5)	<0.01
Haemoglobin (g/l)*	116 (2)†	132 (5)	124 (2)	138 (3)	<0.01
ALP (U/l)*	15 (3)†	6.1 (1.9)	4.0 (0.4)	4.2 (0.5)	<0.01
ESR (mm/h)*	53 (4)†	30 (5)	26 (4)	15 (2)	<0.01
AST (U/l)*	1.0 (0.1)†	0.8 (0.1)	0.5 (0.1)	0.6 (0.1)	<0.01
ALT (U/l)*	0.7 (0.1)	0.8 (0.2)	0.4 (0.1)	0.6 (0.1)	NS

*Normal values: albumin, 36–50; haemoglobin, 132–160; ALP, < 5; ESR, < 20; AST, < 0.5; and ALT, < 0.5.
†P < 0.025 vs. weight-losing controls. ‡P < 0.025 vs. weight-stable controls.
TBK = total body potassium, TSF = triceps skinfold, AMC = arm muscle circumference, ALP = alkaline phosphatase, ESR = erythrocyte sedimentation rate, AST = aspartate aminotransferase and ALT = alanine aminotransferase.

sarcoma, 3 with non-Hodgkin lymphoma, 1 with melanocarcinoma and 1 with malignant xantogranuloma.

Weight-stable cancer patients. 25 patients without any weight loss but some with altered blood biochemistry (Table 1). The carcinomas included testicular (10), hepatic (4), gastric (2), colonic (2), pancreatic (2) and renal (1). There were 2 retroperitoneal sarcomas, 1 melanocarcinoma and 1 non-Hodgkin lymphoma.

Weight-losing controls. 51 patients with a mean weight loss of 13 (1%). All these patients had anthropometric or biochemical signs of undernutrition. None was totally bedridden. The diagnoses were: local or general arteriosclerosis (8), peptic ulcer (7), abdominal pain and admitted for observation (6), cholecystitis (6), anorexia nervosa (4), Crohn's disease (4), aortic aneurysm (3), non-viral hepatitis (1), inguinal hernia (2), hepatic cirrhosis (1), chronic haemorrhoids (1), pancreatitis (1), thoracic outlet syndrome (1), gastric stomal stricture (1), abdominal abscess (1), caval thrombosis (1), ulcerative colitis (1), intestinal obstruction (1) and Raynaud's disease (1).

Weight-stable controls. 45 subjects without clinical signs of undernutrition or biochemical evidence of abnormality. The diagnoses of patients included varicose veins (8), inguinal hernia (9), local or general arteriosclerosis (6), carotid stenosis (3), colonic adenoma (2), Crohn's disease (1), abdominal pain and admitted for observation (1), otosclerosis (1), benign glomus tumour (1), cholecystitis (1), testicular hydrocele (1), pilonidal cyst (1), phimosis (1), osteoporosis (1) and pancreatic cyst (1). This group also included 7 healthy volunteers.

Nutritional status and biochemical tests

Measures included body weight and height with a precision better than 1%. Plasma albumin concentration was assayed with the bromocresol green method. TSF was measured by a caliper on the dorsal midpart of the upper non-dominant arm and midarm circumference (MAC) was measured half-way between the coracoid process and olecranon by a specially trained nurse. AMC was calculated from TSF and MAC [16]. The mean of three measurements of TSF and MAC was used. TBK was assayed in a ^{40}K whole-body counter [3]. TBK index was derived by dividing measured body potassium in our patients by the expected whole-body potassium content in matched individuals from a normal reference population, accounting for age, sex, height and body weight [17]. Blood haemoglobin concentration, ESR and liver function tests (ALP, AST, ALT) were routine hospital measurements. Serum concentrations of thyroid hormones were measured by radioimmunoassay. Thyroid stimulating hormone (TSH) and tri-iodothyronine (T3) kits were from Diagnostic Products. The thyroxine (T4) kit was from Farmos Diagnostica. Amerlex-M kits for free T3 and T4 were from Amersham International. r-T3 was measured by a kit from Serono Diagnostics.

