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The Role of Fat as a Calorie Source in Parenteral Nutrition*)

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With 6 figures and 2 tables

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Endogenous Reserves and Parenteral Supply of Fat

From the point of view of cellular nutrition, there is little reason to doubt that the quantitative and qualitative requirements of several basic nutrients are about the same whether they are met enterally or parenterally. In countries with a higher living standard fat usually contributes up to 40 % of the total daily caloric intake. Recommendations amount to a minimum of at least 20 % or better 25–30 % (1). Accordingly, a German expert group of the International Society for Parenteral Nutrition concluded that 30 % of the total calories of a parenteral regime should be supplied as fat (table 1) (2). This amount might be increased in children, especially neonates (3, 4), since their physiological nutrition by breast milk contains about 50 % of the total calories as fat. The recommendation to achieve a better fat clearance by heparin, however, suggests that there is a metabolic limit. In severely undernourished patients, too, the percentage of fat may be increased to achieve a better caloric supply.

At first sight, it might seem unnecessary to use exogenous fat in a normally nourished patient who is to be fed parenterally for a short or medium term. Compared with the stores of protein and carbohydrate the body has considerable fat stores which can be mobilised without any functional consequences. Indeed, this is the case in certain situations. The adipose tissue is a large organ, amounting to some 8–20 kgms. This

Table 1. Proposal of a fully balanced regime for parenteral nutrition (2, 6a)

Amino Acids	Carbohydrates	Fat Emulsion
~ 20%	~ 50% of total calories	~ 30%

↓ (Fat Emulsion)

appr. dose 80–100 g in adults

↓

infusion rate $\leqq$ 0,15 g/kg and hour ($\leqq$ 10 g/hour)

Essential Fatty Acids important in long term therapy

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corresponds, assuming 80 % fat content in adipose tissue, to a store of between 50.000 and 150.000 kcal. Only in severely cachectic patients does it decrease to 1 kg corresponding to about 7.000 kcal (1). Since the papers of *Wertheimer* and *Shapiro* in 1948 it has been well known that adipose tissue has a considerable metabolic activity which increases rapidly on special demand as e. g. I will show later by reference to our own postoperative measurements. The turnover of non-esterified fatty acids (NEFA) in the blood can amount to up to 30 %/min. With a concentration of 0.5 mmoles per l of plasma or about 130 mgms/l, a normal fasting level of circulating NEFA of 3.6 kcal can be calculated. If 30 % of these calories are made available per minute, the amount per day will be 1730 kcal, that is about the basal metabolic requirement. Assuming that even 100 % of the total caloric turnover is covered by fat, the above-mentioned stores should theoretically suffice for some 30 days. Indeed, there are reports existing of successful long-term nutrition with a high supply of carbohydrates and alcohol instead of fat as a calorie source. One of these examples was reported by *Coats* (25).

In spite of these facts, there is no doubt that intravenous fat may serve as a direct metabolic fuel under certain conditions. Obviously by using parenteral fat sufficient calories may be successfully provided to humans in normal hormonal balance, so that the body does not shift to fasting metabolism. As shown, in fasting conditions the body would certainly be able to live on endogenous reserves, but simultaneously would switch over to gluconeogenesis from proteins with subsequent nitrogen losses. At any rate, such nitrogen losses may well be obviated by fat emulsions. ^{14}C tracer experiments with fat emulsions showed considerable turnover rates [ref. see (5, 6)]. On the other hand we would not quantitatively relate to post-operative patients those data suggesting a rate of 50 % transformation into $^{14}CO_2$ during 24 hours [see (5)] nor even 70 % during 4 hours (7). I will come back to this.

In general the necessity of incorporating fat into a parenteral regime arises at least in short-term nutrition mainly from the technical problems which arise from the intravenous infusion of osmotically highly active solutions of carbohydrates and/or from the tolerance to ethyl alcohol. In contrast to carbohydrate solutions, fat emulsions allow us to supply many calories in a small fluid volume without osmotic damage to peripheral veins and thus they can be of beneficial value, if certain contraindications are observed. [Apart from these questions, fat emulsions play an important role because of their content of essential fatty acids especially in patients with latent or manifest essential fatty acid deficiency, patients with enhanced requirement because of growth or tissue repair, and in long term parenteral nutrition (25).]

