8. PATHOPHYSIOLOGY OF ENERGY BALANCE

An organism can acquire the permanent energy need in support of its tissues through continuous production of molecules featuring high-energy bonds (e.g. ATP). This necessitates the adequate intake and utilization of a variety of nutrients. Additionally, the removal of heat originating from this energy is obviously indispensable. Energy balance throughout the body is best defined as the balance and regulation of energy quantities contained in different forms (calorie-containing nutrients which are stored and can be mobilized, heat-calories) in the body. This balance is established partly by the regulation of food intake, metabolism and body weight, partly by the regulation of body temperature.

Disorders seen in energy balance may be manifested through various abnormalities of the body weight/composition or in abnormalities in body temperature.

8.1. ENERGY BALANCE

8.1.1. PHYSIOLOGICAL BACKGROUND

Basal metabolic rate (BMR) is the minimal metabolism, which is absolutely required by the body to perform basic life functions in a state of total physical, psychological and emotional rest, within a thermoneutral environment, 10-12 hours following the last meal, without peripheral medication, coffee, etc., yet, in a conscious, resting state, such as a recumbent and/or a resting position. During sleep, depending upon its specific phase, it may be slightly less. The BMR's determination is formulated upon the measurement of oxygen used for burning nutrients at the tissue level, and of the concurrently produced CO_2 (indirect calorimetry), or in case of thermal balance, upon the amount of produced and lost heat (direct calorimetry).

In comparison to BMR, the metabolic rate can only increase physiologically. The excess metabolism is used to fulfill the special functional requirements in various states (exercise, stress, cold effect, postprandial state, etc.). No physiological effect can suppress the metabolic rate, and the pharmacological suppression of the metabolic rate by some substances can be demonstrated only in the event if the metabolic rate had already been elevated prior to the suppressing action (e.g., as seen during cold exposure). Naturally, toxic effects can suppress the BMR, too.

Pathologically, BMR may be either too high or too low. Elevated BMR is seen in hyperthyroidism, congestive heart failure, lasting febrile states and the BMR may be slightly higher among athletes featuring unusually large muscle mass. Suppressed BMR is observed in hypothyroidism, defects of the pituitary gland, starvation, old age, peripheral circulatory failures, etc. The differences can be explained partially by the altered tissue metabolism, partially by shifts in the ratio of metabolically active and less active tissues.

Resting metabolic rate (RMR): The RMR is a metabolic rate exceeding BMR in resting states following a few hours of absence of physical or greater mental/psychological activity. Moderate everyday physical activity (NEAT – non-exercise activity thermogenesis), or the transient (postprandial) metabolic rise due to a feeding process (TEF – thermic effect of feeding) further increases RMR. TEF is an excess of metabolism in addition to the nutrient-dependent specific dynamic action (SDA), independent of the means by which the nutrient is introduced. TEF is explained partly by the energy needed for the feeding process (chewing, motility and digestion) or by the heat-calorie introduced by the food, partly by the stimuli from the GI tract, such as seen in the event of stretch (specifically, even calorie-free contrast material stretches the stomach and increases metabolic rate). Diet-induced thermogenesis (DIT, also referred to as, "luxury consumption") is the metabolic excess in cases of prolonged/regular high calorie intake, and this may elevate even the level of BMR (such a diet is not physiological). The basic idea of "luxury consumption" was that some individuals may consume calories above the need, yet they burn it off and therefore avoid obesity. Others lack this ability and eventually, they become obese. This premise has never been fully verified, however, with regards to DIT, it somewhat supports the theory. In addition to all of the above mentioned forms, the metabolic rise is associated

with physical activity and it is worth emphasizing that the metabolic rise can eventually reach several times higher levels than BMR, as well as can the cold-induced thermogenesis (CIT).

The *daily energy need* is determined by all these, and it can be calculated. It is perhaps, more suitably examined in the method* of doubly labeled water. The daily energy need of young men, depending on body size, required during a light workout is ca. 2.200-2.600 kcal (ca. 11.000 kJ), i.e., about 100 kcal/h, and, what should be aptly recovered from food in an appropriate composition. This is specifically expressed by the idea of "isocaloria", according to what the caloric nutrients can replace one another, hence the type of food is not overly important. This is true, however, only for their energy content, and the specialized role of a nutrient cannot be replaced by another nutrient (e.g. proteins cannot be replaced by fats). In regards to heavy physical exercise, contact sports, and performing activities in a cold environment, the daily energy requirement may be several times higher than 2.200-2.600 kcal. The need may decrease with increasing age (the nutrient composition should also be altered). The need is lower among women (except in pregnancy and during lactation) and also in children (however, in regards to children, the energy requirement per body weight is higher, and the appropriate nutrient composition and protein content are even more important). Extraordinarily large caloric requirements are characteristic for teenagers, particularly for boys, even if a young man is not overly physically active or athletic.

To maintain short-term energy balance in homeothermic species, *heat loss* (corresponding to daily energy utilization) is also important, and human beings ideally lose the aforementioned 100 kcal/h or more for maintaining thermal balance. Theoretically, the complete failure of heat loss would lead to retention of such an amount of calories, and in a 70-80 kg male, this would elevate the body temperature by about 1-1.5 ^{0}C/h (since 1 kcal heats up 1 liter of water by 1 ^{0}C). Since the metabolic rate, continuously changes according to physiological activities, heat loss must continuously be adjusted to suitably perform this. In the case of excessive heat loss, such as in a severe cold environment, the metabolic rate (= heat production) must be adjusted and increased as a form of compensation (CIT= cold-induced thermogenesis), what results in an increase in the daily requirement of energy/food.

8.1.2. FACTORS OF ENERGY BALANCE

There is a distinct controversy between the continuity of metabolic rate and the fractionated nature of food intake. The explanation is that hardly any of the consumed food is being used directly, the nutrients absorbed in the postprandial phase are stored to a great extent, and are mobilized from stores according to the actual metabolic needs. Nutrients participate in anabolic processes, if needed, a part of the formed tissues (fat tissue /ca. 15 kg/; muscles plus protein /ca. 10-12 kg/; liver-muscle glycogen /ca. 70+200 g/) and the glucose content of the plasma /ca 20 g/ can be used as nutrient reserves in energy-producing metabolic processes; see Table 8.1.).

Accordingly, energy balance is a dynamic state. Tissue metabolism is not stabile, however, it changes with the actual needs and differs by various degrees from the BMR. On the short run, the changing levels of metabolic rate will endanger thermal stability, therefore, it is counterbalanced by the mechanisms of thermoregulation. On the long run, the energetic balance is defined, as the proportionality between the food taken up and the metabolic rate (energy amount used for physical ex-

Table 8.1.

Body composition (stored energy) in young men

fat tissue: ca. 15 kg (130-140 000 kcal)
protein: ca. 10-12 kg (35-40 000 kcal)
carbohydrates: ca. 0,3 kg (1100 kcal)
water: ca. 42 kg
minerals: ca. 4 kg

*Method of doubly labeled water: Following ingestion of $D_2{}^{18}O$, the consumed D_2 and ^{18}O are distributed in the body. D_2 is diluted in the total water compartment and is excreted by the kidney, while a portion of ^{18}O is similarly diluted in the water compartment and emptied through the kidney, and another portion is forwarded into the bicarbonate-pool, where it is excreted in the form of, ^{18}O-containing CO_2, through respiration. Accordingly, the speed of emptying the two isotopes is different in the course of a three-weeks study, the ^{18}O-content decreases far more quickly in the body fluids than the D_2 content, and the difference is greater at higher daily metabolic rates (and CO_2 production). The method allows assessment of long-term metabolic rate and energy needs during various daily activities, it may be used to determine rationing (however, the short-term changes of energy balance cannot be analyzed by this method).

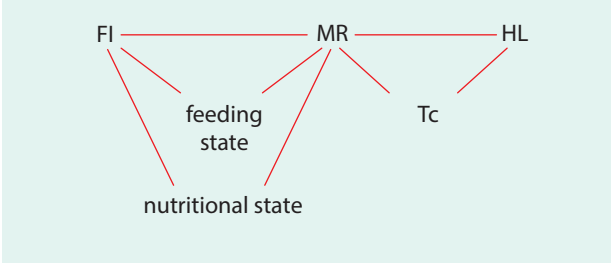

Fig. 8.1.: Components of regulation of energy balance: FI (food intake), MR (metabolic rate), HL (heat loss), Tc (core temperature).

ercise, energy-demanding processes, heat production, etc., what is finally removed from the body), and this is the basis of body weight stability. If there is a lasting imbalance in the relationship between consumed and metabolically utilized energies, the body weight will change (undernutrition, obesity). In the case of an imbalance between the metabolic rate and heat loss, the body temperature will change (hypothermia or hyperthermia). The main components of the dynamic balance are illustrated in Fig. 8.1. In this figure, one regulated factor is the actual feeding state or the more sustained nutritional state, while the other regulated factor represents the body temperature. All are determined by food intake, metabolic rate and heat loss.

Factors of Fig 8.1. interact. Although individual elements of the system can be influenced separately, e.g. satiety is influenced by emotional state, metabolic rate by hormones (e.g. thyroxine), heat loss by vasodilatory substances, and such influences endanger the energetic balance and counterregulatory steps are needed to secure the balance of the system.

In normal regulations, however, signals from the regulated system itself (feeding/nutritional state, body temperature) provide information for adaptive changes of food intake, in regards to the metabolic rate and heat loss. The incoming regulatory signals modify the function of the central regulatory structures and thereby lead to changes in food intake, metabolic rate or thermoregulatory mechanisms.

8.2. FOOD INTAKE AND ITS ABNORMALITIES

8.2.1. REGULATION OF FOOD INTAKE

Food intake is regulated through **hunger**, **appetite** and **satiety**. Appetite is connected with hunger, however, they are not the same. The basic question regarding the

Table 8.2.

Calorie stores and their daily exchange rate

	Store	Daily intake	Intake/store
Fat	130 000 kcal	8–900 kcal	< 0.6%
Protein	35 000 kcal	400 kcal	< 1.2%
Carbohydrate	1100 kcal	1100 kcal	100%

definition of hunger, "is there anything to eat?", while in regards to appetite, "what am I craving for," or, "I could eat from this a bit more!". Following the suppression of hunger (satiety), the appetite allows additional food intake (although this is true for specialized, tasty foods), while a lack of appetite decreases even hunger and the hunger-induced food intake. Due to changes in appetite, food intake may markedly differ from the actual need: food intake may be much higher, or in lack of appetite, it may be much lower than the need. Although the gastric stretch contributes to the feeling of satiety (yet, if the food is of little calorie content, hunger comes on much earlier), hunger develops even following gastrectomy and may be so severe that experimental animals are willing to undergo electrical shock to obtain the food. Still, food intake induced by enhancement of appetite normally produces a longer satiety (hunger is smaller and appears later), the next feeding is delayed or smaller, and such enhancement of appetite normally has only a transient effect (similarly, as transient decreases of appetite, such as seen in febrile diseases, are followed by transient enhancement of hunger during recovery).

From the data of Table 8.2. it is obvious that some sort of regulation must exist for the composition of food (= food selection, e.g. the preferred caloric nutrient is carbohydrate > protein > fat). Isocaloria refers to the idea that nutrients may replace one another by their caloric value, but does not imply that the regulation of food intake occurs exclusively according to the calorie content of the food. While in everyday conditions, primarily the carbohydrate intake changes, and in extreme conditions, as seen in life in the Arctic climate, the daily calorie requirements may be 50% higher than when compared with those in tropical regions – additionally, the intake of fats is also modified.

FOOD SELECTION

The regulated nature of **food selection** can be demonstrated not only for calorie-containing, but also for calorie-free substances (vitamins, minerals and even for non-physiological substances, such as alcohol), i.e., apart from quantitative regulation, there is a qualitative

regulation, as well. This may explain certain preferences, sometimes changes in feeding habits (with altered need or altered state) which may appear strange, like "pica" in pregnancy (ch. A13.1.3.). In regards to feeding habits including quantitative, qualitative aspects and ways of food preparation/presentation collectively, the diet expression is used. **Diet** may change spontaneously in certain diseases, or in a planned way, such as seen in the medical diet, which is defined as a deliberate planned set of rules which affect the quantity, quality and preparation of food according to the actual needs. These possibly differ from the normal due to the current disease. If the patient cannot adhere to the diet, one must consider the possibility that the dietary prescription is faulty (not only that the patient is negligent). Selection often has a compensatory nature, as witnessed in adrenalectomized rats, in which the salt-consumption is several times more than normal, while the PTH deficient animals consume more Ca, or thiamine deficient rats select thiamine-containing water instead of tap-water, etc. Admittedly, not all selection is positive: male rats selected the alcohol-containing water instead of tap-water, except if and when they were pretreated with estrogens.

Out of the quantitative and qualitative regulations, the caloric aspect appears to be far more important. Rats, kept on a diet of a very low protein containing specialized mixture, did not fulfill their protein need (of which, unavoidably, would have caused a higher calorie intake and obesity), rather, they maintained a standardized calorie intake, inevitably resulting in lethal protein deficiency. However, in a cold environment, on the same diet, they survived without notable difficulty, since the cold-induced hypermetabolism evoked a higher calorie intake and, in consideration of the large volumes, the intake of protein proved sufficient.

8.2.1.1. AFFERENT SIGNALS IN THE REGULATION OF FOOD INTAKE

The three groups of afferent methods are described below:

1. **Nutritional state**: The amount of stored calories (in practice, the size of fat stores), and the levels of leptin and related insulin (both are proportionate with the stores) transmit signals to the central regulatory apparatus (primarily to the arcuate nucleus and the area postrema). Additionally, insulin influences leptin production by fat cells. Blood glucose also sends signals regarding calories which can be mobilized. These signals provide *long-term, tonic* influence on the regulation of food intake (the glucose signal is less tonic).
2. Neural or humoral signals representing the **feeding state**, or hunger/satiety: These signals originate from the stretch of the GI system, from nutrients, and from GI peptides evoked by the nutrients. Notably, the level of stretch regarding the GI system gives signals partly through the abdominal vagus and the nucleus of the solitary tract, and partly through direct action in the area postrema. The humoral signals act upon the receptors of the arcuate nucleus. In evoking satiety, the high GI stretch, elevated blood glucose and CCK of the GI system all bear relevance, however, many other peptides have a similar role, too. Hunger is explained primarily by the decreased stretch of the GI system, the moderate decline of blood glucose, and by the ghrelin peptide, which is produced in the stomach while fasting. Characteristically, the act of feeding is regulated as a *short-term* effect of various hunger/satiety sensations.

   Regarding the effector side, the short-term and tonic systems interact and both are capable to influence the act of food intake, but they possess a certain independence: following feeding, satiety develops even among pathologically lean individuals, while in obese individuals, hunger develops upon food withdrawal, well before the loss of body weight and fat mass.
3. **Signals of body temperature** also contribute to the regulation of food intake. Acute cold exposure promptly enhances food intake, while a warm environment or high body temperature inhibits food intake. A clear example is seen in hyperthyroidism, in which the food intake among rats begins increasing only once the body weight and fat mass are considerably low due to the hypermetabolism, and prior to these circumstances, the elevated body temperature prevents the increase in food intake or the orexigenic effect of the NPY peptide within the brain.

The afferent signals participating in the regulation of food intake bear other functions, too. They simultaneously influence the metabolic rate and body temperature. Leptin and central insulin not only have an anorexigenic effect, but also serve in the increase of both metabolic rate and body temperature. Similar central effects have been demonstrated for central CCK. The

intestinal GLP-1 (glucagon-like peptide-1) not only decreases hunger, but also increases the metabolic rate. The peptides NPY and orexin not only increase food intake, but also cause an immediate suppression of body temperature and metabolic rate (in a cool environment) – orexin may gradually increase food-searching behavior, too, and this activity may elevate metabolic rate. Thermal excesses of the environment are obviously important, not so much in the regulation of food intake, but in the regulation of the metabolic rate, however, within a cold environment, the elevation in food intake occurs prior to the enhancement of the effects of orexigenic peptides.

8.2.1.2. CENTRAL NUCLEI, FOOD INTAKE, ENERGETICS

In consideration of the central regulatory elements of food intake, traditionally, the hypothalamus is regarded as the most important. According to classic physiological studies in association ~~to~~ with hypothalamic lesions, the lateral nuclei are thought to be responsible for hunger and food intake, while the ventromedial ones for satiety and discontinuation of feeding. Electrolytic lesions of the lateral nucleus (or fibers extending along here) indeed, result in severe anorexia, while damage to the ventromedial nucleus (VMN) by gold-thio-glucose evokes obesity (however, gold-thio-galactose proves ineffective). This indicates a regulatory role in support of local glucose-binding and utilization. Quite possibly, those data may be of particular interest, according to which the VMN-lesioned obese rats lost weight upon fasting, yet, upon re-feeding, they regained the original obese body weight, i.e. the lesion likely served in altering the regulated level of body weight.

The nucleus accumbens and the forebrain bundle appear relevant in the final execution of the feeding process. These structures (Fig. 8.2.) receive information from the lateral hypothalamus, and the dorsolateral hypothalamic area (DLHA), but primarily from the paraventricular nucleus (PVN). The PVN receives signals from the arcuate nucleus (NA), the DLHA and the nucleus of the solitary tact (NTS); it is connected with the ventromedial nucleus (VMN), medullary nuclei and the spinal cord, and also with the mesolimbic system, which in turn, influences feeding behavior. Regarding the VMN, signals are supplied from the amygdala, higher centers, NTS and the preoptic/anterior hypothalamic (PO/AH) nuclei, and it is in reciprocal connection with the NA, PVN, and the dorsomedial and dorsolateral hypothalamic nuclei positioned just above the VMN. The NA is a main target of peripheral afferent signals. PO/AH collects mainly (though not exclusively, cf. Fig. 8.4.) thermal information. Efferent signals are partly switched over from hypothalamic nuclei in the the medulla, and partly carry information through efferent vagal fibers originating from the dorsovagal nucleus (DVN), extending towards the vagal ganglion and the celiac ganglion, respectively.