Indirect calorimetry

Respiratory gas exchanges were measured with two systems. The first part of the study (119 subjects) was done with the same technique we have used previously [3, 18]. In the second part (83 subjects) we used a commercially available system, Deltatrac (Datex, Helsinki). Both systems are based on paramagnetic measurements of oxygen and represent similar semi open canopy systems. The two methods give the same results in calibration procedures, with a correlation coefficient of 0.96 and each method has an overall coefficient of variation of less than 5%. The Deltatrac equipment is now our standard procedure because of its easier calibration.

Resting energy expenditure (REE, kcal/24 h) was calculated from de Weir's formula [19]: $0.537\,O_2(3.78 + 1.16\,RQ) - 43.2$; where O_2 is the oxygen uptake in mmol/24 h and RQ the respiratory quotient. It was anticipated that complete nitrogen excretion would not be possible to assess during a standardised 3 day period in all patients. Therefore it was not included as a regular part of the protocol. Carbohydrate and fat oxidation were estimated as described by Lusk [20]. Omitting the factor for urinary nitrogen in these calculations gives less than 3–4% error. Predicted energy expenditure was calculated according to the Harris–Benedict equation [21].

Investigative procedure

All subjects were investigated in bed in resting conditions between 0800 and 0900 after an overnight fast, with a rest period of at least 1 h before measurements started. Gas exchanges were measured for at least 30 min [3, 18]. Oxygen uptake and carbon dioxide production were continuously followed on a recorder, which allowed evaluation of steady-state conditions. The first 3 min of all recordings was discarded as an adaption period in the canopy. All values obtained after 3 min and lasting for 30 min were used as the appropriate measurements irrespective of individual variability. Nutritional state, body temperature (rectal), respiration rate, heart rate and blood samples were assessed after measurements of energy expenditure. The subjects were also weighed at this time.

Statistics

Comparisons among the groups were made by analysis of variance (ANOVA) with a complete randomised block design [22]. When significance was obtained a multiple range test was applied to test groups against each other. Weight-losing cancer patients were only compared to weight-losing controls and weight-stable cancer patients against weight-stable controls. No other comparisons were made. Results are also presented according to factorial analyses, among cancer and non-cancer subjects with and without weight loss, as obtained with the complete randomised block design. Regressions were calculated by the least squares method and significance was tested by ANOVA. The slopes between two regressions were compared by parametric statistics. Multivariate analyses were done by multiple regressions and ANOVA. $P < 0.025$ was considered as the level of statistical significance with two-sided tests.

RESULTS

Nutritional status

The groups were reasonably well-matched for nutritional status (Table 1), but weight-losing cancer patients had significantly higher ESR, ALP and AST and lower haemoglobin concentration, probably indicating more severe inflammation and tissue influence compared with weight-losing controls. Weight-stable cancer patients were significantly younger than weight-stable control subjects. However, age-related changes in energy expenditure are probably explained by differences in body composition (our unpublished data). ALT showed a non-significant trend to be higher in cancer patients as a group compared with controls. Weight-losing patients suffered from both energy and protein deficit, while protein and energy status were not significantly abnormal in the weight-stable groups. Serum albumin showed a subnormal trend in weight-stable cancer patients, perhaps related to either insidious inflammation or subnormal protein intake. Anaemia was overt in both weight-losing cancer patients and controls. The frequency of abnormal liver function tests did not differ significantly between cancer patients and controls. Plasma concentration of electrolytes and serum creatinine were normal in all patients and did not differ between the groups (results not shown).

Energy expenditure

REE was significantly higher in cancer patients compared with controls, irrespective of weight loss (Table 2). This finding was independent of whether resting energy expenditure was normalised to body weight or body surface area. Only weight-losing cancer patients had elevated energy expenditure normalised to whole body potassium. However, cancer patients as a group had significantly elevated energy expenditure when plotted against TBK, irrespective of subgrouping (Fig. 1). Predicted energy expenditure agreed with measured expenditure in weight-losing cancer patients, but it appeared to be lower than predicted values in the other groups in weight-stable cancer patients, and weight-losing controls, and reached a significantly lower measured expenditure than predicted in weight-stable controls. This may be explained by the fact that Harris and Benedict's equation was derived from measurements on young individuals, who probably had larger lean body mass than our older weight-stable controls. The elevated energy expenditure in weight-losing and weight-stable cancer patients was associated with an increased fat oxidation and a non-significant trend to a decreased carbohydrate oxidation in weight-losing cancer patients. Factorial analysis showed that both cancer disease ($P < 0.0005$) and weight loss ($P < 0.0001$) contributed to the statistical significance for REE in tumour patients, while only cancer disease contributed to the increased fat oxidation ($P < 0.0001$). When energy expenditure per TBK was compared among the groups, weight loss was a significant factor ($P < 0.002$) while cancer disease represented a trend factor only ($P < 0.07$) to explain the difference in variance in metabolic rate among cancer patients and controls.