Stress, calorie requirement, and lipolysis

These principal considerations in general are valid for all patients to be fed parenterally. Some special conditions seem to apply to post-operative or traumatised patients. Let us start with their enhanced metabolic expenditure at rest. Table 2 shows some examples of newer data on the percentage increase in several clinical conditions. Such figures also seem

Table 2. Examples of percentage increase of basal caloric expenditure under several clinical conditions (taken from [7, 8, 20, 21, 22])

Author	Condition	Calorie Demands
ISPN (2)	normal adults	25–30 kcal/kg BW · day or 1300 kcal/m² · day, resp.
Johnston 1971	abdominal surgery of moderate severity	additionally 10% approx.
Brückner 1969	epigastric laparotomy	additionally 15%
Kinney 1970	multiple fractures	additionally 25%
Edgren 1960	per centigrade fever	additionally 13%
Kinney 1970	infection, inflammation	additionally 25–50%
Davies 1970	burns 10–25%	additionally 25%
	burns 26–50%	additionally 80%
	burns 51–85%	additionally 150%

to depend to a certain degree on the constitution, nutritional condition and age etc. of the patient [see (8, 22)], but let us disregard this. What appears is firstly, the stress of trauma or operation produces a considerable increase in caloric turnover [for a more detailed consideration see (9)]. Secondly, during an average nitrogen supply an enhanced caloric intake essentially should improve the nitrogen balance of the patients [ref. until 1960 see (5), more recent evaluations see 10a–10d]. In this situation it seems to be desirable to cover the increased demands of stressed patients with additional fat. Investigations of this possibility, however, are few and in general without direct comparisons. It is in this situation that the second special condition of stressed patients plays a role, which is the mobilisation of endogenous fat which inevitably occurs.

Fig. 1 shows the nervous and hormonal response of the body to stress. The lower part indicates that the effect is a general ergotropic shift. This is the principle of the enhanced basal metabolic expenditure, this is also the basis of the enhanced protein demand because of gluconeogenesis from

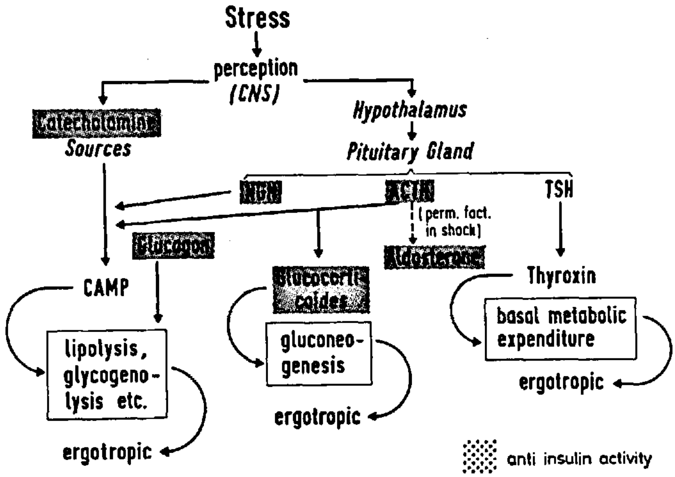


Fig. 1. Some nervous and hormonal responses to stress (24).