Apparently, the relevant neural and humoral signals (vagal afferents activated by GI stretch/GI hormones, nutrients, leptin, insulin) function as modulators of hunger and satiety. The efferent signals act through the brainstem, NTS, dorsomotor vagal nucleus, and they also influence the metabolic rate through the VMN. The role of impulses from other brain regions bears relevance, (e.g., psychological effects may cause either a rise or fall in food intake). Insufficient food intake may have an extraordinary importance amongst teenage girls. The role of psychological factors is emphasized by affective disorders, including *anorexia nervosa*, in which the patient (mostly, but not exclusively a young woman), upon a strictly pathological psychiatric basis, misjudges her or his own body weight and shape, thereby resists all logical efforts in feeding, distinctly, even when she or he is obviously suffering from severe cachexia. *Bulimia nervosa* is yet another psychiatric disorder, one in which attacks of gorging are accompanied by feeling guilty, resulting in forced vomiting and purging. Repeated transient gorging periods characterize *binge eating*, which is associated with obesity.

8.2.1.3. TRANSMITTERS, FOOD INTAKE, ENERGETICS

Out of the **monoamines,** the *catecholamines* (dopa, dopamine, noradrenaline) serve in suppressing hunger/appetite through inhibition of the lateral hypothalamus, yet they enhance it through the PVN ("orexigenic" effect). *Serotonin* (5-hydroxytryptamine) is characterized as "anorexigenic", and it serves in decreasing food intake, its antagonists used in the medical practice increase food intake and body weight. Upon insulin action, the brain cells take up more amino acids, however, disproportionately, therefore the tryptophan level and the tryptophan-serotonin supply in support of the brain increases, partly explaining the anorexigenic effects of insulin.

The **neuropeptides** form orexinergic and anorexigenic groups (Table 8.3.).

Table 8.3.

Orexigenic and anorexigenic peptides

Orexigenic peptides	Anorexigenic peptides
neuropeptide Y **(NPY)**	cholecystokinin **(CCK)**
agouti-related protein **(AgRP)**	pro-opiomelanocortin (POMC) **(MSH, melanocortin)**)
orexin-A and -B (hypocretins)	corticotropin releasing hormone (CRH) (urocortins)
melanin concentrating hormone (MCH)	cocaine-amphetamine regulated transcript (CART)
ghrelin	pancreatic polypeptide (PP, PYY)
galanin	glucagon-like peptide (GLP-1)
nociceptin	thyreotrop releasing hormone (TRH)
cannabinoids (not peptides, but may be related to peptide effects)	else (galanin-like peptide, bombesin, neurotensin, tachykinins)
	leptin (from periphery, but central effect)
	insulin (from periphery, but central effect)

Central NPY and the endogenous melanocortin agonist AgRP are orexigenic peptides of utmost importance, together with the orexin which is responsible for wakefulness and food searching behavior. In regards to anorexigenic peptides, CCK causes satiety by both central and peripheral action, the similarly anorexigenic central melanocortin system is beneficial in adaptive responses to food intake, while CRH participates in the metabolic adaptation to environmental factors. In view from the periphery, information regarding the nutritional state is conveyed by leptin of the fat tissue and by insulin, both possess anorexigenic roles.

The actions of all these substances are exerted through the corresponding **receptors**. One peptide is able to act upon various receptors. For example, NPY features no fewer than five different receptors which contribute to a variety of functions. This increases the spectrum of their actions. In regards to food intake regulation, not all receptor-bindings bear importance. NPY produced in NA acts upon Y1 and Y5 receptors of NA and PVN, and in doing so, enhances the intake of food, particularly that of carbohydrate. Galanin, also produced in NA, enhances uptake of fat. Melanocortins are similarly produced in NA, and their anorexigenic effect is exerted upon MC3 and MC4 receptors of DLHA (with several differences seen in other effects). NA is also the area for the production of endogenous melanocortin antagonist AgRP. CRH and urocortins produced in PVN bind to CRH1 receptors of NA or CRH2 receptors of PVN. In regards to food intake, the latter appears to be far more important (while CRH1 is more important in stressful reactions). CCK acts upon peripheral type-A and central type-B receptors of PVN, VMN,

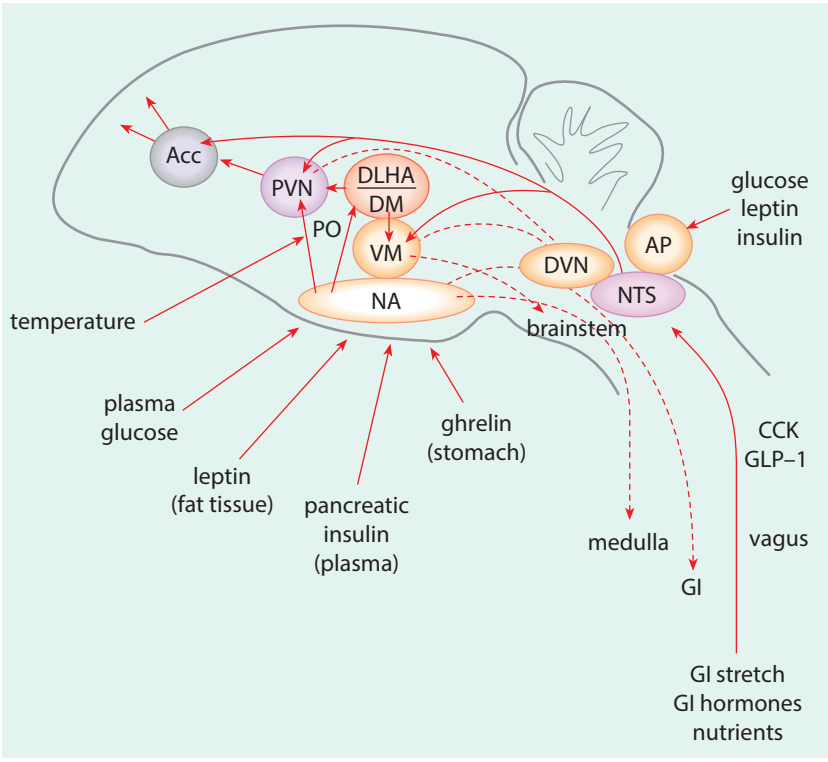

Fig. 8.2.: Important afferent and efferent factors of food intake regulation in rats (the main lines are similar in humans). AP: area postrema, NA: arcuate nucleus, VMN: ventromedial nucleus, DMN: dorsomedial nucleus, DLHA: dorsolateral hypothalamic area, PVN: paraventricular nucleus, Acc: nucleus accumbens, NTS: nucleus of the solitary tract, DVN: dorsovagal nucleus, PO: preoptic-anterior hypothalamic region, CCK: cholecystokinin, GLP-1: glucagon-like peptide. NA contains mainly NPY/AgRP and POMC/CART peptide-producing neurons, while DLHA mainly orexin and MCH producing ones, and the PVN region CRH/urocortin producing cells.

Table 8.4.

Effects of peptides in metabolic regulation – anabolic and catabolic peptides

States	FI	MR Tc	Examples
"Anabolic"	↑	↓	NPY, OREXIN-A AgRP
"Catabolic"	↓	↑	CCK, POMC, CRF, LEPTIN, INSULIN, TACHYKININ
"Hyperthyroid"? "Cold-adapted"?	↑	↑	?
"Hibernation"?	↓	↓	NEUROTENSIN, BOMBESIN

in both cases it does so as an anorexigenic substance. Orexin and MCH from DLHA bind primarily in PVN and VMN. The receptors (Ob-Rb) of peripheral leptin can be effectively demonstrated, apart from NA and AP, in PVN, VMN, DMN and DLHA nuclei, while insulin binds mainly to receptors of NA and AP. Receptors of GLP-1 only are partially known, yet its agonist exendin-4 evokes (equally as RYGB) both anorexigenic and hypermetabolic effects.

In consideration of aspect of energetics, the orexigenic/anorexigenic effects upon food intake (FI) can be evaluated as coordinated regulated reactions, only if they are coupled with concomitant regulatory changes (Table 8.4) of metabolic rate (MR) and body temperature (Tc). A hyperphagia with hypometabolism and Tc depression is an *anabolic* state, in contrast to the hypophagia with hypermetabolism and Tc elevating effect what is a *catabolic* state. Interpretation of other combinations is indeed difficult within a physiological system.

8.2.2. DISORDERS OF FOOD INTAKE

Disorders of food intake which are not due to the lack of food may likely be explained primarily due to regulatory abnormalities. Changes of the afferent and central (or transmitter) components of the regulation may lead to hypophagia or hyperphagia, and thereby to changes of body weight (cachexia and/or obesity). These factors are often altered secondarily, e.g. illness-related anorexia, or the hyperphagia due to diabetic decrease of insulin-sensitivity.

8.3. METABOLIC RATE AND ITS DISORDERS

Components of the obligatory metabolic rate include the followings: BMR, and additionally, its elevation due to SDA, TEF (ch. 8.1.1.), and pregnancy/lactation growth, thyroid hormones and eventual tumors. Facultative enhancement is induced by physical exercise, sports, athletics, NEAT, DIT or CIT. An increase in the metabolic rate necessitates the increase of food intake, together with elevation of heat loss, otherwise the body weight decreases or body temperature increases. A decreased metabolic rate is coupled with characteristic diminishing of food intake and heat loss, otherwise the body weight increases and/or body temperature decreases.

The importance of energy utilization and loss in regulation of the energy balance is emphasized by the experience according to which the intensity of the physical activity (higher metabolic rate) inhibits, while a decrease in physical activity promotes the development of obesity. In hyperthyroidism body weight decreases, in contrast to hypothyroidism in which it eventually demonstrates some increase (ch. 10.5.2. and 10.5.3.).

The efficacy of energy utilization may be genetically different. If energy-dependent processes, such as in the maintenance of Na^+/K^+-pump, function with more energy, it is more difficult to see an increase in body weight. Another possibility is in which DIT, or the cold-induced thermogenesis (CIT) proves insufficient, since, within the brown fat, or within tissues of similar function, the thermogenesis does not increase in association to the given stimulus, however, the energy is stored. Brown fat had first been demonstrated in neonates and cold-adapted adults of certain species. In consideration of brown fat, uncoupling proteins (UCP) should allow vast amounts of energy being transformed to easily dissipated heat, instead of ATP. In such cases, primarily, the β_3-adrenergic receptor-deficiency of brown fat is regarded as the cause of obesity. For years, it was a common belief according to which adult human individuals do not possess brown fat, however, recent data demonstrate how fat cells may be modified: upon various influences their morphology changes and they function similarly as brown fat like cells. Interestingly, "beige" cells or definitely brown cells have been demonstrated in humans even without lasting cold exposure.

In genetically leptin-deficient ob/ob obese mice catecholamines do not enhance the heat production in brown fat, i.e. leptin may have a role not only in the regulation of food intake, but also in the regulation of the metabolic rate. In obese individuals, catecholamines are less effective in enhancing metabolic rate when compared to those in lean ones, although no significant differences were found regarding their BMR-s.

Most neuropeptides/transmitters participating in the influence of food intake also influence the metabolic rate and apparently, cause coordinated changes both in food intake and the metabolic rate. To cite a distinct example, NPY or orexin not only enhances food intake, but they suppress the metabolic rate (if it exceeds BMR), thereby, both bear a coordinated **anabolic** activity. Other peptides have coordinated **catabolic** effects, e.g., the melanocortin system and CRF, because these inhibit food intake and enhance the metabolic rate. In changes of energy content and body weight, the anabolic and catabolic systems bear particular relevance.

8.4. BODY WEIGHT: ITS REGULATION AND PATHOLOGICAL CHANGES

8.4.1. NORMAL BODY WEIGHT (BODY MASS)

Body weight, regarding the ideal, vastly differed through history. Venus of Willendorf, and Venus of Milo, or the various female figures of Rubens, including the widely popularized Barbie Doll in contemporary times, all were seen as equally "idealized" female models in their respective ages, however, these are essentially different forms and the ideal is still not considered a standard. The challenges regarding the "normal" body weight was first investigated by *life-insurance* corporate entities, in which investigators revealed how both below and *above* a certain body weight, the corresponding health risk increases. Expressively, the normal body weight as a problem in *physiology,* was studied only later.

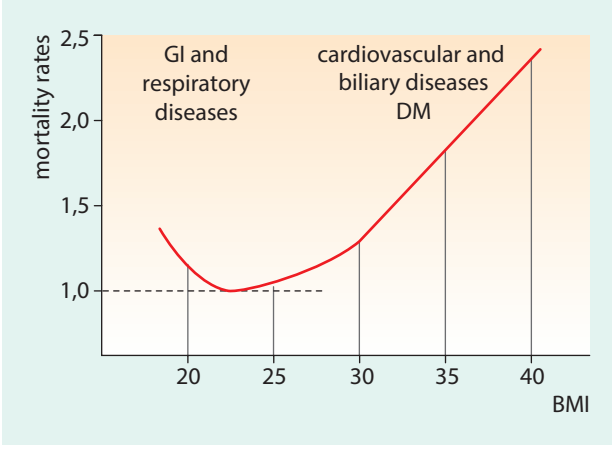

Fig. 8.3.: Expected death rates (minimum taken as 1.0) in a group of adults of the same age, but different body weights. At low BMI diseases of the GI or the respiratory systems are main causes of earlier death, at high BMI the cardiovascular and biliary diseases or diabetes are the most important.

In assessing the normal body weight, the absolute weight (mass) is most often related to the height of the person. One assessment is the ***Broca-index*** (= height above 100 cm expressed in kg minus 10%, as seen in the case of 170 cm, it implies 63 kg is regarded normal, or in men slightly higher, and in women slightly lower values). Another method is the body mass index (***BMI***): body weight in kg, divided by the square of the height in meters (not square-m surface!). The normal BMI value is 20-25 (at lower end of the spectrum in women, and at the higher end in men) (Fig. 8.3.). BMI can easily be applied in statistical analyses, while Broca-index is generally more preferred by patients.

In reality, these assessments demonstrate how and why nearly all body building athletes or patients suffering from edema or ascites could be regarded obese, therefore it is not the body weight itself, rather the size of fat mass which yields far more interesting data. However, there are no easily applicable methods in the routine practice regarding the measurement of fat content. Admittedly, it is mostly seen in the measurement of skinfold thickness, however, this can be only used in obesity, and not with regards to cachexia. The approach which provides a more precise form of measurement is the value calculated from the determination of water-space and bone mass. The most precise form in measuring body weight is the specific gravity value calculated from the differences of body weight measured in air and during immersion in water, and is one which can be calculated according to the role of Archimedes. Recently, measurements of body plethysmography and body impedance are also used. In routine practice, the simple yet careful judgement by inspection of the patient is of great importance, also in considering the various constitutions such as muscle and bone qualities.

Apart from body weight, body **composition** is also essential, which is not depicted in BMI (Table A14.1). This may have special relevance in the consideration of seniors, or the aged, when due to sarcopenia the muscle amount is sufficient probably only if the BMI is higher than the "optimal" 20-25. To potentially increase the

survival rate, the chances are deemed far better if the BMI is slightly higher.

Body weight which is characteristically defined as normal, may be regarded optimal as far as the general functions of life (growth, development and reproduction) and quality of life are concerned, however, it may not be optimal in all aspects. In experiments, the lifespan of chronically underfed thin rats was consistently longer (by 50%!) when compared to that of "normal body weight" rats, kept on an "optimal" diet (Fig. 8.4.). The question posed is: what is optimal? It may be assumed in which the "optimal" (ad libitum) diet, specifically regarding life span, was not suitably optimal for the rats reduced to restricted movements, as it led to obesity and consequently, to a shorter lifespan. This observation characteristically comparing different calorie intakes vs. lifespan was not entirely true regarding monkeys, however, they were not restricted in their movements and did not become obese, since they had big cages. Notably, a persistently moderate calorie intake also extends longevity in humans, although the mechanisms have not thoroughly been clarified.

The regulation of body weight is, in fact, the regulation of a prolonged balance of food intake and the metabolic rate. According to the balance, a change in one of the components is followed by change in the other one. It is easy to accept that a high metabolic rate (e.g. physical exercise) induces a higher food intake. However, for years, it was questioned, whether or not the reversal is possible. Is the metabolic rate adjusted to food intake? This was first proven regarding starvation, in which a decrease in food intake serves in a decrease in the metabolic rate and physical capacities. Today, it proves valid to a certain extent, in support of the other end of the spectrum, in which prolonged moderate overfeeding leads to a somewhat higher metabolic rate (DIT), what may limit the weight gain. The amount in overfeeding is the problem: lasting severe overfeeding cannot be overcome by an increase in the metabolism ("luxury consumption" leads to obesity).

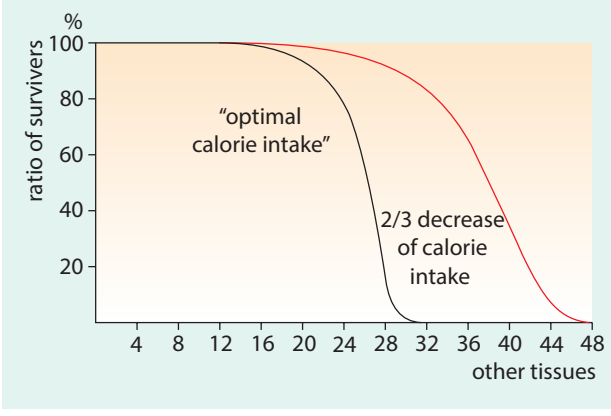

Fig. 8.4.: Survival rates of rats with assumedly "optimal" (ad libitum) calorie intake and others maintained on diet of decreased (2/3) calorie content.