Thyroid hormones and physiological varables

Body temperature and respiration frequency were similar and normal in all the groups, while heart rate was significantly higher in both weight-losing and weight-stable cancer patients (Table 3). Both cancer disease and weight loss contributed to explain the significantly altered serum concentration of thyroid hormones in undernourished patients with and without malignancy. Lowered free T3 was primarily explained by weight loss ($P < 0.01$), while rising rT3-levels were explained by cancer disease ($P < 0.025$, Table 4) according to factorial analyses.

Co-variates

REE was positively correlated to heart rate and was negatively correlated to blood haemoglobin concentration in all groups. SR was significantly correlated to REE in cancer patients only (Figs 2–4).

Table 2. Whole body energy expenditure and substrate oxidation

	Cancer patients		Controls		
	Weight-losing	Weight-stable	Weight-losing	Weight-stable	*P*
Oxygen uptake (μmol/min)	9216 (231)*	10651 (296)†	8009 (228)	8613 (215)	<0.01
Oxygen uptake (μmol/kg/min)	160 (2.8)*	148 (3.9)†	139 (3.2)	121 (2.3)	<0.01
RQ	0.80 (0.006)*	0.80 (0.006)†	0.83 (0.007)	0.83 (0.007)	<0.01
REE (kcal/day)	1365 (36)*	1586 (48)†	1181 (34)	1273 (33)	<0.01
PREE (kcal/day)	1322 (27)*	1642 (46)	1310 (34)	1483 (38)	<0.01
REE (kcal/kg/day)	23.6 (0.4)*	22.0 (0.6)†	20.5 (0.5)	17.9 (0.4)	<0.01
REE (kcal/m²/day)	815 (14)*	839 (20)†	710 (13)	683 (12)	<0.01
REE (kcal/TBK/day)	0.52 (0.02)*	0.41 (0.02)	0.45 (0.02)	0.41 (0.01)	<0.01
CHO oxidation (mg/kg/min)	1.32 (0.15)	1.41 (0.11)	1.65 (0.12)	1.40 (0.09)	NS
Fat oxidation (mg/kg/min)	1.24 (0.07)*	1.07 (0.04)†	0.87 (0.04)	0.78 (0.04)	<0.01

*$P < 0.025$ vs. weight-losing controls. $P < 0.025$ vs. weight-stable controls.
PREE = predicted REE and CHO = carbohydrate.

Serum concentrations of thyroid hormones were related to energy expenditure with a borderline significance ($P < 0.06$) without a clear cut significant contribution from any single hormone measurement in multiple regression analyses based on all the subjects. Free T3 and rT3 which had the highest partial F value in regression analyses against energy expenditure, were therefore included in further multiple regressions.

Analyses of correlation coefficients showed that body weight, TBK, ALP and ESR were correlated significantly to REE, based on pooled observations from all the subjects. However, when these variables were used in multiple regression analysis vs. REE only heart rate contributed significantly ($P < 0.0001$) to explain the variability in resting expenditure in both cancer patients and controls with the same degree of influence ($\beta = 0.06$ [$P < 0.044$] vs. $\beta = 0.07$ [$P < 0.057$], respectively).

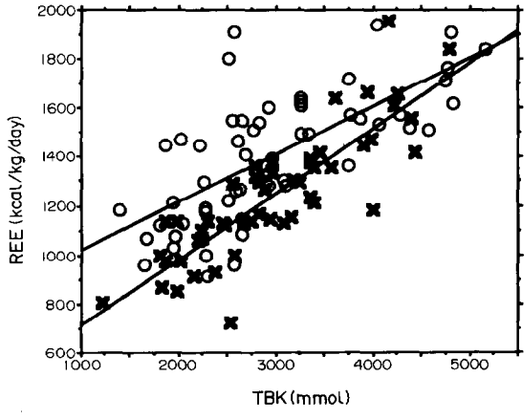

Fig. 1. Relationship between TBK and REE in cancer patients (○) and controls (×) irrespective of preceding weight loss, undernutrition or abnormal biochemical tests. Slopes are significantly different from each other ($P < 0.001$: cancer $y = 822 + 0.196x$, $r = 0.69$, $n = 57$; controls $y = 451 + 0.267x$, $r = 0.85$, $n = 52$.