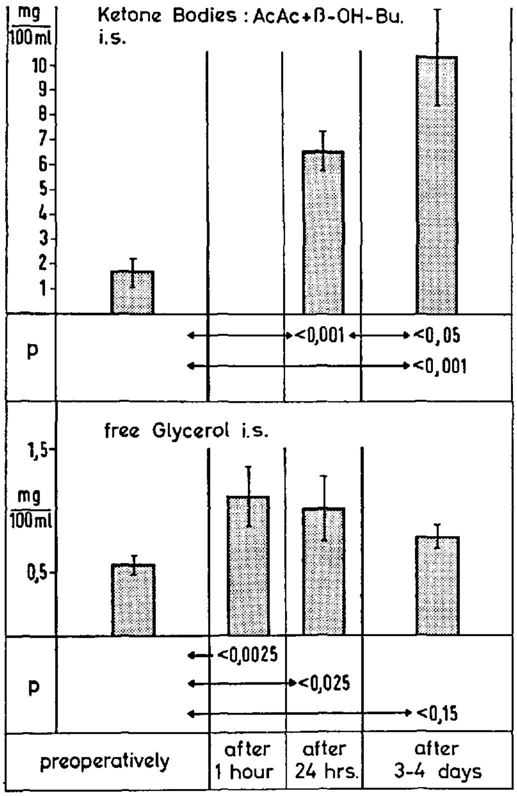


Fig. 2. Ketone bodies and free glycerol i. s. indicating lipolysis after operations (24).

amino acids and, moreover, of an enhanced lipolysis which serves ergotropy (24).

The local mediator for the enhanced lipolysis is cyclic-3'-5'-adenosinemonophosphate (CAMP). The concentration of CAMP is itself increased by adrenaline from the stimulated adrenal medulla as well as by noradrenaline which is formed at sympathetic nerve endings in the adipose tissue. In the same way human growth hormone is active (11, and ref. cit.) which according to *Hunter, Fonseka* and *Passmore* (12) may rise 20 fold in the blood within 30 mins. on ergotropic demand, e.g. with a man taking moderate exercise. These lipolytic activities are supported by the activity of the hormones, indicated in figure 1 by shading, which counteract the lipogenic insulin. The immediate start of lipolysis in adipose tissue may be illustrated by our data given in fig. 2 showing the highly significant rises of ketone bodies and free glycerol in connection with operations (24).

Free glycerol and ketone bodies are good parameters of mobilisation and utilisation of NEFAs. As is known, ketone bodies are formed by the liver. Inhibition of citrate synthetase by intracellular increase of long-chain acyl-CoA esters is probably responsible for this (13). This means inhibition of entry of acetyl-CoA into the cycle of final oxidation and consequently diversion into ketogenesis with regeneration of free CoA. That is useful as long as a severe keto-*acidosis* does not result. Skeletal and especially cardiac muscle are able to meet their energy demands with ketone bodies while due to the effect of preceding stress a so-called pseudo-diabetes exists since the utilisation of glucose is impaired.

Caloric Influence on Metabolism after Injury

The physician confronted with such conditions hopes that exogenous fat will improve cellular energy supply. The observation of nitrogen balance which means the difference between nitrogen input and output is the best parameter to monitor. Nitrogen represents the amount of functional tissue. Its pool without tissue function is extraordinarily small and as an alternative irreversible metabolic pathway only conversion to urea which is excreted in the urine is possible. During an inadequate caloric intake additional body proteins will be degraded to another caloric substrate and the nitrogen balance will become more negative. The relationship between caloric intake and nitrogen metabolism has been reviewed by *Munro* [(14), further ref. see (5, 22)].

So, some years ago we started to compare differently constituted caloric regimes with identical nitrogen supplies with respect to the N-balances to be achieved. Fig. 3 contrasts: group I receiving a fluid supply without calories, groups II and III receiving a regime almost covering the basal metabolic expenditures either with ethyl alcohol (Eth.) or with fat and group IV receiving a high-caloric intake, in general exceeding even the