8.4.2. STARVATION, PATHOLOGICAL LOSS OF BODY WEIGHT

Food intake may lag behind the needs of metabolic rate for a long, and starvation is in fact an exaggerated, longer form of the normal interruptions in feeding. Starvation refers to the generalized deficiency of energy-containing nutrients. It is a specialized form when certain nutrients, such as proteins are missing, without the others being affected. Generalized starvation features two basic forms:

1. *Complete starvation*: The intake of water, vitamins and minerals is not reduced, however, no calorie-containing nutrients are consumed. Apart from unique situations, as seen in natural catastrophes, complete and utter starvation only occurs in hunger-strikes. Hunger strikes often result in death, yet the effects are often questionable. The hunger strikes of Gandhi alarmed the British empire and, ultimately, Gandhi achieved his goals – however, recent hunger-strikes result without the intended outcome. In the medical practice, when feeding is mechanically blocked, starvation is prevented by parenteral nutrition. The possible duration of complete starvation is limited by protein and fat stores of the body and by the burdens (work, cold, etc.) effecting and countering the body.
2. *Partial starvation*: The process of starvation is repeatedly interrupted by nutrient intake, however, it is never enough to essentially provide a normal balance. In contrast to complete starvation, this may still be enough in support of the stabilization of body weight and the metabolic rate, albeit, at a much lower level and thereby for survival. In addition to energy deficit, the consequences of a shortage in vitamins and minerals may also be expected, in contrast to complete starvation, in which these aspects do not develop due to the abbreviated length of time, which is too brief for their development. The prototypes of partial starvation were the various concentration and POW camps, gulags, products of war-time starvations, however, similar refugee camps are still common. Partial starvation is routine problem in the developing countries of the Third World, however, amongst the homeless

population, and due to growing poverty, it is an increasing problem in slum neighborhoods of developed countries, too. Natural catastrophes may also be a cause of general starvation. Additionally, it may occur in any part of the world, at various economical levels, and in cases of pathological states, including GI diseases, chronic inflammations, TBC, enhanced energy need, tumors, etc.

8.4.2.1. COMPLETE STARVATION

Phases of complete starvation include the following:

- Postprandial (first 12 hours following feeding – routine daily event, yet, not definitive starvation)
- Postabsorptive phase (from 12 - 18 hours, and up to a few days of fasting)
- Early, non-adapted phase (from ca. 1 - 4 days, lasting up to a week)
- Late, adapted phase (starvation exceeding 7 - 10 days) – followed by death

Biochemistry of the process of starvation

In comprehension of the nutrient stores, it is perhaps, understandable in which, first the carbohydrate stores will be depleted, and these will have to be replaced. It is also clear that the depletion of the protein stores typically precedes that of the fat stores.

In the ***postprandial period*** (immediately following feeding), the body resumes its needs from the nutrients which are now undergoing absorption. This period lasts for several hours following food intake (e.g. from supper up to breakfast). In this period, most tissues use carbohydrate nutrients in the form of freely available and easily catalyzed substrates. There is still enough insulin for the utilization of blood glucose among insulin-dependent tissues. The excess of consumed carbohydrates is developed in the form of glycogen in the liver, kidney and muscles, or it is transformed into lipids and is stored as such. Other nutrients are either used for production/reconstruction of various tissues (most proteins), or they are stored (fats). Typically, the burning of proteins and fats is maintained at a low level and it is extended only among certain tissues (Table 8.2.).

The situation changes in the ***postabsorptive*** phase (ca. 12 hours following the last food intake), when there is no further absorption from the GI tract and the body must rely on its pre-existing stores. The nearly exclusive source regarding the replenishing blood glucose is glycogenolysis in the liver. Minute quantities, and only in special cases, glucose may be mobilized from the kidney, while the muscle glycogen cannot be broken down directly to glucose, it can be used exclusively in glycolysis. However, the breakdown of liver glycogen to glucose (glycogenolysis) is limited, and the small amount of released glucose can secure the stability of blood glucose and tissue glucose supply for at most 12 - 18 hours, and accordingly, blood glucose would begin falling very soon. However, such a decrease does not happen, since already at the very early part of this phase, the replenishment of liver glycogen stores begins (gluconeogenesis) its acquisition from the available substrates, including, glucoplastic amino acids (mainly from muscle), pyruvic acid (transformed from lactate) from muscle glycogen, and glycerol from the breakdown of triglycerides. This process is promoted by a moderate decline in blood glucose to (yet not below) the *lower limit of the normal zone*, and the resultant smaller stimulation of pancreatic β-cells and the low insulin level, in the face of the α-cell activity and the glucagon level which remain high, the latter characteristics enhance gluconeogenesis.

In the following non-adapted phase, two tasks are to be managed by the body. The first, to provide glucose for those tissues which are strongly dependent upon glucose utilization (e.g. the nervous system normally utilizes exclusively glucose, over 70% of total glucose utilization of the body takes place here), and equally important, to provide other sources of energy in support of various tissues. In the adapted phase, saving the protein content of the body will be an additional task even earlier, and the burning of fatty acids helps to save proteins. Without these criteria, the utilization of proteins in support of gluconeogenesis will dominate in the non-adapted phase.

In the phase of ***non-adapted*** starvation (Figs. 8.5. and 8.6.), the slightly (yet not pathologically) low blood glucose and low insulin levels and the consequent deficiency in the GLUT-4 transporter protein; (ch. 9.2.1.1.) all act in the direction that glucose is nearly unavailable for the insulin-dependent tissues, what now must rely entirely upon other sources of energy. This necessity becomes a possibility by an increase in fat mobilization: the hormone-sensitive lipase enzyme of fat cells is released from insulin-inhibition, and the breakdown of triglycerides provides free fatty acids (FFA) for these tissues (additionally, the glycerol can be used in gluconeogenesis). The fatty acids are burned by β-oxidation and they supply ATP energy for these cells. The

end-product of β-oxidation is acetyl-coenzyme-A (acetyl-CoA), what is to be taken up typically by the TCA cycle to burn it, converting it into CO_2 and water, and ultimately, providing additional energy in support of the cell. However, the capacity of the TCA cycle is dependent upon the partially insulin-dependent enzymes (e.g. citrate-synthase) and, when considering the diminished levels of insulin, the capacity of the cycle decreases (below normal) and cannot effectively take up the significant acetyl-CoA excess from β-oxidation. The accumulating acetyl-CoA should enhance the synthesis of fatty acids in the liver, however, this is also insulin-dependent, and one in which the synthetic process ceases following the first step, and by condensation of aceto-acetyl-CoA and its derivative, aceto-acetate, β-hydroxy-butyrate, and ultimately resulting in acetone, collectively in the form of ketone bodies, which, as a result, are produced and of which the first two are characteristically acidic.

Naturally, these cells burn fat only if and when fat is available, and consequently, in its absence (very lean people), they continue to use glucose from gluconeogenesis, using amino acids.

Not all cells are able to operatively switch in support of fat utilization. The obligatory glucose-utilizing tissues, including red blood cells, nerve tissue, and in particular, the brain, take up and consume immense amounts of glucose, and this act is independent of insulin levels or GLUT-4 (they use other glucose transport ways). Characteristically, this is equally similar to the insulin-dependency of the glucose uptake among the performing muscles during a robust, intense physical activity, which often results in in hypoglycemia. In regards to these tissues, an additional supply of glucose is indispensable, and it can be achieved with the aid of gluconeogenesis, therefore, the protein breakdown increases. It is important that the protein loss leads to the loss of specific protein functions (ch. 9.1.), instead of easily mobilized proteins, in which more and more structural proteins are used up. Consequently, the blood urea nitrogen level increases. In this phase, the ketoacidosis leads to ketonuria, thereby the calorie content of ketone bodies is lost, although several tissues begin utilizing ketone bodies.

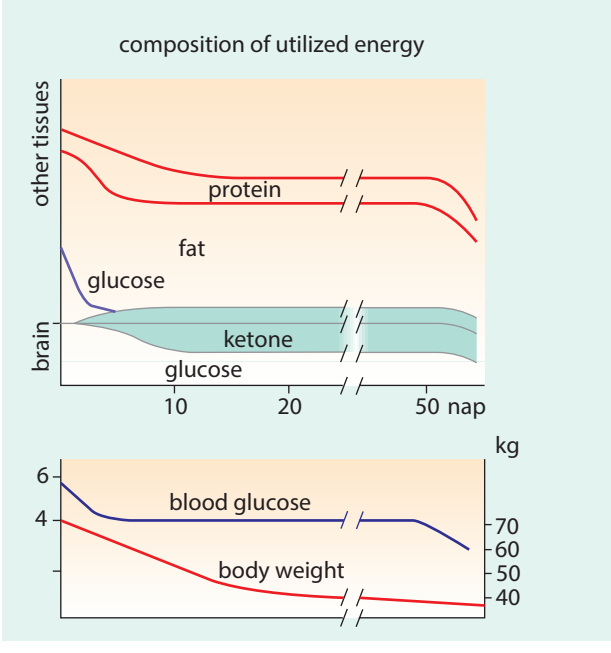

Fig. 8.5.: In the course of complete starvation (abscissa: days), the composition of consumed caloric nutrients is changing. The early decline in blood glucose is not hypoglycemia, pathologically low blood glucose levels develop only by the end of the process.

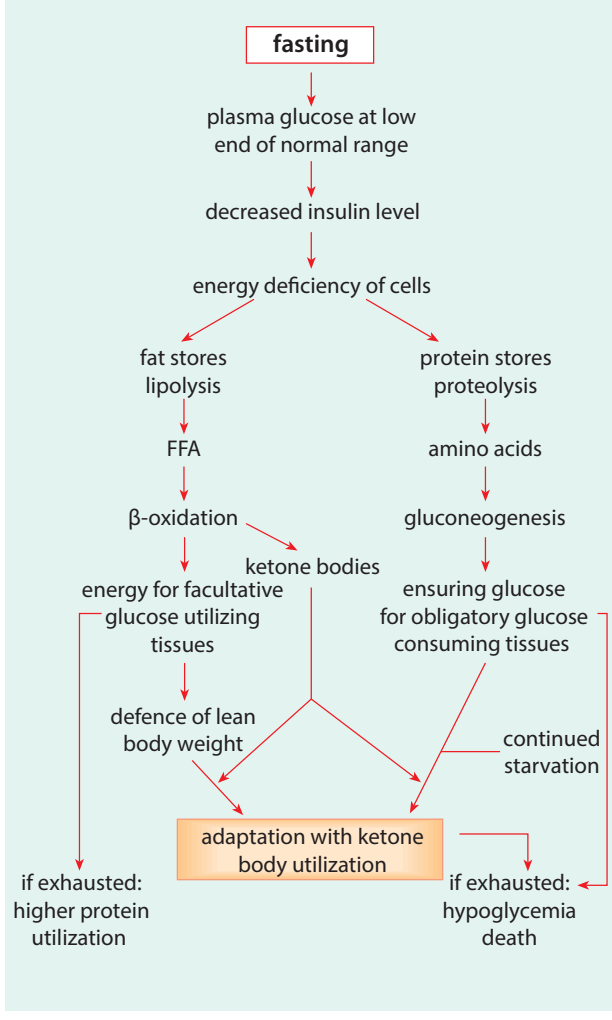

Fig. 8.6.: During starvation energy is obtained partly from fats, partly from proteins. Utilization of ketone bodies is a protein-saving adaptation.

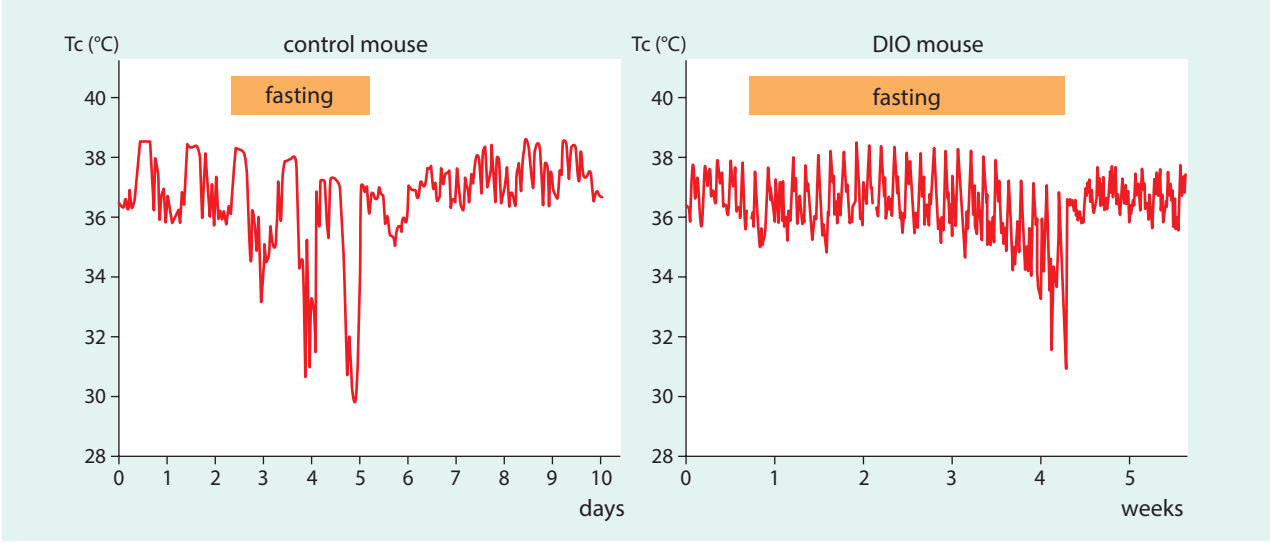

Fig. 8.7.: Circadian changes of core temperature during food deprivation in a normal mouse (24 g) and in a mouse made obese by high-fat-containing diet (dietary obese, DIO, 55 g). The daytime hypothermic period developed in both animals when their body weight decreased to 20 g due to starvation.

Accordingly, in the ***late adapted*** phase of starvation, the body strives to save its protein stores. This is possible only in the case of large glucose consumers, such as the brain, which now become able to moderate their glucose requirement through burning several other substances in addition to glucose. Such substances may be the ketone bodies, as, in this phase, the brain utilizes some ketone bodies in addition to glucose, therefore, the proteolysis subserving gluconeogenesis may be less pronounced. The ketone bodies themselves also inhibit gluconeogenesis.

The possible survival time in complete starvation is not determined primarily by the size of fat stores, rather it is the amount of proteins which can be mobilized, what is far more important. However, if lipid stores are inadequately insufficient, the mobilization of proteins is faster, and in this sense, fat utilization becomes a protein-saving mechanism.

Death occurs mainly due to the subsequent functional disorders, due to the breakdown of structural proteins, in particular, the *respiratory muscles*, or it is due to immune disorders and associated infections. At this stage, there is not enough of structure proteins which can be utilized, the gluconeogenesis is entirely insufficient, *now* resulting in manifest *hypoglycemia*.

In healthy mice, the phases and course of complete fasting is similar to that among humans. In the experiments of Szelényi et al., normal (22-25 g) mice including leptin deficient ob/ob obese (>50 g) mice, tolerated complete starvation for ca. three days, and during this duration their body weight decreased to ca. 20 vs. 45 g. Interestingly, their resting (daytime) temperature decreased gradually, however, plummeted quickly, and by day-3, all were suffering from hypothermia even at nighttime. The mice did not live much beyond day-3, unless refeeding started. In additional studies, in place of the standard diet, normal mice received a fat-rich diet (mice normally prefer fat in their diet), which resulted in obesity, and their body weight was ca. 55 g (diet-induced obesity = DIO). These DIO mice endured complete starvation and maintained the diurnal temperature rhythm for a much lengthier period of time. The resting temperature began to slide down after the 3rd week, the night-time temperature at the 4th week, when their body weight was ca. 20 g (Fig. 8.7.). In the case of the DIO mice, the weight-excess was from fat, however, it is not precisely clear, what the energy source for the brain was during this lengthy starvation. Upon refeeding the original DIO weight was regained.

8.4.2.2. PARTIAL STARVATION

Features of partial starvation

The *biochemical changes* are essentially similar to those seen in complete starvation, except that the repeated, although insufficient, intake of nutrients delays the utilization of bodily stores. In particular, the intake of carbohydrates and proteins may have a protective role, by reducing the breakdown of body proteins. Factually, this protection implies that the late adapted phase

Table 8.5.

The extent of the possible weight loss in partial fasting

fat tissue:	95%
liver	50%
muscle	30%
myocardium	25%
bone	8%
brain	3%

The BMR may decrease by about 30%.

of starvation is prolonged or becomes a chronic state. The weight loss in partial starvation may significantly exceed the loss seen in complete starvation, but at an extremely low body weight a new balance may be established (Table 8.5.), one in which individuals survive utilizing this new balance for years to come.

Of course, in chronic starvation, several physiological functions may become affected, including circulation, hematologic and endocrine functions, GI functions, bone formation, immune functions, salt/water balance (edema formation), psychological and even mental functions, etc. The BMR decreases (abnormality of the thyroid hormones is relevant), and the resting body temperature may be low. Many of these characteristics are reversible, although not simultaneously (e.g. normal psychological functions are retained only later), and to do so often requires an extended period of time.