Since abnormal concentrations of ALP showed a statistically significant impact on energy expenditure when heart rate was omitted, recalculation was done on cancer patients vs. controls with and without the exclusion of all subjects with abnormal liver function tests. Cancer patients with normal liver function expended 22.5 (0.6) kcal/kg per day ($n = 36$) and controls with normal liver tests expended 18.9 (0.4) kcal/kg per day ($n = 64$) ($P < 0.001$). Calculations based only on subjects with pathological liver tests showed 23.0 (0.5) kcal/kg per day in cancer patients ($n = 62$) and 19.1 (0.7) in controls ($n = 23$) ($P < 0.001$). Likewise, cancer patients without any obvious sign of inflammation (normal ESR) expended 21.8 (0.8) kcal/kg per day ($n = 20$) compared with 18.2 (0.5) in controls ($n = 47$) ($P < 0.0001$).

DISCUSSION

Complete measurements were not available in all patients, particularly for TBK. The long period that was necessary to recruit the subjects may explain limitations in design, especially for the measurement of inflammation. However, it is our experience that ESR correlates well with additional measures of inflammation, such as the plasma concentration of acute phase proteins, when chronic changes are monitored.

Our results confirmed elevated energy expenditure in many cancer patients with solid tumour of various types and aetiology

Table 3. Body temperature, respiration and heart rate

	Cancer patients		Controls		
	Weight-losing	Weight-stable	Weight-losing	Weight-stable	*P*
Temperature (°C)	37.1 (0.1)	36.8 (0.1)	36.9 (0.1)	36.9 (0.1)	NS
Respiration rate (/min)	17 (0.4)	16 (0.6)	16 (0.6)	16 (0.5)	NS
Heart rate (/min)	81 (2)*	79 (3)†	75 (3)	66 (2)	<0.01

*$P < 0.025$ vs. weight-losing controls. †$P < 0.025$ vs. weight-stable controls.

Table 4. Serum concentrations of thyroid hormones

	Cancer patients		Controls		
	Weight-losing	Weight-stable	Weight-losing	Weight-stable	*P*
T4 (nmol/l)	97 (6)	87 (5)	78 (8)	89 (5)	NS
T3 (nmol/l)	1.25 (0.09)	1.85 (0.09)	1.44 (0.28)	1.86 (0.10)	NS
Free T4 (pmol/l)	13 (0.8)	15 (0.9)	12 (1.2)	14 (0.7)	NS
Free T3 (pmol/l)	3.2 (0.3)	6.8 (0.5)	4.7 (1.0)	6.3 (0.5)	<0.02
rT3 (nmol/l)	0.54 (0.05)*	0.36 (0.02)	0.35 (0.04)	0.35 (0.02)	<0.02
TSH (nmol/l)	2.83 (0.32)	2.25 (0.27)	5.33 (1.9)	1.75 (0.16)	NS

*$P < 0.025$ vs. weight-losing controls.

[1–5], although this is not a consistent finding [7]. Our study also demonstrated that elevated basal metabolism in cancer patients is a statistical finding, which means that not all patients with cancer have increased expenditure. We have previously reported that this may vary in individual patients with disease progression [1].