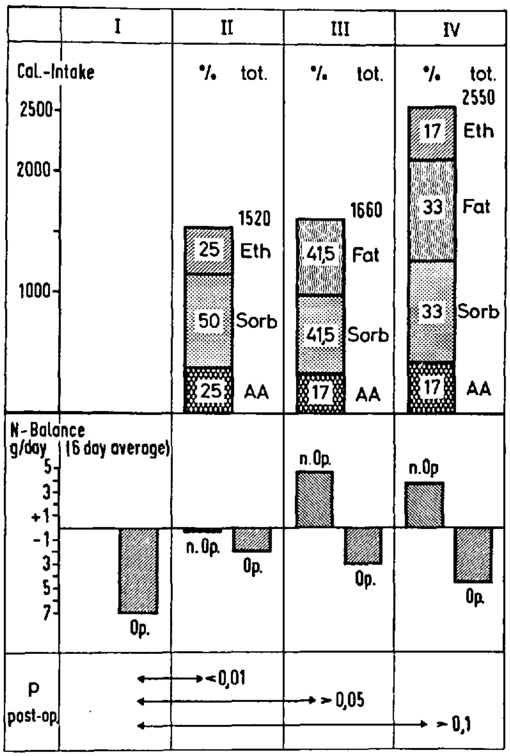
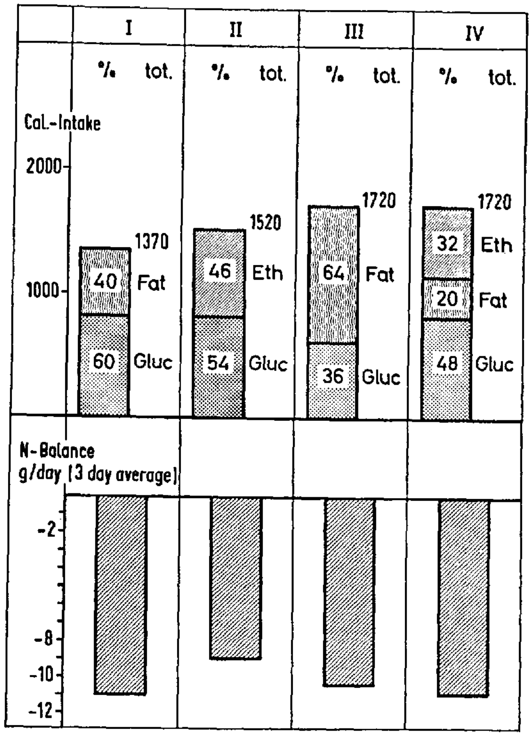


Fig. 3. The influence of different fully balanced regimes on nitrogen balances in stressed and unstressed patients.



acc. to KAZDA (1971)

Fig. 4. The influence of different, exclusively caloric regimes on nitrogen balances after stress.

increased requirement and consisting in addition to the amino acids (A.A.) of carbohydrates (Sorb. = Sorbitol), fat, and alcohol and thus offering 2550 kcal. The nitrogen balances make clear two different principles:

Firstly the transition to the calorically suboptimal intake of 1500 kcal without fat after operation (Op. = operated patients) produces a highly significant improvement which no surgeon should ignore. Replacement of the ethyl alcohol in group II, with some fat in group III, increases the calories slightly, but worsens the nitrogen balance to such an extent that it is no longer significantly different from group I. Obviously at least in operated patients the regime of group IV fails in spite of being high-caloric. One reason may be a metabolic incompatibility of fat and alcohol. Also it must be concluded that 35–40 % of calories as fat is too high in the early postoperative phase, because it will not be oxidised and therefore the theoretically calculated supply of total calories is misleading.

Second, a very clear contrast is seen between the postoperative phase and a situation without immediately preceding stress (n. Op. = non-operated patients). There being no preceding stress, the different regimes serve very well to achieve an equilibrated or even positive nitrogen balance. In such a situation 35–40 % of calories as parenteral fat can obviously be utilised. It is interesting to note that without preceding stress the combination of fat plus alcohol also proved disadvantageous. – The number of cases without stress, however, is too small to calculate significance and obviously unstressed patients maintained exclusively on parenteral nutrition for long periods are rare.

Kazda (15) in April this year published similar data. Fig. 4 contains the early postoperative results of groups of 5–6 patients each of whom had undergone abdominal operations because of tumors, illustrated from data of the original work. The more negative nitrogen balances are consistent with the severity of the operations and most likely also with the lack of amino acids. As this author included only one group with amino acids (for reasons of his own particular topic) and as no comparison with our present problem is possible, it was omitted. The whole situation accords with our view that there is an insufficient N-sparing effect given by fat in the postoperative phase. *Kazda* correspondingly found no difference between his groups I with 40 % of calories as fat and III with 64 % of calories as fat in spite of the additional 350 kcal. A slight improvement of 1.4 gms. of N-retention was observed by comparison with one group not shown here which received only 820 kcal exclusively as glucose. *Kazda* found also less negative balances with a supply of ethanol corresponding almost to the fat ratios (group II). The addition of 350 kcal in the form of fat plus ethyl alcohol in group IV did not exert any additional effect in his study. Fat and alcohol seem to exclude each other metabolically. No reason can as yet be given.