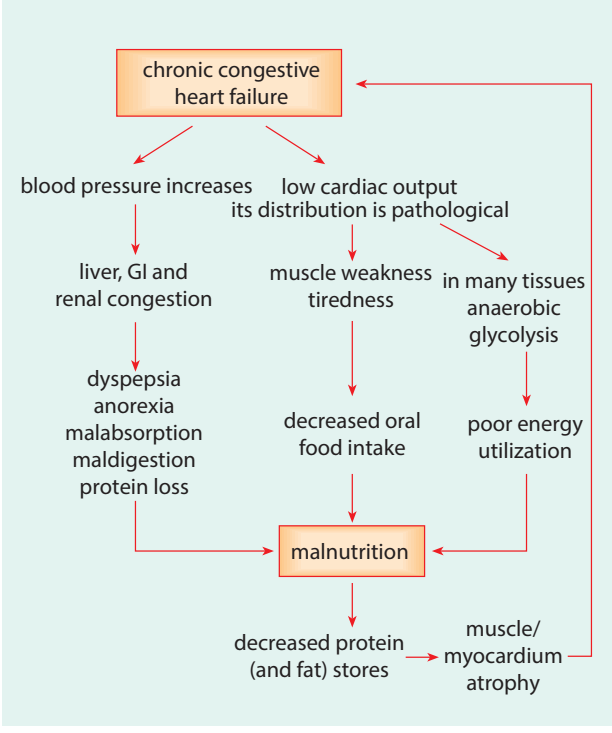

Fig. 8.8.: Development of malnutrition/starvation in chronic congestive heart failure.

Occurrence of partial starvation

It is important that it is not only the deficiency of nutrients in developing countries, wars, concentration camps, gulags, etc., but a low calorie intake due to endogenous causes, such as sustained anorexia in prolonged diseases (Figs. 8.8. and 8.9.), including congestive heart disease, COPD, anorexia nervosa, etc., may evoke states corresponding to partial starvation. Central regulatory disorders may explain decreased food intake and loss of body weight after lateral hypothalamic lesions or in some cases of pituitary abnormalities (Simmonds' disease). It can also be observed in various disorders of digestion or absorption, in states of high metabolic rate (tumor, hyperthyroidism, extreme physical activity, etc.), or if calorie-containing substances are lost (e.g. diabetic glucosuria). Regarding tumors, the high metabolic rate generated by TNF and other cytokines, is accompanied by simultaneous anorexia, resulting in an abrupt loss of body weight

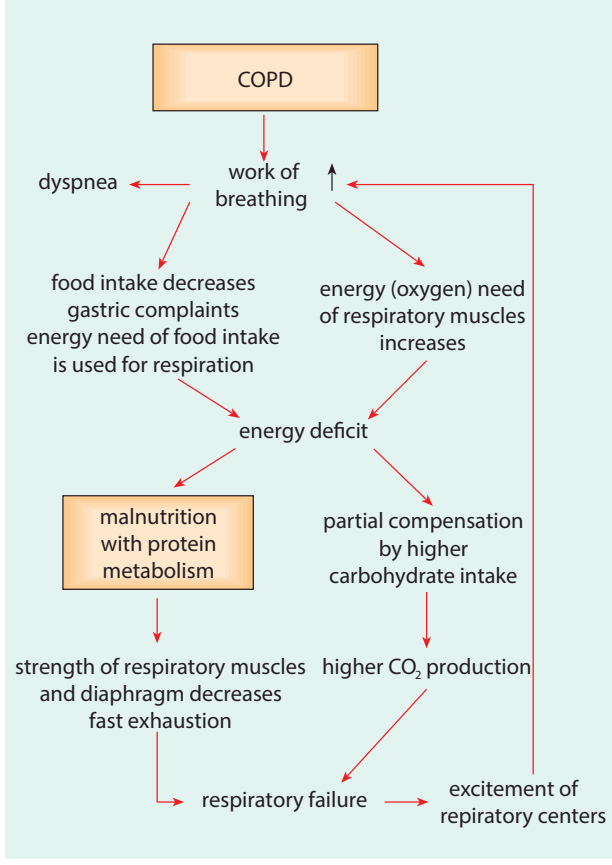

Fig. 8.9.: Development of malnutrition/starvation in COPD.

(N.B: dating back to 1985, the original nomenclature regarding TNF was cachectin). Among the elderly, it is also more frequent, and one in which a monotonic diet, denture problems, decreased activity and appetite, a decreased sense of taste and poverty may all serve to explain its development. As commonly seen in the elderly, the sarcopenia is much more pronounced than compared with the loss of fat. A disorder of food intake regulation can be detected in all forms of endogenous or disease-related partial starvation.

Physiological consequences of partial starvation

Wasting (BMI <20); In particular, the size of fat stores and the amount of muscle, including the myocardium, all decrease, yet the mass of visceral organs simultaneously decreases (although by a smaller extent), with the exception of the brain.

As the **BMR** decreases, the physical working capacity is poor, the resting body **temperature** and cold tolerance decrease, and even the **mental performance** worsens (concentrating, combinatory functions and learning ability all decrease, as seen in the example: students were promised a prize in the event of taking successfully an exam, yet the lower the calorie intake, the less success rate was found. In the later stage, lethergy, bizarr antisocial behavior and/or confusion are possible.

In **circulation,** heart rate, blood pressure, cardiac output decrease, tissue perfusion is slower and anemia is frequent. Total and alveolar **ventilation** are plummet and the **renal** excretory functions decrease. The glycogen content of the **liver** is low, its fat content (%) increases, and the sensitivity to toxins increases.

In the **GI system,** severe villus atrophy develops rather quickly. The exocrine hypofunction of the pancreas, the low amount of digestive enzymes, and the villus atrophy may aggravate the starvation due to a tendency regarding malabsorption, while the endocrine pancreas produces insulin yet at a diminished level, of which, may result in abnormalities regarding glucose tolerance tests. Bile is scarcely purged, due to the lack of food stimuli, and biliary congestion predisposes to gallstone formation.

Hypoproteinemia is a regular finding. The starvation-induced **edema** (≥10% relative rise in ECV) is characteristic. In its generalized form, it also appears throughout various body cavities. The pathomechanism has not been clarified. Among individuals just freed from concentration camps, inexplicably, the hypoproteinemia did not explain the severe edema. Additionally, a thiamine deficiency and disordered myocardial function may also contribute to the condition. Quite possibly, there is a disorder of the ECV regulation: In the 1950-ies, studies upon voluntary individuals were conducted, in which it was demonstrated the ECV was the same in the 24th week of partial starvation when compared to that of the beginning, yet when expressed in % of the decreasing body weight it increased from 24 to 34, i.e., the ECV was too high for the actual body weight even without the development of hypoproteinemia, at least partly explaining edema formation.

A number of **endocrine** dysfunctions may be present, including, infertility and/or infecundity, in all likelihood, due to low FSH and LH, and the decreased fat tissue produces less estrogens from androgens of adrenal gland origin. In bone, osteoporosis is characteristic. Starvation-induced hyperpigmentation (melatonin effect) has been demonstrated even among starving children of the Sudan. Particularly in anorexia nervosa, the appearance of lanugo (soft, downy, fine white/light hair that grows mainly on the arms, chest, back and face) is characteristic (lanugo may be natural in babies).

While in complete starvation the hunger ceases after about three days, in partial starvation hunger persists throughout the starvation period. It is strong and may lead to severe **psychological** changes, including apathy and strongly antisocial behavior. It is realistically described in the novel of Knut Hamsun (Hunger). In respect to the Holodomor, a man-made famine which occurred in the Ukraine, 1932 – 33, various accounts surfaced suggesting cannibalism.

The resistance decreases primarily against **infections** (Fig. 8.10.) of the respiratory and GI systems. Respiratory infections (pneumonia, tuberculosis) and GI infections accompanied with diarrhea and or dysentery are far more frequent among starving populations and bear an immense mortality rate.

In contrast to these cases, several reports illustrate how the diabetic coma and the ischemic heart failure are considerably rare. The Siege of Leningrad is consistently cited as a prime example for this: in this siege from September 1941 through January 1943, the catastrophic results of an intensified blockade equated to over one entire year of minimally rationed supplies that ultimately resulted in the loss of nearly 1 million citizens, but the diabetic coma and AMI cases were reportedly low. Admittedly, it is questionable precisely how the fatality cases were clinically or post mortem analyzed. Inexplicably, a decrease of certain viral infections (measles, viral meningitis, common cold, and rheumatic fever) among starving populations has been verified.

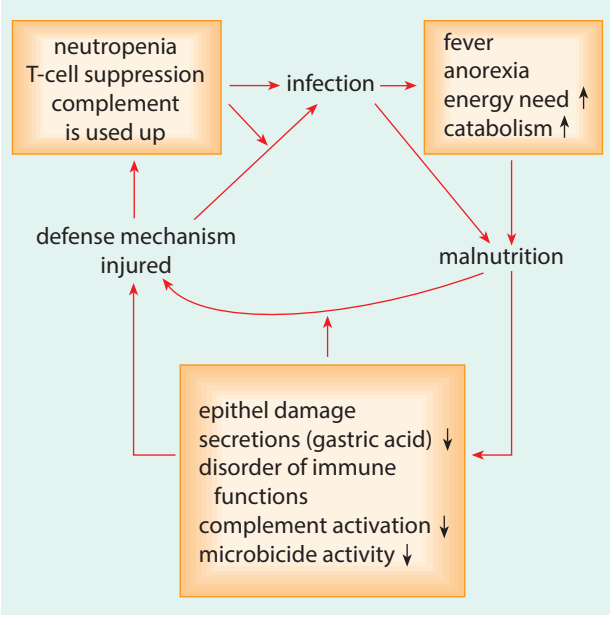

Fig. 8.10.: Malnutrition and starvation cause a vicious cycle to suppress the resistance of the body: the tendency for infection (due to malnutrition) evokes again a disorder of feeding and energy balance.

Refeeding following starvation: The somatic/physical disorders are normalized relatively quickly, although, not evenly, yet, in parallel regarding the body weight, however, the psychological cases reportedly do so much more slowly. Learning ability is suppressed even after six months. Extreme care is needed with re-feeding, specifically, to avoid potentially lethal acute pancreatitis (the thickened juice in the ducts may cause occlusions), the food intake has to be increased gradually, and a diet rich in carbohydrates and easily digestible proteins can be applied. The villus atrophy which soon develops during starvation also tends to be a source of malabsorption, resulting in diarrhea and salt/water balance abnormalities, all of which are life-threatening. At the onset of re-feeding, the replacement of vitamins and accessory nutrients proves to be entirely beneficial.

Rapid enteral or parenteral re-feeding of chronically underfed individuals (particularly children) loaded with a carbohydrate-rich diet may yet yield another potentially risky consequence, the development of the so-called "re-feeding syndrome". From one perspective, the myocardium is not quickly normalized. Yet, from another perspective, due to the simultaneously increasing insulin levels, glucose, K, P, Mg and water all enter the cells and, primarily due to hypophosphatemia and hypokalemia, inevitably, severe symptoms (heart failure, rhythm abnormalities, respiratory failure, muscle spasms, coma) may easily develop.

Accelerated starvation

Starvation has several accelerated forms, which often rapidly reach a critical form.

In ***pregnancy,*** the fetus ("as a perfect parasite") takes up from the maternal circulation, and in doing so absorbs all what is required for fetal growth and development, in particular, immense quantities of glucose, for so long as possible, regardless of maternal starvation. The mother soon reaches the stage of severe ketoacidosis and protein deficiency. As a means of adaptation, the maternal brain begins burning ketone bodies earlier than in simple fasting, however, hypoglycemia may easily develop. Unfortunately, both hypoglycemia and ketone bodies cause damage to the fetal brain.

Another characteristic form occurs in ***alcohol intoxication***, most often among alcoholics. The patient is typically undernourished, the intoxication inevitably leading to vomiting, and very quickly reaches the stage corresponding to the postabsorptive phase, one in which the glucose level can be stabilized only through gluconeogenesis. However, alcohol inhibits gluconeogenesis, and, due to its redox action, lactate cannot be turned into pyruvate, which would be the real source of gluconeogenesis (ch. 7.6.1.3.), therefore, hypoglycemia rapidly develops. Glucagon synthesis is increased, but in this situation it cannot increase the glucose levels – besides, the enhanced utilization of fatty acids results in ketoacidosis.

It should be emphasized that the combination of a high metabolic rate and low food intake, what is not rare in the medical practice, may also result in accelerated starvation. This occurs in ***trauma, infections, tumors and postoperative states***. It is of utmost importance to stabilize the calorie and protein supply in these cases. Accelerated starvation (ch. 8.4.2.2.) may easily affect patients suffering from a protein deficiency, as seen in ***sarcopenic seniors*** (ch. 8.4.4.).

8.4.3. OBESITY

8.4.3.1. DEFINITION OF OBESITY

Essentially, obesity is best defined once the fat content of the body exceeds the normal value. In the everyday meaning regarding obesity, the body weight exceeds the normal by at least 15-20%, yet it is regarded as a moderate degree ("overweight") until it reaches upwards of 40%. In excesses reaching 40-70%, the obesity is now defined as medium severity, between 70-100% the obe-

sity is declared severe, and above 100%, it is extreme. Such categorization according to % is considerably arbitrary and not entirely uniform.

Morbidity rates regarding obesity differ throughout various countries and regions. Beyond the age of 35, it increases globally. In 1999 ca. 30% of the population in the USA was obese (BMI>30) and another 34% was overweight (BMI 25-30). Today, throughout Central/Eastern European countries, the obesity/overweight ratio may reach levels of 40-50%. The prevalence correspondingly grows with urbanization, particularly among youth. In the urbanized (Americanized) environment, 12% of girls and 16% of boys were found to be overweight, and/or obese (in rural environments this was 2 vs. 1%). At the last turn of century, in China and Japan, the incidence doubled within 20 years. Even in developing countries, it is characteristic that certain (not extreme) forms of poverty are predisposed to obesity – feeding, without selection, becomes a main pleasure of life. In the USA, from 1986 up through 1998, the population of Afro-American and Hispanic children witnessed an increase in obesity ratio from 20% to 40%, and strikingly, in adults far more. In Hungary, the prevalence of obesity is very high, including childhood obesity. Notably, among youth aged from 6 through 19 years of age, not only is anorexia a distinct possibility, but 15% represents the ratio of obesity. Undeniably, this may lead to psychological trauma and behavioral disorders among youth.

According to its appearance, the male-dominant apple-type (localized primarily in the abdomen, viscera, yet also extra-abdominally) and female-dominant pear-type (gluteal region, thighs and hips) characteristics of obesities can be differentiated, one in which the latter bears a less poor prognosis. Other categories include, hyperplastic (beginning at childhood and coupled with the larger number of fat cells) and hypertrophic obesity (developing later at adulthood, reaching a maximum upon age 40-60 years of age and associated with greater cell size). In general practice, both types may be combined and intermingled.

8.4.3.2. PATHOMECHANISM OF OBESITY

As seen in starvation, earlier exogenous and endogenous forms were described for obesity, as well. However, all obesities are exogenous in the sense that more food is needed (from exogenous source) to increase body weight, and endogenous in the sense that there is an endogenous factor that urges the individual to consume larger amounts of this food (with the exception of forced-feeding, in excess of the actual daily requirement).

Regarding the pathomechanism of obesity, a role for **genetic factors** has long been assumed. Concordance studies involving monozygotic and heterozygotic twins demonstrate how the concordance of body weight is greater among homozygotes, proving a potential role for the genetic factors regarding obesity. If both parents are obese, the transmission to their descendants increases to 73%, in in the case of one obese parent, it only reaches 41%. Stunningly, amongst offspring of non-obese parents, the level is 9%. Obese strains of various animal species are also suggestive regarding genetic factors, such as the comparison of pig and wild-boar. It is assumed that genetic factors participate in at least 50-70% of human obesity. However, recognizing the potential role in support of genetic factors, in itself, does not disclose relevance regarding other mechanisms in the development of this state.

A role for genetic factors can be demonstrated in the case of Pima Indians, specifically the population residing in the USA, and not defined as Mexican by origin, however, genuine members of the tribe, in which feeding became more regular with the advent of civilization, and one in which obesity affected nearly all those living in the USA. A "thrifty gene" is presumed to have played the potential role in this enigma, regarding an earlier

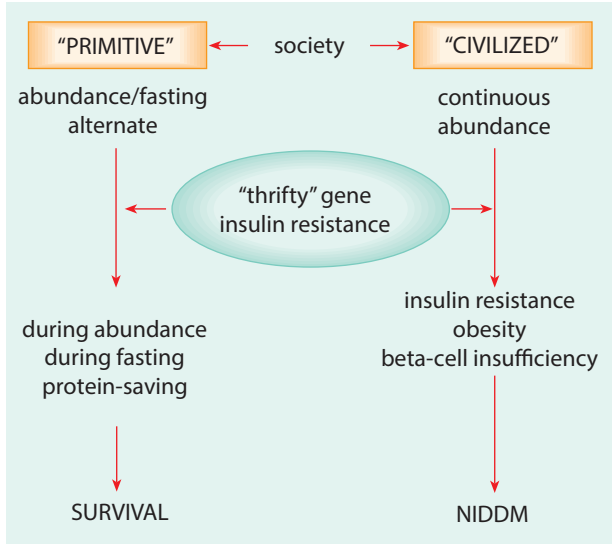

Fig. 8.11.: The thrifty gene leads to different phenotypes if the social environments are different.

Table 8.6.