Alterations in body composition may introduce seemingly altered energy expenditure among study and control groups when measurements are normalised to body weight. Elevated metabolic rate in cancer patients was, however, independent of whether expenditure was normalised to body weight, body surface area or TBK. TBK showed the strongest correlation to energy expenditure ($r = 0.83$) compared with any body measure, while body weight had a correlation coefficient of 0.60 on pooled observations. Elevated expenditure in cancer patients was also obvious when energy expenditure (kcal per day) was plotted against actual body weight or body potassium without any grouping into weight-stable and weight-losing subjects. To reduce the risk of misinterpretations further, we have also analysed the data based on classification into subgroups with either weight loss or stable weight. Weight-losing cancer patients

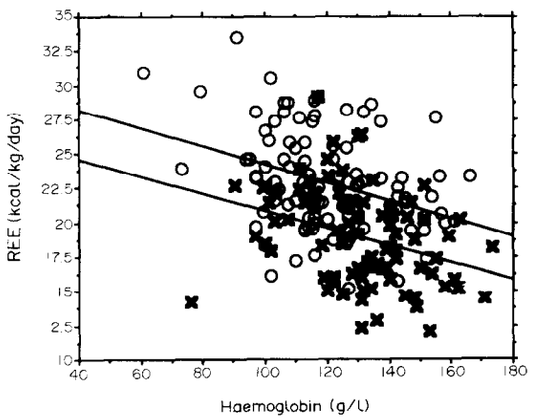

Fig. 2. REE and blood haemoglobin concentration. Cancer (○): $y = 30.8 - 0.065x$, $r = 0.35$, $n = 100$, $P < 0.0004$; controls (×): $y = 27.1 - 0.063x$, $r = 0.33$, $n = 87$, $P < 0.0016$.

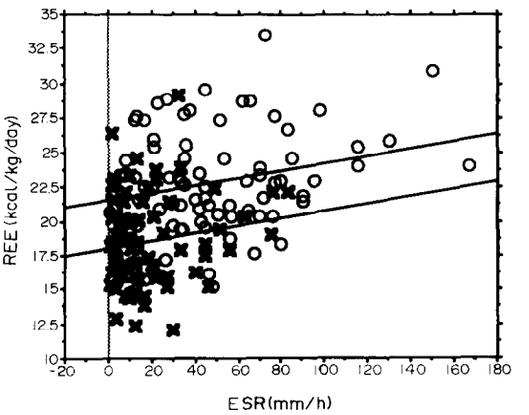

Fig. 3. REE and ESR. Cancer (○): $y = 21.58 + 0.027x$, $r = 0.25$, $n = 83$, $P < 0.023$. Controls (×): $y = 18.05 + 0.028x$, $r = 0.16$, NS.

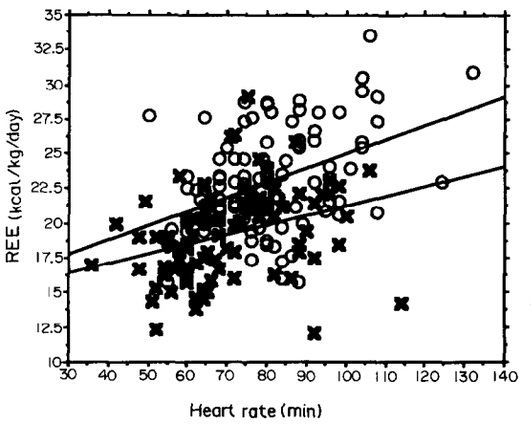

Fig. 4. REE and heat rate. Slopes are significantly different from each other ($P < 0.001$). Cancer (○): $y = 14.68 + 0.103x$, $r = 0.42$, $n = 105$, $P < 0.0001$; Controls (×): $y = 14.34 + 0.070x$, $r = 0.32$, $n = 90$, $P < 0.0021$.

were only compared with weight-losing subjects without cancer and weight-stable cancer patients were compared with weight stable subjects without cancer. Although this approach can never guarantee complete stratification of background variables, our subjects in the various groups were reasonably similar in measures that are known to explain variation in REE. Variables not measured (e.g. genetic traits, physical activity, food selection) could theoretically influence energy expenditure. Even with this limitation our results demonstrated a significantly elevated metabolism in both weight-losing and weight-stable cancer patients, to which both cancer disease and weight loss contributed as significant factors, while increased fat oxidation in cancer patients only was delineated by cancer disease. Therefore, we conclude that increased energy expenditure is of true metabolic origin and is not only a mathematical finding that appears when the expenditure values are normalised to dependent variables. The finding that elevated expenditure was independent of a preceding weight loss also suggested that it is not only a secondary adaption to undernutrition in cancer patients but may also represent something else appearing early in the clinical course.