Why is it not possible in the early postoperative phase to influence positively the metabolic situation by giving fat? Firstly, we ought to discuss whether or not the above-cited lipolysis after stress results in a maximal combustion of endogenous fat. In 1959 *Kinney* (9) pointed out that the top priority need for "two-carbon-fuel" (acetyl-CoA) is seldom a limiting factor for the *Krebs* cycle in surgical situations. During a discussion on the activation of different endogenous calorie sources after injury several years later it was also *Kinney* (22) who reported that he found "anywhere from 75–90 % of the calories come from fat". Likewise, *Carlson* (23) found in dogs after fracturing their hind legs or after infusion of noradrenaline for 24 hours a mobilisation of endogenous free fatty acids excessively above caloric needs. So, the high $^{14}CO_2$ exhalation rates from labelled parenteral fat cited above might hardly be valid in these immediate post-stress situations. On the contrary, the frequent observations of a ketone body rise after fat administration, however [ref. see (6)], suggest overloading of the final oxidation system with acetyl-CoA.

Secondly, another biochemical reason for the bad N-balances may be advanced. Increased supply and increased breakdown of the fatty acids activate gluconeogenesis shown for example by the increased transformation of alanine into glucose (16). The activator can be acetyl-CoA which in 10^{-4}-molar concentration activates about 40 fold the pyruvatecarboxylase, a key enzyme for gluconeogenesis (17). If the state of increased fatty acid breakdown lasts for a longer period, enzyme induction might support the spontaneous activation. For instance additional tryptophan pyrrolase will be synthetised. By eliminating the essential amino acid tryptophan from the balanced pool of amino acids, diversion of the other amino acids into gluconeogenesis is favoured because tryptophan will then become the limiting factor for the utilisation of the entire amino acid pattern (18).

Thus, in conjunction with the repeatedly mentioned increased ketosis occurring with fat emulsions as a result of accumulation of acetyl-CoA, the bad nitrogen balances observed are further explained.

Thirdly, a more trivial reason may be the eventual renal loss of ketone bodies, which means a real loss of calories. These calories, too, must be subtracted from the regime as must those of administered fat which is stored intact.

Based on these considerations, we have a study running to determine a tolerable caloric percentage of fat for conditions of stress bearing in mind that the carbohydrates must be increased if fat is to be reduced (Fig. 5).

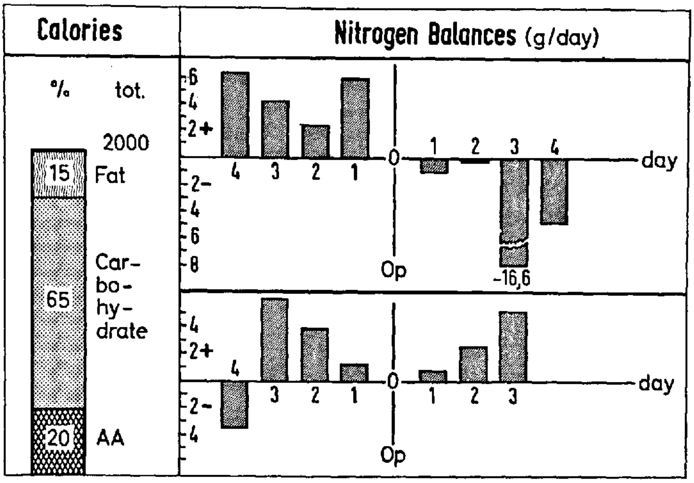


Fig. 5. Post-stress nitrogen balances with a low fat-high carbohydrate regime.