Genetically determined factors that may have a role in development of obesity

inheritance of taste preference (sweet!)
inheritance of palatability preferences
hereditary differences in molecular/chemical control
leptin and leptin receptor disorders*
MC4 receptor-expression disorders**
POMC disorders (insufficient POMC function)
PPAR-γ disorders***
hereditary differences of the energy loss****

* Leptin and leptin receptors: Leptin is produced in fat tissue and its level is proportionate with the amount of fat tissue, in which it is dependent upon the nutritional state rather than on actual feeding state. It leads to the suppression of food intake by inhibiting NPY release/action in the brain. Genetically obese ob/ob mice produce no normal leptin, which explains their monogenic obesity. In other cases, such as seen in db/db obese-diabetic mice, the sensitivity of leptin receptors is missing. In consideration of humans, real leptin deficiency is rare, yet more frequent is the receptor deficiency, however, both mechanisms are characteristically possible when considering human obesities (hyperphagia, decreased metabolic rate and type-2 diabetes mellitus). Frequently, high leptin levels found in obese individuals implies an ineffectiveness of the peptide.
**MC4-receptor gene mutations occur in human forms of obesity. It is often coupled with diabetes mellitus. The receptor is normally stimulated by the agonist α-MSH (POMC-derivative) and its activity suppresses food intake. It is inhibited by the endogenous antagonist agouti-related peptide (AgRP). The AgRP was demonstrated to cause obesity among mice. Leptin and insulin inhibit AgRP production in the arcuate nucleus.
*** PPAR-γ disorders: gene mutations of this transcription factor may speed up differentiation of adipocytes and may be the cause of extreme obesity.
**** Inherited disorders of energy dissipation:

- Inheritance of physical activity types (NEAT) is not yet proven, although enhanced activity decreases body weight. However, there may be characteristics associated with inheritance regarding the type of muscles and their structure: Among obese individuals, an increase in the number of fast-twitch fibers were found (these have low oxidative capacity and shorter productivity), while when compared with athletes and in individuals with a normal BMI, fibers of higher oxidative capacity and metabolic rate dominate.
- In the regulation of the mitochondrial proton pump among muscles, an uncoupling protein (UCP3) participates, and proves influential upon the metabolic rate of muscles, thereby also the resting metabolic rate of the individual. In the case of low UCP3 mRNA expression, the resting metabolic rate of the muscular system is correspondingly lower, of which, may result in energy retention. Although mutation of the UCP3 gene has been described among Afro-American obese individuals, a general role of this mutation is unlikely.
- Polymorphism of the β3-adrenoceptors influences (suppresses) the oxidation of fats, and in doing so, may promote the development of obesity (low DIT, CIT).

era, in which famines were survived only by those who featured mechanisms intent on saving calories, and in which only these individuals inevitably transmitted their genes onto the next generation, and subsequently, their descendants continue saving calories, despite the absence of famine (Fig. 8.11.).

Known genetically **inherited** factors which may contribute to human obesity (the polygenic inheritance is more common when compared to a monogenic aspect) include the following:

Nevertheless, the presence of an inherited factor is not unavoidably associated with obesity. In the maintenance of an adequate diet including physical activity, the normal body weight usually can be maintained (if a person does not consume too much food, no obesity develops, although in consideration of aging, the ratio of fat will be higher in the body composition: Table A14.1.). From another perspective, obesity may develop without hereditary factors (e.g., injury of the satiety center and/or insulinoma), yet high-calorie containing diet leads to obesity among experimental animals (diet-induced obesity = DIO). This may affect "genetically lean" animals, as seen in dogs, too. In consideration of veterinary practice obese, diabetic pets, such as dogs, are well known. Accordingly, in addition to hereditary factors, several other, albeit exogenous, acquired **environmental** factors also participate in the development of obesity.

Lurking in the background of any obesity is the presence of a disproportionality between intake and utilization/dissipation of energy, and as a result, the surplus energy is stored. Only the fat tissue is suitable for significant energy storage. The cause of disproportionality may be due to the following:

1. Excessive energy intake
2. Decreased energy utilization/dissipation
3. Disorder in the system of food intake regulation.

ad 1) Although it is certain that the *primary over-enhancement of energy intake* leads to obesity (e.g., DIO mice, ch. 8.4.2.1.), it is not entirely specified, precisely how this applies for the human practice. In consideration of the development of obesity, patients do not necessarily eat outstanding amounts or take in a disproportionate amount of food. According to earlier calculations, daily 1-2 cubes of sugar in excess of the daily energy need lead annually to several kg-s of weight gain (yet, for maintenance of the higher weight, the energy need becomes correspondingly higher, and a new balance is established with the 1-2 cubes – only further

calorie excess, e.g. 3-4 sugar-cubes, etc., could keep a further weight-rising tendency). In those individuals who are already obese, the high body weight may be maintained at near-normal energy intake. Thus, it may be difficult to clinically clarify the various methods in which obesity develops. When the regulation of food intake is normal, and the hunger/satiety mechanisms bear a normal influence (i.e., excess food suppresses subsequent appetite, as described earlier, ch. 8.2.1.), it is difficult to accept that simple overfeeding is the direct cause of obesity, although the repeated intake of delicacies in satiated states may indeed, have such a role. It is far more likely that the regulatory mechanisms are changed for yet some unknown reason, such as in the case of learned behaviors and the impact regarding specific feeding habits over subsequent generations.

ad 2) The importance of *decreased energy utilization/ dissipation* has been mentioned earlier (ch. 8.3.). Currently, no relevant genetic disorders appear to exist in support towards explaining obesity by this way. In an acquired form, however, a sedentary lifestyle is an important cause of overweight, however, in consideration of normal regulations, this should be associated with a decreased food intake rather than increased body weight, suggesting again, changes in the regulation. Cessation of robust, active sports, and change for sedentary lifestyle is often followed by – sometimes significant – weight gain.

ad 3) *Changes in the regulation of food intake*: This possibility has been experimentally verified: following the lesion of the "satiety center" regarding the ventromedial hypothalamus, the animals ate more and inevitably, became obese. Among humans, the injury of central structures is possible, e.g., in consideration of basilary injuries and bleedings, however, they are extremely rare and they alone, cannot explain the frequent occurrence of obesity. However, the central functions may be altered by other means, too. Various examples include the leptin lack/resistance or decreased cerebral insulin sensitivity, and both generate a tendency for obesity and for the multiple disorders of the metabolic syndrome. The enhanced activity of the anabolic monoamine-peptide system or suppression of the catabolic systems may equally contribute to the development of obesity.

Acquired and environmental factors in the pathogenesis of human obesity:

Endocrine obesities (insulinoma, Cushing's disease/ syndrome, hypogonadism)

Neuroendocrine disorders (hypothalamic injury)

Psychosocial factors

- Feeding habits: (partly responsible in association with familiar occurrence), consumption of "junk food" including high fat content (chips, chocolate) or food causing a high glycemic index and hyperinsulinemia/insulin resistance, thereby increasing fat accumulation
- Lack of physical activity, inactive lifestyle, and restricted movement (in Hungary, less than one third of the population participates in sports/ activities for 2.5 h/week, and in contrast, most adults sit for 12 h/day)
- Social, economic, cultural causes (amongst poor, yet not poverty-stricken individuals, in which obesity is more frequent, as per example, African Americans and Spanish-speaking people in the USA and the Roma throughout Hungary and Mid-Europe and, as a form of "compensation", the abundant food intake without selection is characteristic – in the USA, those individuals in the lower socioeconomic status reflect a 6 times increased risk regarding obesity)
- Psychiatric anomalies: grief-induced eating, bulimia nervosa, and various forms of depression)

Metabolic diseases in connection with "civilization factors" of metabolic syndrome

Aging: with increasing *age*, the body weight increases until ca. 65 years of age, then stagnates for 5-10 years, while later, the body weight decreases (mainly attributed to loss of the active tissues, and less characteristic of fat loss).

Pre-existing obesity: the metabolic disorder of pre-existing obesity definitely supports maintaining the level of obesity. Due to insulin antagonism, hyperinsulinism develops, and this enhances fat production and deposition among fat cells. The low insulin sensitivity leads to diabetes, yet the sensitivity is correspondingly lower in the brain, too, therefore the anorexigenic effect is lost and the food intake remains high. In obesity, the leptin cannot pass through the blood-brain barrier normally, therefore the anorectic and hypermetabolic/catabolic effects of leptin are missing.

8.4.3.3. CONSEQUENCES OF OBESITY

Longevity decreases among obese (high BMI) individuals (Fig. 8.3., Table 8.7.) or in obese animals (Fig. 8.4.). Obesity *per se* appears to be a causing factor of premature death: in genetically obese rats the very short life

Table 8.7.

Excess mortality within 5 years of 45-year-old men of various body weights (above normal BMI) as compared with the average mortality in the same age group with normal BMI

BW-excess (kg)	excess mortality rate (%)
4.6	8%
9.0	18%
13.5	28%
18.0	45%
22.5	56%
27.0	67%
31.5	81%
40.5	116%

expectancy was normalized on a low-calorie diet which secured normal body weight (i.e. not the genes, but the body weight is the determinant factor). This has been demonstrated in genetically obese ob/ob mice as well, although in consideration of these mice, the relative fat content remained high, despite the normalized body weight. What are those consequences of obesity (Fig. 8.12.) which may be direct causes of shortened lifespan?

1. Disorders of circulatory system: Hypertension (insulin resistance induces hyperinsulinism, the consequence is increased salt/water retention, hypervolemia in which there is additionally enhanced catecholamine sensitivity – concurrent leptin-resistance also contributes: it leads to hyperleptinemia with consequently high sympathetic activity, and at the same time, the enhanced angiotensin production by the visceral adipocytes enhances the RAAS activity). In addition to hypertension, atherogenesis, chronic heart failure, a tendency for venous thrombosis (venous congestion in the leg, while the visceral adipocytes produce more PAI-1 with the consequence of decreased fibrinolysis) and also various cardiovascular/cerebrovascular consequences.
2. Disorders of the respiratory system: Pickwick syndrome, sleep apnea syndrome, pulmonary hypertension and tendency for respiratory insufficiency.
3. Postoperative cardiovascular/respiratory complications are more common.
4. Metabolic disorders: diabetes mellitus (2DM, hyperinsulinism + insulin resistance), high plasma cholesterol-, triglyceride-levels, gout.

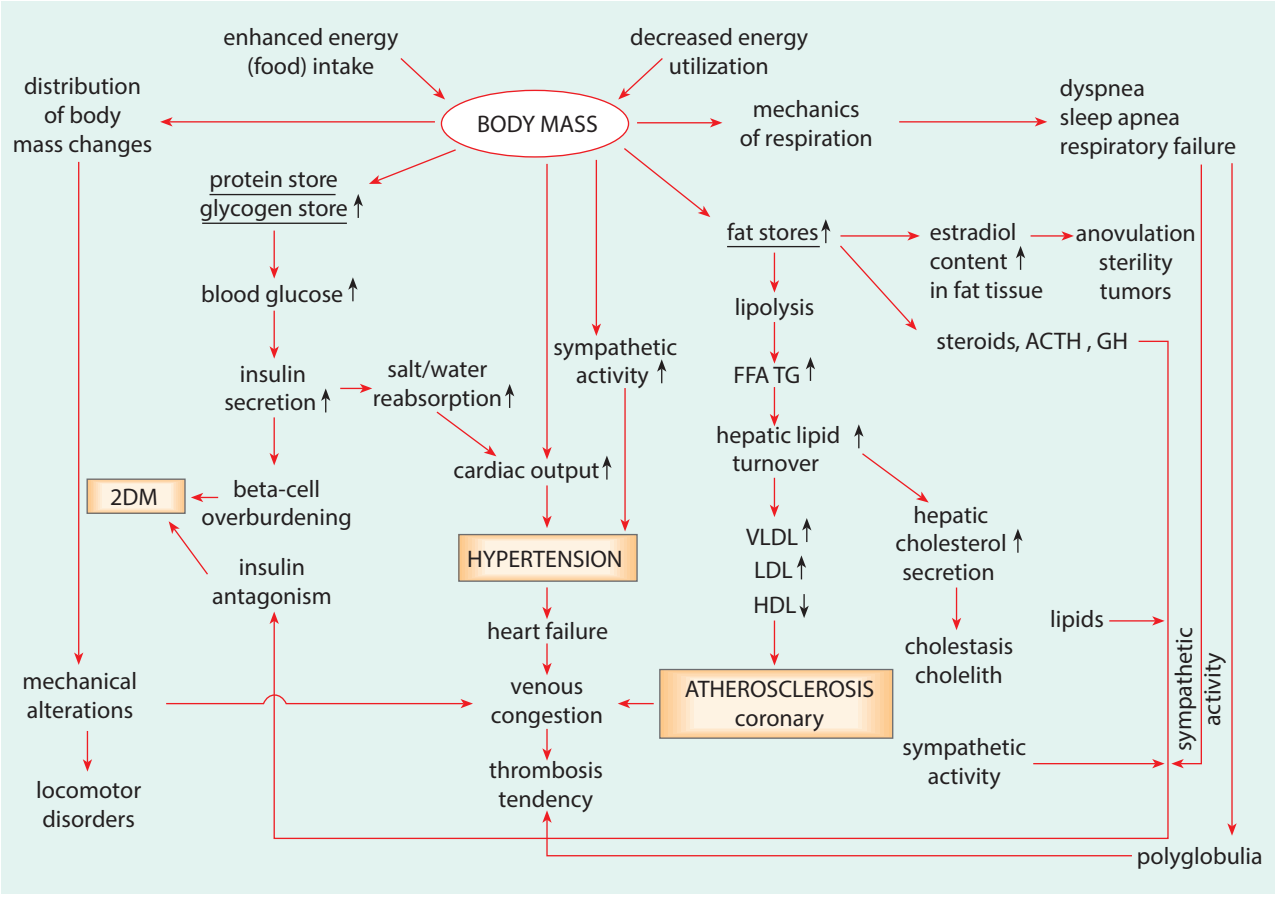

Fig. 8.12.: Summary of the most important consequences of obesity.

5. GI disorders: steatosis hepatis and gallstones
6. Chronic renal failure: due to hypertension, diabetes, hyperlipidemia, and to high coagulability
7. Musculoskeletal disorders: arthrosis of the knee and/or the hip, however, there is little association to osteoporosis – any restriction of mobility aggravates obesity
8. Endocrine disorders: estrogens originating from the fat tissue may cause an anovulatory cycle including sterility, while the enhanced cortisone-cortisol transformation suppresses the activity of the immune system
9. Several tumors occur more often, including those associated with the breast and/or endometrium, because fat tissue binds high amounts of prolactin, estrogen/androgen (and the resultant estrone) and cortisol
10. Inflammatory mediators produced in fat tissue: IL-6, TNF-α, eicosanoids, both leptin and resistin, and lastly, growth factors: IGF-1, TGFβ serve to enhance insulin resistance. (Obesity is regarded a low-intensity chronic systemic inflammation)
11. Plasminogen activator inhibitor-1 (PAI-1) production results in high coagulability and a tendency in support of thrombosis
12. Psychological disorders: eventually severe depression, hypomania, integration disorders except in the case of Falstaff-type obesities, in which the obese individual is compensatorily hedonist for a period, yet the early 2DM and its consequences (e.g. stroke) will eventually stop this behavior

8.4.3.4. ASPECTS OF THERAPY IN OBESITY

In addition to the restriction of calorie intake (diet, surgery, etc.), the sufficient amount of accessory nutrients is important, as well as that of the intake of dietary fibers. To save the protein content, physical activity should be increased (with fasting, protein catabolism is enhanced, and for its prevention, dietary protein intake alone is not enough, active muscles retain more protein). The patient and the family environment have to be psychologically prepared for the relevance and challenges regarding therapy. A slimming diet initiated in time and performed successfully can prevent nearly all of the potential complications. Unfortunately, occasionally, the therapy has to be rather drastic, and too often risks the development from a formerly "healthy" obese person into a complaining patient now saddled with depression – this appears to question the actual benefits regarding various therapeutic methods.

Following a successful slimming diet, the patient often regains the original or even higher body weight, and this can happen repeatedly (yo-yo syndrome). Meanwhile, the body composition undergoes unfavorable changes: the fat ratio increases disproportionally and the muscle mass gradually decreases. This calls attention to the importance of continued therapy even following a successful slimming diet regimen.

Recently, the surgical treatment of obesity is frequently considered. Starting with the simple lipid-suction procedures, today there are several newer methods, such as the narrowing or resection of the stomach. In cases of extreme obesity, a relatively ideal and lasting effect is seen by the application of the Roux-en-Y gastric bypass surgery (RYGB, see Fig. 7.1.). The stomach is dissected into two parts, a small, egg-size upper part (pouch) and also dissected is the jejunum, slightly after the duodenum. The distal jejunum portion is inserted into the pouch, and the sutured lower part of the stomach including the duodenum and early jejunum is connected into the jejunum at a more distal point, carrying digestive enzymes and bile. Therefore, the small pouch does not allow the intake of a large amount of food, and the absorbing surface decreases (short-bowel syndrome). An additional limitation of food intake likely describes the early and late dumping syndrome, in which the patient is careful not to over indulge, or overeat, and in particular, avoids an abundance of sugar. Additionally, these symptoms, likely due to the fast passage, are associated with activation of the endocrine L-cells of the intestinal epithelium, which produce more galanin-like peptide (GLP-1) incretin, as a result, the GLP-1 effect is stronger, as it enhances insulin secretion, enhances metabolic rate and slows down the passage. Thus, diabetes starts improving well before significant weight loss. Other regulatory factors promote anorexia, as seen in the decreased production of anabolic ghrelin in the stomach. Unfortunately, this very intensive operation is often not enough for effective motivation of patients in making quality of life decisions. With time, the pouch may distend and obesity may reappear, therefore the diet remains very important even after the operation.

8.4.4. ANOMALIES OF BODY COMPOSITION

According to the data demonstrated in ch. 8.1.2., as seen among young adults, the fat content of the body is ca. 15-20% (in females, a little more), the protein

content is nearly the same (in females, a little less), the carbohydrate store in reference to percentage is negligible, and in addition to the ca. 4 kg mineral content, the greatest component of the body is water (60-65%). The body composition is important, e.g., in the perspective regarding drug distribution and concentration within the body (e.g. digitalis is distributed in the water, diazepam in the fat compartment). If and when the BMI is too high or too low, it is usually accompanied by differences regarding body composition. In consideration of a pathologically low body weight, it is primarily the fat component which is insufficient, therefore it is unable to serve not only the energy-store function, but also the mechanical defense function, which now is considerably marginalized, limiting the availability of fat-soluble substances/vitamins, including vitamin E. A deficiency of fat mass may be seen among body builders, too. Apart from this specific group of men, the body weight excess originates in nearly all cases from fat (except in cases of fluid retention in the third water-space).