Heart rate was the single most powerful factor that predicted alterations in REE in both cancer patients and controls, but cancer patients had a significantly steeper slope between heart rate and energy expenditure compared with controls. This fact confirms the validity of our previous studies where we estimated energy expenditure in cancer patients from continuous daily recordings of heart rate; a technique that was used for measurements of both non-resting and resting metabolism [1]. We have reported that oxygen consumption is increased in perfused working hearts from tumour-bearing animals in a way that was not seen in either malnourished or well-nourished control animals without cancer [26]. Further experiments have suggested that alteration in the adrenergic state (i.e. whole-body catecholamine sensitivity and production) may be upregulated in cancer-bearing hosts. This hypothesis has support in our and other findings that many cancer patients have both elevated plasma concentrations of catecholamines and increased urinary excretion of adrenergic substances [27, 28]. Such patients also have an increased cardiovascular and metabolic response to adrenaline infusion [29]. On the contrary, undernourished individuals without cancer generally show a decrease in the adrenergic tone and catecholamine turnover [30–32]. The explanation behind an increase in the adrenergic state of cancer-bearing hosts may in part involve the appearance of a cardiac β-receptor with extremely high affinity to adrenergic agonists [33]. The appearance of this receptor seems to some extent to be secondary to the undernutrition, as confirmed by ourselves and others [30, 33]. It is interesting that our cancer patients had a significantly higher heart rate which, however, was not primarily dependent on malnutrition although undernutrition may contribute. This was supported by factorial analysis in addition to the finding that weight-losing controls had a significantly higher heart rate compared with well-nourished controls ($P < 0.0025$, Table 3). These alterations in heart rates were independent of body temperature and respiration frequency.

We and others have suggested that various cytokines, particularly interleukin 1 (IL-1), tumour necrosis factor alpha (TNF-α) and interleukin 6, may be inducers and promoters behind wasting in clinical conditions associated with inflammation [34–36] and tumour disease [37, 38]. Injection of recombinant cytokines elicits similar changes in metabolism and nutritional state as found in cancer cachexia [39], trauma and infection [40–42]. Insertion of the TNF-α gene into tumour cells by transfection made tumour-bearing animals become cachectic [43]. Our studies have indicated that altered and increased spontaneous expression of the TNF-α gene in an experimental tumour-bearing host significantly contributed to wasting, especially body fat but also lean tissue [44]. It is, however, still unclear to what extent these cytokines might explain the progressive wasting in conditions with solid human tumours, although it is obvious that the infusion of recombinant cytokines elicits metabolic alterations that are similar to findings in cancer disease. Previous measurements on subgroups of our patients could not confirm any increased plasma levels of TNF-α or IL-1 [45].

Inflammation and anaemia were significant stimulators of REE. The two factors were, however, of similar magnitude in both cancer patients and controls, although the lack of a significant correlation in controls between metabolic rate and inflammation may seem suggestive. However, the two regressions had almost identical slopes, although one was significantly different from zero (cancer) and the other was not (controls). Based on the finding that heart rate was the most powerful predictor of energy expenditure in both groups and the fact that cancer patients had higher heart rates irrespective of weight loss, and a regression (Fig. 4) that was significantly steeper than that found in controls, we find it more likely that the "cancer-associated part" of the elevated energy expenditure may depend on altered adrenergic state rather than on the effect of cytokines or the degree of inflammation. However, adrenergic and cytokine effects may also be interrelated and act in concert to stimulate thermogenesis [46]. We have reported that our malnourished cancer patients had significantly increased plasma adrenaline [29].

We have confirmed the highly controversial issue that many cancer patients with solid tumour have elevated REE independent of malnutrition. Whether this represents a lack of adaption in energy expenditure to undernutrition or a true increase in metabolic rate is unclear. The significantly higher fat oxidation in cancer patients without weight loss may suggest adrenergic stimulation of lipolysis and subsequent changes in oxidative metabolism, to which the adaption in thyroid hormones counteracts when the nutritional deficits become significant. Statistical analysis suggests that inflammation and cytokines are not the

specific promoters behind high metabolism in cancer patients, although anaemia and inflammation are general factors behind elevated energy expenditure in such patients. Adrenergic factors seem to be more important in this respect. It cannot be excluded that anxiety may be a significant and early factor.

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