To avoid other variables we will refer only to those cases in which there is no objection to a comparison between the postoperative results and the preoperative ones of the individual patients. Because of this limitation we have only a few cases observed long enough preoperatively as well as postoperatively without other variables such as intercurrent complications, necessary additional medication and so on. Therefore it will be permitted to present as a preliminary reference results from only two different, but typical patients after operation for a cancer of the colon (upper half of the figure) and a cholecystectomy (lower half of the figure). As far as can be concluded, the lower fat intake of 15 % of calories is in better accord with the postoperative metabolic conditions, the basic pattern being principally the same. This is supported by the fact that acetoacetate and β-hydroxybutyrate in the serum of the patients did not rise to the extent seen with higher fat intakes. The very slow infusion rate averaging 0.07 gms/kg body weight and hour may also be involved.

Additional Fat Supply?

In the former view of a necessary supply of additional calories, it might perhaps be interesting finally to make a comparison with evaluations on normal daily nourishment. *Wirths* and *Nakamura* (19) recently conducted a 1-year survey on the nutritional habits of a rural population in Germany. In Fig. 6 we have related the caloric requirements according to the corresponding monthly activity and the composition of the food eaten. In those months, when the peasants work harder, i.e. during cultivation of the soil in spring and harvesting in July and August, the percentage of their fat intake drops in favour of carbohydrate intake. In other words: these people cover their additional requirements for calories by eating more carbohydrates instead of eating food rich in fat.

Acknowledgments: This paper contains some date taken from the thesis of *H. Hofmeister*, Gießen 1969. Supported by J. Pfrimmer + Co., Pharmazeutische Werke, Erlangen, W. Germany.

Summary

Summarizing we would say: approximately 30 % of the total calories of a fully balanced parenteral regime are assumed at the moment by many workers to be an optimal fat ratio in patients without the immediately preceding influence of stress Very many patients are fed parenterally after operations or trauma. The caloric requirements of these patients are increased. The possibility of covering these requirements, however, by the use of high-caloric fat emulsions is rather limited as is demonstrated by the deterioration of N-balances. One reason may be the combustion of endogenous fat reserves maximally activated after the stress – which of course means an abundant availability of fat at a

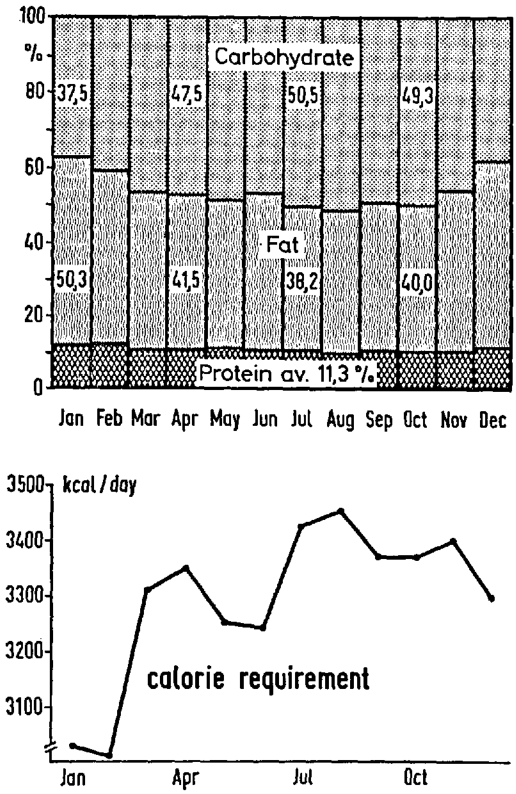


Fig. 6. Monthly intake of basic nutrients (% of total calories) in comparison with caloric requirement in a rural population (acc. to 19).

cellular level. Another reason may be the activation of gluconeogenesis by congested acetyl-CoA as a specific biochemical interrelationship in cellular metabolism. An optimum for the fat ratio in postoperative states is not as yet known. Fat emulsions and ethyl alcohol – in spite of both being valuable high-caloric substrates – are metabolically incompatible both in stressed and unstressed patients.

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