The body composition may pathologically change with aging, particularly at the threshold of old age. It is independent of the size of whole body mass, since only the fat mass increases and the quantity of muscle and other proteins decreases, sarcopenia develops (ch. A14). In these cases, the fat mass does not necessarily refer to the fat stored in fat cells, as in advancing age, due to the rising levels of leptin and cytokines, a decrease occurs among the a peroxisome proliferator activated receptor (PPARγ) activity (Fig. 9.13.), thus decreasing the differentiation of preadipocytes and the accumulation of fat in these cells. As a result, mesenchymal adipocyte-like default (MAD) cells are produced (ch. A14.2; Fig. A14.3.). At the same time, burning of lipids decreases. The accumulated lipid-excess is deposited throughout the various cells, tissues and their interstitia (e.g. myocardium, liver) and by their commonly referred lipotoxicity, they damage their function. Among seniors, the greater fat mass does not represent the same obesity when compared to youth. Apparently, obesity among seniors may linked with immobility largely due to sarcopenia. Interestingly, sarcopenia, at the same time, implies a tendency for accelerated starvation (e.g. in simple infections or transient nutritional or salt- and water-balance disorders), even with maintained fat mass.

In consideration of the yo-yo syndrome, the slimming diet based exclusively upon relative starvation and dietary calorie restriction (not on physical activity and protein supplementation) corresponds to a relative starving condition – the consequent gluconeogenesis results in an exaggerated loss of proteins, while following the diet, the restoration of body weight is due exclusively to fats. In this regard, the body composition gradually worsens, and sarcopenia ensues, despite the relatively or absolutely high body weight. Inevitably, the accelerated starvation may easily develop, and the sarcopenia may be limiting factor as regards the expected lifespan.

8.5. REGULATION OF BODY TEMPERATURE AND ITS DISORDERS

In homeothermic species, the inner "core" temperature (Tc) is relatively stable, while the temperature of the skin (Ts) and outer surfaces (or the outer shell) changes in a wide range between the environmental and core temperatures, primarily according to the environmental temperature (Ta). The human Tc is ca. 36-37 ^{0}C, however, it is not strictly standard even physiologically, since there are, among others, circadian changes, shifts related to the ovulatory cycle, rises to exercise or food intake, etc.

The regulation of body temperature relies on the information coming from warm- or cold-sensitive thermoreceptors at different points of the body (Figs. 8.13. and 8.14.). Summation and processing of the thermal information is the task for primarily, yet not exclusively, for the hypothalamus. The effector path of the regulation involves partly the mechanisms of behavioral regulation,

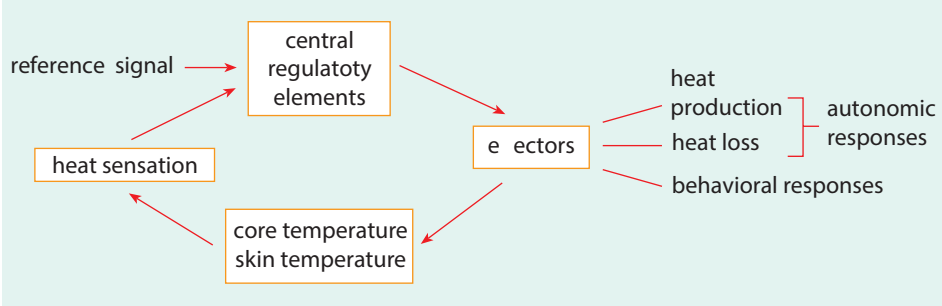

Fig. 8.13.: Basic mechanisms of the regulation of body temperature. An assumed reference signal determines the "set-point" or "set-range" of the system (see also next Fig.).

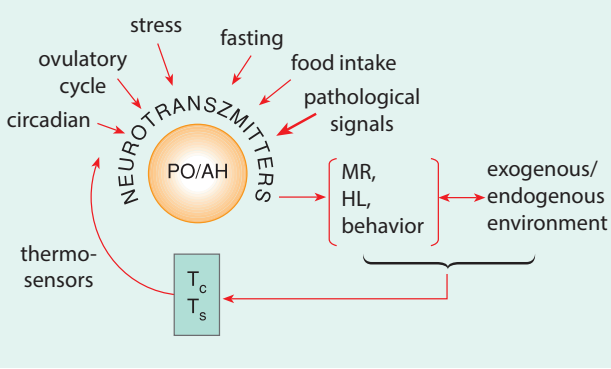

Fig. 8.14.: Explanation of the set-point concept: The "**reference signal**" should not be interpreted as a thermal signal at some point of the body, to which the incoming thermal signals are compared. This signal is a functional state "tone" (and the consequent state of heat production and heat loss) of the central regulatory system as influenced collectively by various humoral/hormonal factors, neural signals and neurotransmitters (stress, time of the day, ovulatory cycle, feeding state, etc.). This reference state may be modified to some extent by the incoming thermal signals or the neurotransmitters evoked by them, thereby appropriate changes of heat production and heat loss may be initiated. As a result, body temperature may be modified, and the transmitters evoked by signals of the new temperature do not differ any more from the reference signals. The modification depends on temperature, i.e. the nature and extent of the modification will be different to cold and to warm information – the response will also be different. The thermoregulatory state determined by the reference signals, which is practically not altered by the incoming thermal signals, is called the **set-point** of the signal. In fact, it should be rather called **set-range**. In other situation (e.g. fever) primarily the state of the central system is altered, this initiates effector function changes and consequently the temperature changes – the transmitters induced by the new temperature secure a new balance (shifted set-point)

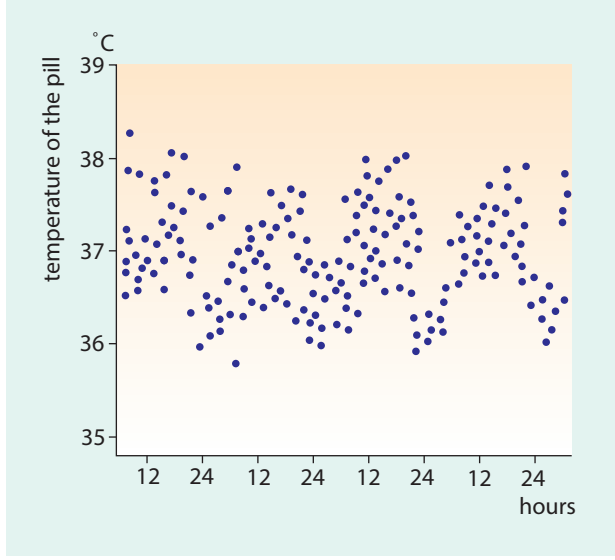

Fig. 8.15.: In human studies the examined persons swallowed a pill which gave temperature-dependent radio signals. The great scatter and the circadian changes are shown on the figure.

such as clothing, heating, air-conditioning, yearning for sunshine or shade, a shower or bath, etc., and, partly due to the mechanisms of autonomic regulation. The autonomic aspect of the regulation comprises shivering/non-shivering thermogenesis induced by cold, in excess of BMR (cold-induced thermogenesis = CIT) and of the mechanisms of heat loss. The latter includes radiant heat loss (by skin vasodilatation and the elevation of skin temperature) and evaporative heat loss due to sweating/perspiration (or panting and grooming in some species). The conductive (direct contact with cold/warm surface) and convective (wind) forms of heat loss cannot be influenced by autonomic means. In consideration of the aid of the arsenal of these mechanisms, the core temperature can be maintained when confronted with variable changes of environmental factors. Among heterothermic species, the basic difference is that they rely entirely on behavioral regulatory modes.

According to Fig. 8.14., it is understandable that the premise of homeothermia does not imply a rigidly standard temperature, definitely, it infers a relative stability, in which there are many influencing factors. In reality, among the spectrum of individuals, there may be a large scattering, but even within an individual the Tc is not standard, either. The individual differences and the diurnal changes of Tc are shown in Fig. 8.15., in which the "normal Tc" is, albeit subjectively, higher than 36 °C, and on average, less than 37.2 °C at night/morning and 37.7 °C by the evening.

Disorders of thermoregulation may originate from the failure or breakdown of a sufficient defense mechanism against the influence of strong cold or severe warmth, despite normal thermosensation and central regulatory functions commonly referred to as **hypothermia** or **hyperthermia**. Other disorders affect primarily the mode of functioning of the complex central regulatory systems and the balance of various signals ("set-point") and, inevitably, the processing of a thermosensor signal, in which the examples are **fever** and its polar opposite, **anapyrexia**.

Various exogenous factors (high/low external temperature, vapor content, wind, etc.) may alter passively the body temperature, without an active contribution of the organism, if the external influence is strong enough that the organism cannot avert it by the available, eventually reduced autonomic and behavioral effector means. Endogenous disorders of the effector functions (enhanced heat production in Graves' disease, a decreased sweating capacity for any reason, decreased metabolism in hypoxia or hypothyroidism,

etc.) also induce passive shifts in body temperature. According to earlier, simplified views, changes in the central regulation lead to the shift due to the change in the regulated temperature level (a virtual "set-point" as single reference signal). A single anatomical substrate in support of such signal does not exist. It may be determined by the balance or a shift in the balance of various central influences (Fig. 8.14.), as seen in cases of body temperature, which actively change due to fever or anapyrexia, yet, not as a defective defense against an external/internal load. General disturbances of thermal sensation (sedatives, alcohol, etc.) lead to the lability of thermoregulation, and one in which the defense is not sufficient against combating either cold or warm loads, therefore, the regulated limits of body temperature become wider (*broad-band control*). Instead of a set-point, the set-range expression may be more appropriate in these cases. In still other cases, the range is presumably narrowed, as presumed to happen in menopause, in which heat loss can be activated more easily (hot flush) and in the response easily triggers shivering.

The disorders originating from overburdening the system or from primary changes of central regulation are schematically demonstrated in Fig. 8.16.

The same effectors deemed fundamental in thermoregulation may bear relevance regarding their role(s) in other regulatory circuitries (vasodilatation in vasomotor regulation, panting in the regulation of respiration and sweating in salt- and water-balance), thus, the association among these systems is worth considering. From one perspective, thermoregulatory reactions and body temperature may be influenced by factors which are primarily non-specific regarding thermoregulation (feeding, hormones, drugs, hypothalamic perfusion, etc.).

8.5.1. DISORDERS OF COLD DEFENSE, HYPOTHERMIA

In the simplest form, a disorder of defense against cold is defined as a decrease in core temperature, and subsequently, the development of hypothermia. However, prior to this state, a prolonged cold effect may cause relative starvation and weight loss due to the hypermetabolism. In a warm environment hypothermia cannot develop, and as such, external cold is an indispensable although not necessarily sufficient prerequisite of its development (until a certain degree, the body is able to defend Tc). The defense mechanisms may be insufficient even among healthy athletes in extreme cold (snow-storm, accidents

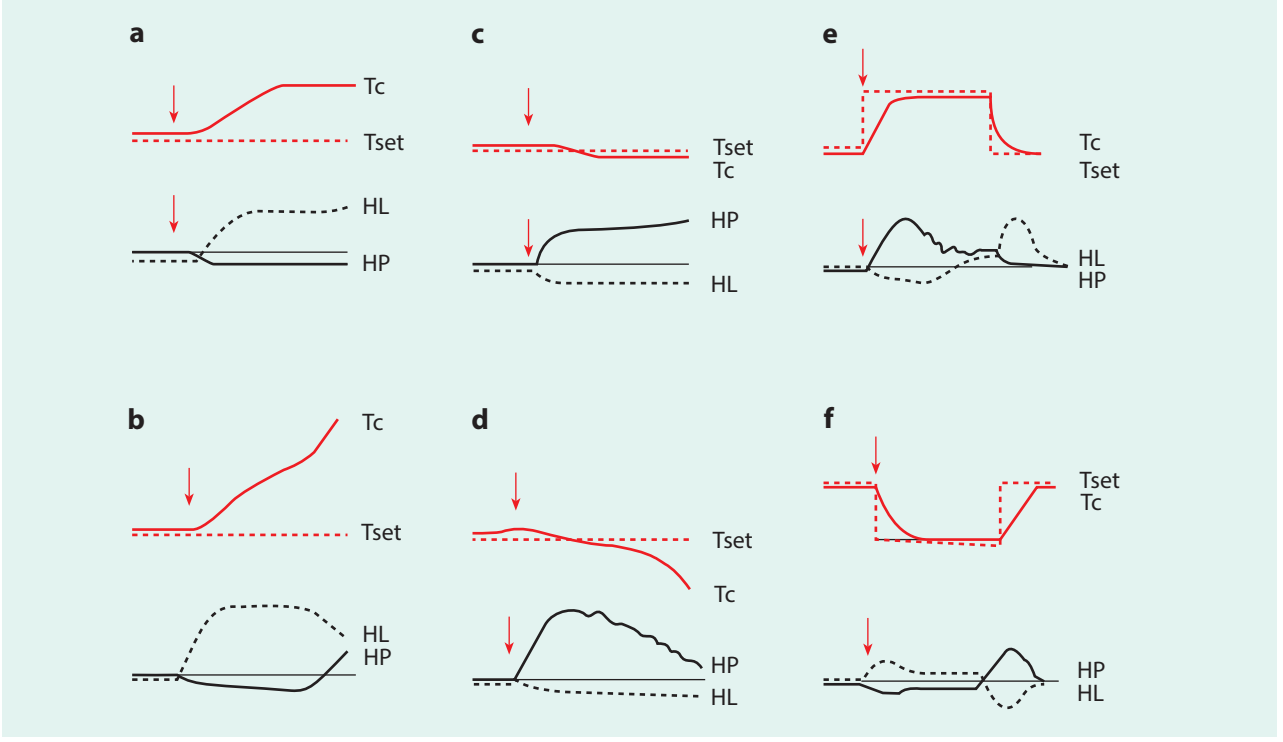

Fig. 8.16.: Changes of core temperature (Tc), active heat loss (HL), heat production (HT) and set-point (T_{set}) in various disorders of thermoregulation. "A" moderate, compensated hyperthermia, "B" severe hyperthermia (development of heat stroke). "C" moderate cold effect, "D" severe cold effect with insufficient compensation, development of hypothermia, "E" development and termination of fever, "F" development and termination of anapyrexia.

in water, etc.). Still, extreme cold is not always necessary for the development of hypothermia. Mild cold may evoke hypothermia, if the cold-sensation is defective (e.g. the effects of alcohol and/or sensory neuropathies), if the effectors are insufficient (e.g. starvation, low BMR, exhaustion, hypoxia and vasomotor disorders), or in case of defective/abnormal function of central regulatory systems (e.g. the effects of alcohol, narcotics, toxicoses or neonatal/old age). Immobilization or a wet-and-cold environment promotes the development of hypothermia, as seen among the elderly persons, who, in the case of a fall while in the bathroom, quickly become immobilized. Those individuals at the lower income and or poor social status (homeless, unheated flats, etc.) are particularly exposed to the risks regarding hypothermia. Clearly, apart from the external cold, a combination of a number of endogenous factors contribute to the development of hypothermia. Slow cooling to hypothermia eventually develops without symptoms (symptomless cooling, discussed later). Without using appropriate thermometers, hypothermia often remains unrecognized (best is to measure tympanic temperature).

The hypothermia may be **accidental** or **induced,** of which, the latter is used deliberately in the premedication at the onset of surgery (e.g. prior to cardiac surgery). More recently, it is used among premature babies, brain injuries in the form of moderate local hypothermia to decrease the oxygen need of the brain and prevent high risk of serious damage.

***Severity of hypothermia**:* In mild hypothermia the core temperature is 34-35 ^{0}C, and below this the shivering decreases, vasoconstriction, muscle weakness and uncoordinated movements are characteristic, and eventually, various sensory disorders (false feelings, hallucinations) may appear. Next, shivering gradually stops and in moderate hypothermia the core temperature decreases to ca. 30 ^{0}C. Tc falls precipitously, circulation and respiration decrease, and disorders of consciousness are becoming increasingly severe. Below 30 ^{0}C the hypothermia is severe, coma develops and the diminished microcirculation endangers tissue metabolism. At ca. 28 ^{0}C, typically ventricular fibrillation leads to death of the patient. In induced hypothermia, even deeper cooling is possible. The hypothermic death ("freezing") does not necessarily mean body temperatures below the freezing point, it only refers to lower temperatures and the minimum regarding survival: it often happens that alcoholics "freeze to death" by the roadside on a mildly cool night.

Rewarming has to be performed by **slow warming of the trunk**, with continuous monitoring of the circulation, respiration and salt- and water-balance. Dangers of rewarming include circulatory shock or the commonly referred to, "afterdrop" (see later). Causes of such shock are attributed to hypovolemia, tissue ischemia and widespread acute vasodilatation.

Pathophysiological consequences of hypothermia:

Within the cooling tissues, the developing vasoconstriction decreases local perfusion. At the capillary level, this refers to a reduced hydrostatic pressure, therefore fluid moves in from the interstitium and the circulating volume increases. The circulation is centralized and the higher central venous/atrial pressure activates natriuretic mechanisms, which initiates the cold-induced diuresis, a decrease in salt- and water-content and hemoconcentration. The initial hypervolemia and vasoconstriction tend to cause a rise in blood pressure, and a sudden cold effect, or meteorological cold front is often coupled with a sudden increase in blood pressure.

Since metabolic rate and the oxygen need also decrease within the cooling tissues, the disorder of microcirculation is not immediately obvious. However, circulation may decrease further, bradycardia, a decrease in cardiac output and local vasoconstriction develop, and over time, microcirculation will not suffice even among the lower needs, hence ischemic metabolic products and K^+ from cells accumulate. At this stage, due to the ischemic disorder and substances from the consequent cellular damage, the direction of fluid flow at the capillary level changes, now fluid is lost to the interstitium and marked hypovolemia develops. The damaged cells start swelling and lose potassium. The fall in respiration also exceeds the decreasing needs, areas of atelectasis are growing, and inevitably, respiratory failure is characteristically the result. The disorder of microcirculation is particularly obvious during re-warming, in which the hypovolemic and distributive type of shock may develop. The state of shock is accompanied by respiratory and metabolic acidosis and hyperkalemia.

Depending on the speed of cooling, a different duration of characteristic motor incoordination develops, physical exhaustion, sleepiness, often delusions, hallucinations occur, with manifest mental disorder. Occasionally, these make the patient stop, to "have a rest", and the result is that it speeds up the cooling rate and the patient becomes disoriented, then unconscious and develops spontaneously irreversible hypothermia, which is often lethal. In other cases, at slow cooling, the

body temperature hovers at 34-35 °C, and eventually falls to 32 °C. Among elderly patients with restricted mobility *"symptomless cooling"* may develop, in which the slow cooling develops yet without severe symptoms and the autonomic cold-defense reactions are not activated, however, disorientations and hallucinations may manifest themselves – in such cases most investigators consider the possibility of psychiatric disease, therefore do not even measure body temperature. Treatment of unrecognized hypothermic patients with sedatives and/or antipsychotic medication serves only to aggravate hypothermia.

One risk regarding re-warming is referred to as *"afterdrop"*, in which the hastened, fast return of the cold blood from the periphery leads to a decrease in the core temperature, and due to its suddenness, Tc attains a critical low level. The other risk is the development of hypovolemic/distributive circulatory shock and hyperkalemia.

Defense against cold suggests an increase in sympathetic activity. This may prove consequential, even without hypothermia. Fig. 8.17. shows the seasonality in an all-cause mortality, and notably, during the winter season, the rate is higher. Finnish studies described elevated cardiovascular mortality in the winter season, either from AMI, or rhythm abnormalities, or from thromboembolic complications. Uncoordinated movements enhance the occurrence of falls, some resulting in fractures, of which may be explained by cold extremities, yet not necessarily by any drop in core temperature.

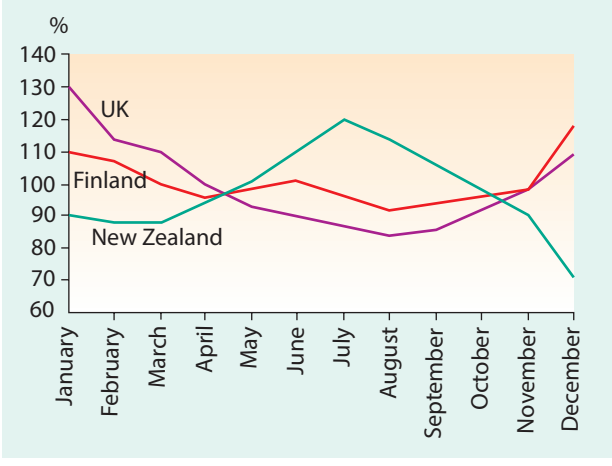

Fig. 8.17.: As compared with the whole-year all-cause mortality rate, in England the relative rate is higher in the winter months (Dec-Jan) and lower in the summer months. In Finland the seasonal changes are smaller, because isolation and heating of homes is better. In New Zealand the British habits are rather strictly observed, the mortality rate is high in the winter months (June-Aug).

Lasting cold exposure causes a sustained high metabolic rate – this is cold adaptation. The high metabolic rate can only be compensated by an adequately enhanced food intake. Maintenance of body weight may be difficult in the cold and energetic insufficiency may develop more easily.

8.5.2. HYPERTHERMIA AND DISORDERS OF HEAT DEFENSE

Disorders of heat defense mechanisms do not necessarily imply hyperthermia (Fig. 8.18.). This defense is supported by mechanisms of the circulatory system and the salt- and water-household, such as skin vasodilatation and sweating. A disorder may occur in the functions of these supporting systems, whilst core temperature may be well maintained. In other cases, core temperature is indeed elevated (hyperthermia). In consideration of global warming (climatic change), the challenge is becoming increasingly serious. In the summer heat-wave of 2003, in France alone, nearly 10.000 fatalities occurred in excess of the usual death rate, and throughout Europe the toll climbed to 30.000 deaths, primarily affecting the elderly population. With the advent of the global change regarding our climate, an increase in meteorological extremities is to be expected, including swells in both warmth and cold weather abnormalities.

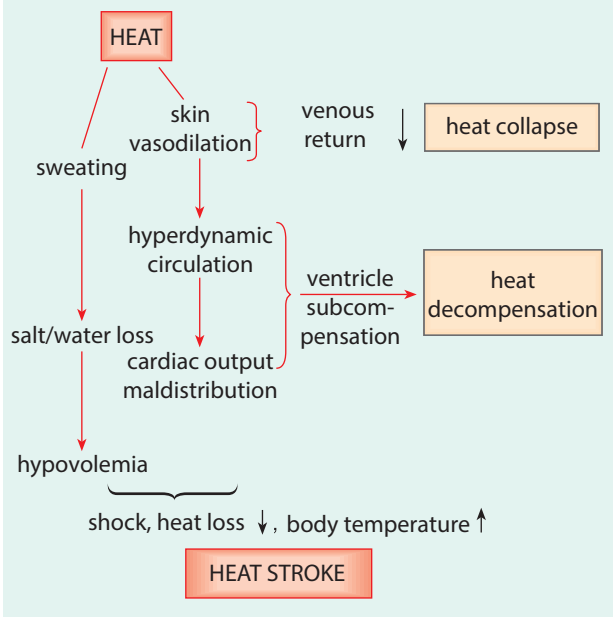

Fig. 8.18.: The main important consequences of heat.

8.5.2.1. CIRCULATORY DISORDERS ADJOINING HEAT EXPOSURE

Heat syncope

To enhance radiant heat loss, skin vasodilation develops, primarily the a-v shunts are open. Additionally, in regards to effective heat exchange, the speed of flow through the skin decreases, and the contact with the cooler environment lasts longer. At the same time, the venous tone decreases and a large amount of blood stagnates in the capacitance vessels, therefore the skin blood content is higher. Large amount of fluid is released from the capillaries to the interstitium, and in the summer season the skin is swollen. These changes result in decreased venous return, the central venous pressure and ventricular filling decrease, as seen in hypovolemia. Salt- and water-loss by sweating (evaporative heat loss) further contributes to this picture. In association to all these, within a hot environment, an orthostatic position may easily cause a fall in brain blood flow and collapse (ch. 2.2.1.). In a cool environment, and in the supine position, the situation can be quickly normalized. The core temperature does not rise.

Heat-decompensation

This occurs primarily in sub-compensated elderly heart failure patients. Due to the heat, cells of the tissues which are more active, should have a higher tissue metabolism, what would necessitate an elevation of tissue perfusion, while skin blood flow should also increase to dissipate more heat. In athletes, the resting 400 ml skin blood flow may exhibit 10-15-fold rise, well exceeding the resting cardiac output. Such adaptive changes require marked rises in cardiac output, but this may be difficult among patients. They can increase cardiac output only by the aid of the Starling-mechanism, which means increasing the EDV and EDp. The diastolic "overfilling" of the ventricles unavoidably leads to venous congestion and symptoms of backward failure (e.g., swollen legs). Still, the rise in cardiac output often lags behind the needs, and its distribution must change, hence the skin is better provided and all other tissues receive less blood (least affected is the brain). This is manifested primarily as a forward failure, as seen in case of the muscles: perfusion is not only not-enhanced, it is definitely decreased, leading to severe muscle weakness, and the patient may not be able to maintain an orthostatic position. This collapse is not identical with the described heat syncope, since, in consideration of the brain, the hypoperfusion is minimal, therefore unconsciousness is rarely reached, although the patient may be confused. The lack of unconsciousness is often misleading: in reality, this is far more severe disorder than heat syncope (associated with unconsciousness), here simply a supine position cannot normalize the disorder, and the acute decompensation of heart function must be normalized and ultimately hospital care is required.

Body temperature typically does not rise. In the event it still does, the cardiac decompensation worsens, since heat directly suppresses myocardial contractility, inducing a tendency for pulmonary edema. Otherwise, body temperature may rise rather easily, since the circulatory failure may prevent the required increase in skin blood flow.

Other disorders of the circulatory system

An acute myocardial ischemia with subsequent angina pectoris, AMI, or fatal arrhythmia may easily develop during heat stress. This is understandable, since, in order to increase cardiac output (primarily by tachycardia) the effort of the heart increases, yet the coronary blood flow does not, or adversely, it even decreases. The rising body temperature contributes to several disorders, as seen in the hyperthermic tissues, in which the capillary permeability is high and in hyperthermia the catecholamine level increases. Hypovolemia is compensated by aldosterone, and therefore it is combined with hypokalemia. The extensive vasodilatation, consequent hypovolemia, and relatively insufficient cardiac output leads to suppression of blood pressure. This may be particularly important in the treatment of hypertensive patients, since in a hot environment or in heat waves the sensitivity to medication is enhanced, and unexpected hypotensive complications (fainting, brain hypoxia, etc.) may occur.

8.5.2.2. HEAT STRESS AND DISORDERS OF SALT- AND WATER-BALANCE

Sweat is a fluid of low osmotic pressure (Na-level 70-100 mmol/l). The maximal sweat rate in non-adapted young individuals is at or about 1.5 l/hour. Following heat adaptation this may be doubled, however, its Na-concentration becomes even lower. Among the elderly and heart failure patients, sweating or perspiration occurs later, at a higher body temperature, and its maximum peak does not reach the amount seen in young persons. In the course of warm-adaptation both aldosterone and ADH secretions are enhanced. Loss of large amount of sweat or only partial replacement of it may cause problems in the volume and/or osmotic pressure of fluid compartments.

Water-depletion type heat exhaustion

It occurs primarily among non-warm-adapted individuals performing heavy physical work within a hot environment, or if in a very warm environment fluid is not sufficiently replaced among disabled patients. Additionally, tormenting severe thirst gradually worsens concerning hypovolemia and subsequently, hyperosmolarity develops. Among elderly patients, the sensation of thirst may be absent, and therefore water depletion may be severe without taking any notice of it. Hypovolemic circulatory shock is associated with the deterioration of the mental state due to hypertonicity. Body temperature, which may be normal at the beginning, begins rising with the exhaustion of further sweating, and inevitably, soon severe hyperthermia is likely to develop. In regards to treatment, the slow infusion of slightly hypotonic solution is advised, together with cooling the patient. This type of heat exhaustion often occurs repeatedly in the same patient.

Salt depletion type heat exhaustion

It develops if the fluid lost due to heavy sweating and perspiration is replaced by pure water or a sweetened soft drink (please note your hospital bedsides), in which the sugar will be burned and converted to CO_2 and water, and done so without replacing the lost salt. Additionally, in regards to the decreasing osmotic pressure, the water compartments are shifted, the IC volume increases, while the EC one decreases, particularly as seen in the plasma. The hypovolemia and hyponatremia induce secondary hyperaldosteronism with K-loss. The hypovolemia enhances non-specific secretion of ADH and the ADH-related water-retention aggravates the hyponatremia. Sweating is maintained until the development of hypovolemic shock, and until this point the body temperature does not rise. The fall in se-Na (hypotonicity) causes characteristic muscle cramps in the calves, and low osmotic pressure in brain cells, increased intracranial pressure (ch. 2.6.2.4. and ch. 6.1.4.1.), nausea, vomiting (this further worsens Na-loss), and later also mental confusion. The depletion of salt occurs more often in heated or unusually warm environments, such as deep mines, metal/asphalt workers, etc. Repeated occurrence is not rare.

8.5.2.3. HEAT STRESS AND HYPERTHERMIA

A shorter or longer imbalance of heat load and heat loss, at the expense of heat loss, leads to "congestion" of heat and to hyperthermia (Figs. 8.18. and 8.19.). Notably, the high body temperature, *per se*, is able to damage the organism.

The heat may originate from external sources or may be produced within the body (effect of thyroxine, amphetamine, etc.) in an amount which cannot be released by the mechanisms of heat loss. A superb example is witnessed within a hot environment in which intensive, robust exercise is performed, yet the classic forms are generally mentioned for seniors and/or neonates, upon pure external heat load against their limited heat loss capacity. The ability to increase heat loss may be restricted, as in the case of atropine therapy in ulcer disease, and hyperosmolarity regarding diabetes in which the tendency is the inhibition of sweating and perspiration, while among the elderly the sweating ability is considerably low. As mentioned earlier, without external heat loss, even BMR could contribute to an increase in body temperature at a rate of about 1-1.5 ^{0}C/hour. Disorders in thermal sensation in a warm environment generate a tendency for hyperthermia, such as high levels of alcohol consumption in the tropics.

Body temperature may stabilize at a variety of escalated levels, often at critically high ones. In other cases, it does not stabilize yet keeps increasing until demise. The clinical state in consideration of critically high or non-stabilizing body temperature is defined as heat stroke (Fig. 8.19.).

Heat stroke

By definition, heat stroke consists of *hyperthermia* ≥40.5-41 ^{0}C, *anhidrosis* (= lack or discontinuation of sweating), and the resulting *coma*. None of these symptoms should be taken too rigidly. The outcome is influenced by the severity of the state and by the duration of hyperthermia. There are examples of surviving even higher yet short-term heat stroke episodes, and the other way around, often less severe, however, longer lasting hyperthermia may prove lethal.

Admittedly, heat stroke develops far more easily in non-heat-acclimatized individuals, in neonates, and in individuals over 40 years of age, and also among hypovolemic patients, in heart failure or diabetic patients, and in patients with ascites. Generally speaking, heat stroke manifests if and when the compensatory role of either the circulation or the salt- and water-balance is limited. Immense numbers of cases were reported from the pilgrimages to Mecca, specifically, when the Makkah Hajj turns to the hot summer season: amongst the non-acclimatized pilgrims, who are often elderly, have heart failure, diabetes, other diseases, and who also do some ritual physical exercise, the resulting incidence of heat stroke is very high.

Due to its complexity, therapy in treating heat stroke is rather difficult. The circulatory changes correspond

Table 8.8.

Basic characteristics and organ consequences of heat stroke

HEAT STROKE:	HYPERTHERMIA ANHIDROSIS COMA + MODS
	SHOCK (HYPOVOLEMIC, DISTRIBUTIVE)
	DIC (INWARD BLEEDINGS, BLOOD LOSS)
	GI-LIVER DYSFUNCTIONS
	ARDS (RESPIRATORY FAILURE)
	KIDNEY (ACUTE FAILURE)
	MYOCARDIUM FUNCTION DECREASES
	TOXICOSIS, SALT/WATER AND pH DISORDERS
	CEREBRAL CIRCULATORY/METABOLIC DISORDERS

to the distributive shock with its two phases, yet water and electrolyte abnormalities complicate the scenario.

Mechanisms of pathological effects of high body temperature

1. *Direct thermal effects:*
   - Heat induced denaturation and precipitation of cell proteins
   - Changes of cell membrane lipids and high Ca^{++}-permeability
   - Intracellular Ca^{++}-levels rise (mitochondrial injury) and K^+ loss from cells

2. *Secondary effects due to circulatory changes:* Hyperthermia reduces myocardial contractility. Briefly, a severe acute form of high output circulatory failure develops, and the forward failure gradually worsens the tissue perfusion. The oxygen need of the hyperthermic tissues is high, while the perfusion of many tissues decreases due to the redistribution of cardiac output and to fall in blood pressure. All these issues begin adding up, including the opening of the shunts in the skin, and the state quickly progresses to a distributive type of shock. Tissue damage over the entire body causes DIC and severe disturbance or insufficiency of various organs or organ systems, such as the heart, kidney, GI tract, lung, brain, liver, salt- and water-balance, etc. The capability to lose heat is limited by these processes, and body temperature progressively increases. The rapid and extensive tissue injury leads to elevation of se-K^+. The ability for heat loss decreases by the shock-induced hypoperfusion of the skin. The characteristics of late form of distributive shock are combined with the sustained high skin temperature.

3. *Secondary effects due to hypertonicity and hyperkalemia:* Hypertonicity non-specifically inhibits cell metabolism, and hyperkalemia is important primarily due to its cardiac effects.

Malignant hyperthermia

By definition, malignant hyperthermia is an abnormality, which is inherited through autosomal dominant means. It is manifested only in the event when the patient encounters some inhalatory narcotics (halothane) or depolarizing muscle relaxants, as seen during surgery, and

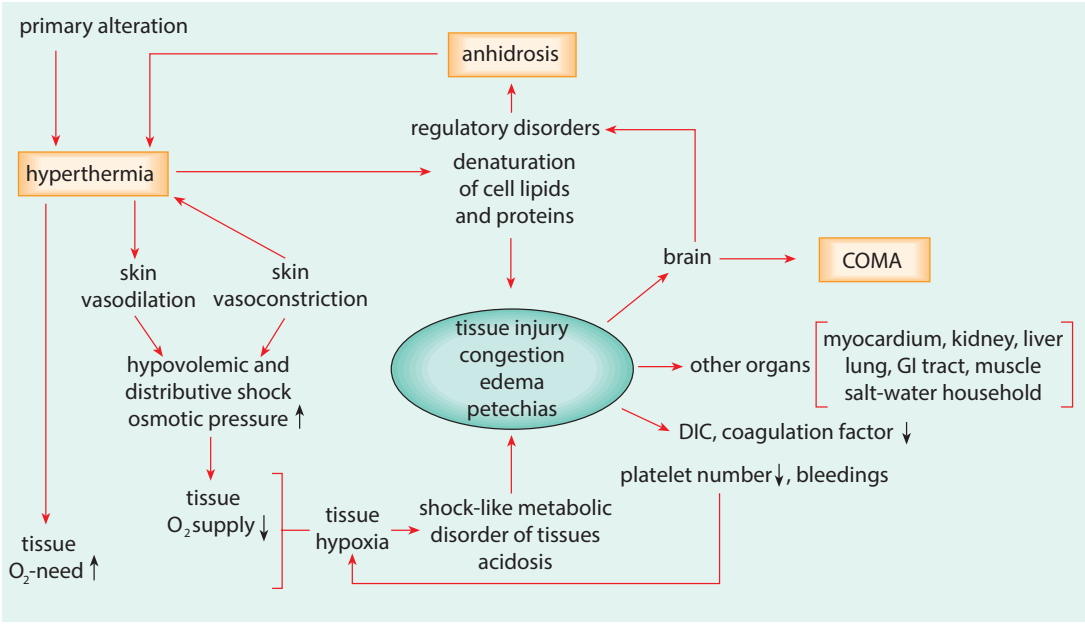

Fig. 8.19.: Pathomechanism of heat stroke development. The process is similar, irrespective of the origin of hyperthermia, i.e. the evoking factors may be different.

without this there are no symptoms. Upon the effect of these substances, the abnormality of muscle Ca^{++} metabolism leads to the spontaneous, unceasing fast rise of an extraordinary extent of metabolism and the body temperature. The myocardium is also affected. Additionally, extreme hyperthermia, acute heart failure, pulmonary edema, shock, DIC, and inevitably, coma, all potentially develop. It is important to be prepared for the possibility of the disease in accordance to the family history, or to recognize the symptoms in time, during surgery. Cooling alone does not solve the problem of the muscle metabolic disorder, and specific treatment (Dantrolene) is required, in addition to cooling.

Neuroleptic malignant syndrome

Treatment with antipsychotic drugs may suddenly induce severe hyperthermia associated with enhanced muscle activity and rhabdomyolysis. The basis is likely due to a change in the activity of central monoamines.

Medical applications of hyperthermia

Following the Nobel-prize winning discovery of Wagner-Jauregg, in which the premise implies how malaria "cures" the symptoms of late, incurable neurosyphilis, hyperthermia was used in the first half of the 20th century by neurologists as a form of "artificial fever" in the treatment of late neurological complications of syphilis and later, in the treatment of other diseases. According to our present knowledge, a high temperature, *per se*, may indeed be beneficial in conquering several infections, (please note the biological value of fever, ch. 8.5.3.). Recently local/regional hyperthermia is used in the treatment of certain tumors, and is done so by heating the blood which perfuses the tissues: the critically high temperature is thought to cause more severe damage of the highly vascularized tumors including a high metabolic rate and high multiplication rate, therefore the normal cells are relatively spared.

8.5.3. FEVER (FEBRIS, PYREXIA)

Definition of fever:

Fever is defined as an intense rise in core temperature which is clinically not a passive hyperthermia due to the deficiency of counter-regulation against heat load, but an active temperature elevation due to the altered functional activity of the regulatory centers. At its initiation, the centers misjudge the normal temperature as being too low, thereby, constitute coordinated autonomic and behavioral steps, including wrapping up and/or blanketing, shivering, skin vasoconstriction, etc. These all elevate the core temperature until it reaches the level, in which the new higher value is appreciated by the various centers as now characteristically normal. Thereon, this newly acquired high temperature is maintained and defended against external cold or warm influences. This regulation at the higher level is usually described, using engineering terminology on thermostats, in which the set-point or set-range is shifted to a higher level (Fig. 8.14.). In reality, set-point/range should be considered as a new balance regarding the functioning of several

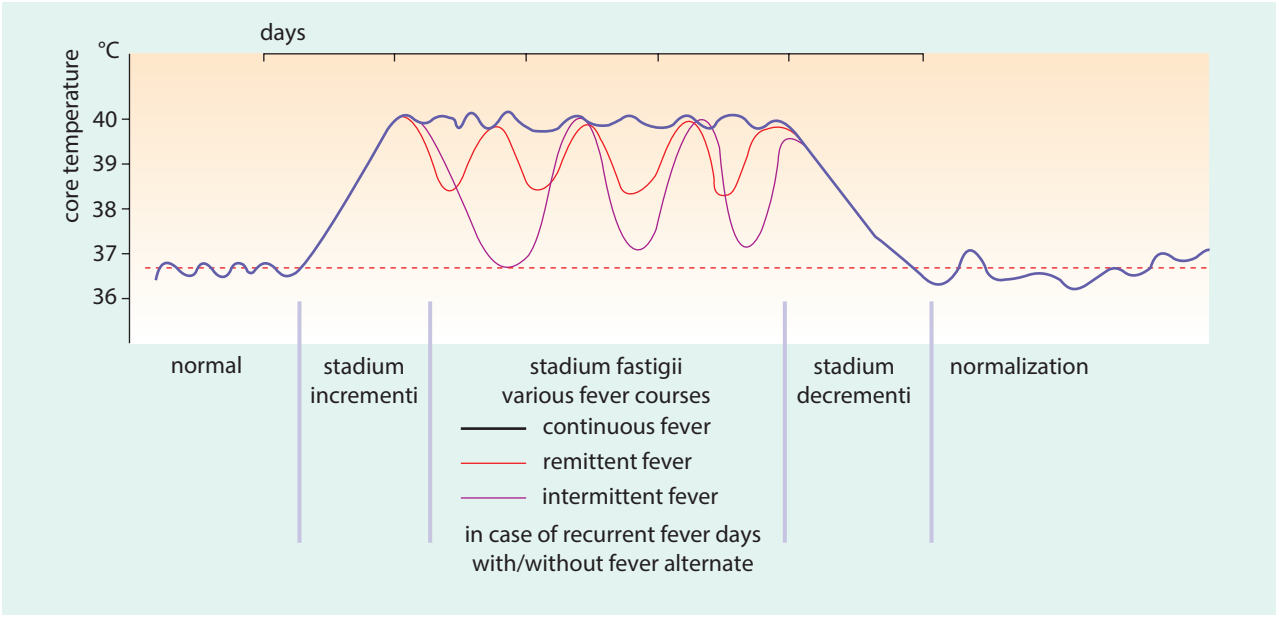

Fig. 8.20.: Fever stages and types of fever course.

regulatory circles involved in thermoregulation, or affecting it, which circles determine not so much a fixed level, but a zone of core temperature. The zone is not stabile and is dependent upon the diurnal rhythm, in which the upper end measures at or about 37.2 °C in the morning, and 37.7 °C by evening (Fig. 8.15.). Values exceeding these are abnormal and may refer to either passive hyperthermia, or active elevation in fever.

Process of fever:

A simple febrile reaction can be divided into stages (Fig. 8.20.). At its initiation *(stadium incrementi),* the body temperature rises due to the afore-mentioned coordinated effector functions, including variable symptoms, dependent upon the speed of the rise, originating from trembling up through entire body shivering, as seen in malaria. During the maintenance phase (*stadium fastigii*), heat production and heat loss are balanced at a higher level. This stage may involve wavering in temperature, and accordingly, as seen in febris continua with daily ΔTc <1 °C (e.g. typhus abdominalis); febris remittens: diurnal ΔTc ≥1 °C (e.g. acute bronchitis), febris intermittens: febrile and non-febrile or even hypothermic periods within a day (e.g. sepsis) or febris recurrens: febrile/non-febrile days alternating (e.g. malaria). The maintenance phase may last for shorter or longer periods. The course of fever in this phase likely bears relevance regarding diagnostic value but its diagnostic importance has decreased due to the inclusion of modern diagnostic methods. In the stage of defervescence *(stadium decrementi)* once again, imbalance is apparent, however, it is now in favor of heat loss, with heavy perspiration and immense sweating.

The extent of fever:

- Subfebrility (until 37.9 °C)
- Fever (until 39 °C)
- High fever (39.1-40 °C)
- Hyperpyrexia (above 40 °C)

It is an old observation in which the presence of normal cardiorespiratory system fever usually does not exceed 41 °C, which is a critical level in regards to heat stroke. This suggests that such risky situations activate extraordinary fever-blocking defense reactions, preventing any further rise in temperature.

Pathomechanism of fever (Fig. 8.21.):

A salient feature of fever is defined as a certain alteration in the central regulatory processes, which is responsible for the elevation of the body temperature (Figs. 8.13. and 8.17.), and any pyrogenic substance or effect must act by somehow altering the central regulatory processes.

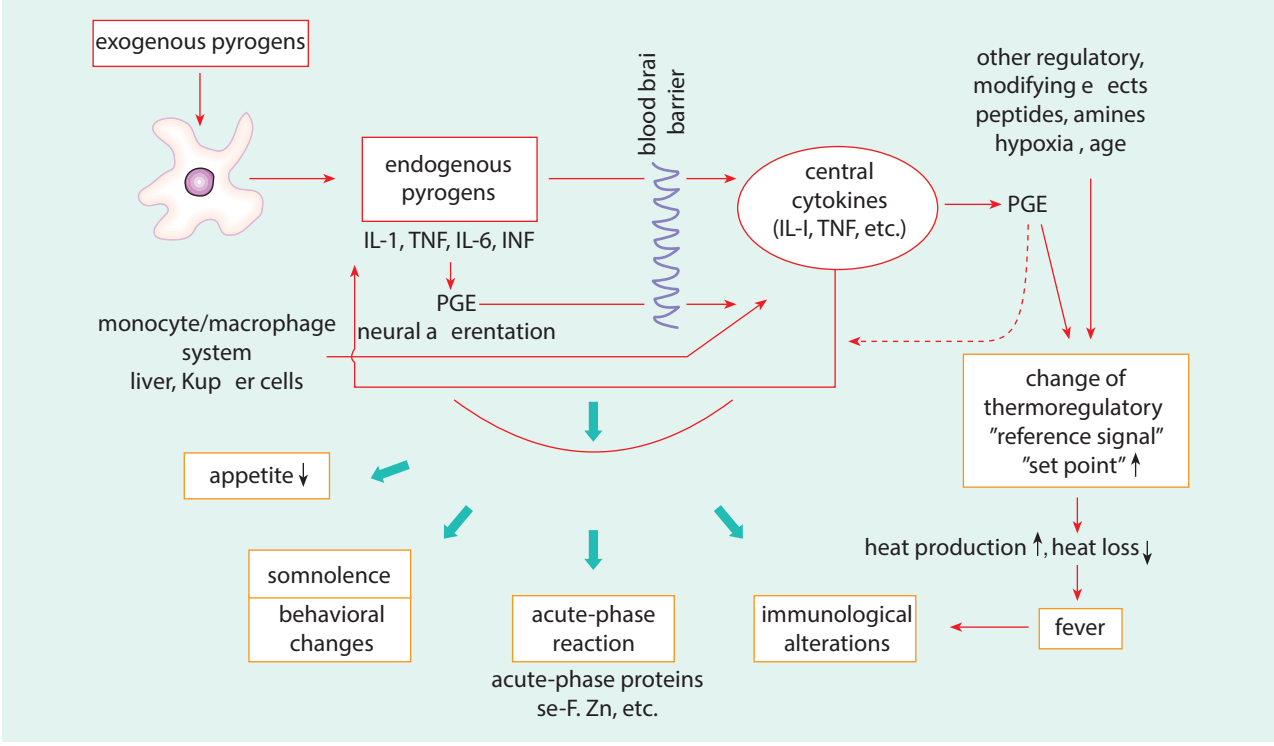

Fig. 8.21.: Pathomechanism of febrigenesis.

According to current viewpoints, a variety of exogenous pyrogens, such as bacterial endotoxins, do not act directly upon the central regulatory system. The exogenous substances are taken up by elements of the monocyte-macrophage system, which react by producing endogenous pyrogens, and these will influence the central regulation. The most important endogenous pyrogens belong to the cytokine group, such as interleukins (IL-1, IL-6, IL-8), tumor necrosis factor (TNF-α), interferons (IFN) and others, and these are produced not exclusively upon the exogenous, bacterial pyrogens, but also in the course of sterile inflammation or cell destruction. Cytokines appearing in the brain exert their action upon central thermoregulatory processes by altering the hypothalamic prostaglandin (PGE_2) content what, in turn, shifts the set-point to a higher level and leads to the elevation of core temperature. This simplified model still needs clarification, in many details, both regarding the participating substances and regarding the method of action upon regulation.

Newer data indicate that the fix macrophages of the liver (Kupffer cells) also produce cytokines and PGE, which contribute to the rapid development of the initial part of fever *1)* partially due to exciting the vagus and sending a message to the central systems while evading the blood brain barrier, *2)* partially by entering the central nervous system, since the albumin-bound PGE of the plasma may cross the blood-brain barrier.

Direct injury of the central nervous regions responsible for thermoregulation may also result in fever. This likelihood explains the occurrence of fever in some cases of stroke, of neurosurgical intervention, or the high premortal fever in some tumors including brain metastases.

Various external and internal factors may influence fever. In a cold environment, pyrogens occasionally cause hypothermia, as opposed to fever, particularly in high doses. Hypoxia also reduces the febrigenic effect of pyrogens. In neonates, as compared with bigger children, infectious fever may be absent or hypothermia develops instead of the typical fever. Similarly attenuated febrile reactions have been reported among the elderly or for those in very poor general health. Starvation may inhibit febrile reactions. These all call attention to the fact that the extent of fever and the severity of the disease are not parallel, and in diagnostics many other disorders of thermoregulation can be regarded as fever-equivalents, moreover the absence of an expected fever typically implies very serious conditions, as seen in sepsis, in which hypothermia may be more characteristic than fever.

The question of antipyresis is a source of old disputes. Since fever bears a diagnostic value, older doctors maintained that before a proper diagnosis, the antipyresis is forbidden. However, the recent diagnostic methods may allow early antipyresis. Since fever is just a sign of a potential disease and not the disease itself, by resolving the original problem, the fever will be spontaneously resolved. In some cases, a rapid antipyresis may be necessary, as seen in the cases involving the febrile convulsions of children, in other cases, only the febrile hyperalgesia and/or malaise is alleviated. In regards to this, the abnormality of the central regulation should be stopped, such as administering aspirin-like COX-antagonists which inhibit PGE-synthesis. Strictly speaking, additional forms of cooling can be applied, such as a lukewarm bath, cold-wet pack, washing the body repeatedly, etc., except in consideration of the aforementioned febrile convulsions when quick cooling is necessary.

Biological value of fever:

In the strict sense, fever is an alteration of thermoregulation (Fig. 8.16.), however, in practice, it is only a byproduct of the complex inflammatory defense process. Other central nervous system effects, including anorexia, sleepiness, tiredness, malaise, etc., comprehensively characterize the "sickness behavior". In generalized infections, this behavior is a constant attendant to fever. Primarily, the same or similar factors are responsible in the development of these changes including fever. These complex central nervous system changes are not autotelic, i.e. they are rather tools within the inflammatory defense reaction. A sick animal, for example, is not only febrile, but hides (defense), and due to anorexia does not search for food, restricts its movement, stores energy and prevents being attacked. In consideration of humans, sleepiness and anorexia decrease the metabolic demand and store energy for other purposes, therefore the febrile elevated temperature may be a useful tool in this process by other means. Nevertheless, some of these changes are just byproducts of the disease.

Those metabolic changes which accompany fever (acute phase proteins, change of plasma levels of trace-elements, etc.) improve the defense capacity of the body. A fall in se-Fe, for example, restrains the proliferation of bacteria, and this effect is particularly pronounced at high temperature. High temperature, *per se*, even passive hyperthermia, is bacteriostatic for some bacteria and, even bactericide for others (e.g. gonococcus). Still, fever-related changes of immune

functions are the most important, as seen when cytokines enhance T-lymphocyte proliferation, this effect is 5-6-fold stronger at 39 ^{0}C than at 37 ^{0}C. In fever, both the cellular and the humoral immunity are enhanced. Fever mediators in addition to the elevated temperature together can better serve the body's defense mechanism.

However, there may be unfavorable consequences, too, in fever. Consequently, if and when these aspects dominate, antipyresis is objectively indispensable, even considering the possible side-effects of the antipyretic treatment.

1. Although rarely, the febrile temperature may be critically high (hyperpyrexia) reaching the level of heat stroke.
2. A much lower fever may evoke severe febrile convulsions, and depending on the genetic basis, in children between ages of 6 months to 6 years. Immediate entire body cooling is necessary. The convulsions may be followed by potential damage of the central nervous system, and epileptic fits may follow.
3. A metabolic disturbance of the brain is suggested by the febrile delirium and hallucinations, which are more frequent in children, yet eventually, may be observed among adults.
4. In heart failure patients, and among the elderly, the febrile increase of cardiac output may be difficult and fever may evoke cardiac decompensation. Another circulatory problem is the tendency for syncope (at any age), what is appreciated as a disorder in the regulation of circulation.
5. In fever, the ventilation as well as the effort of respiration is increased. If the respiratory functions are already damaged, the probability of developing a respiratory failure is high.
6. Metabolic changes: A combination of anorexia and high metabolic rate implies a form of severe malnutrition, with all of its consequences, particularly in prolonged febrile states. The metabolic balance of diabetic patients soon worsens, due to the appearance of insulin antagonist hormonal substances and cytokines, while in other cases the fasting condition leads to hypoglycemia.
7. The possibility has arisen according to which, during early pregnancy the high body temperature is teratogenic, therefore not only fever, but any heat load (e.g. sauna), should be avoided.
8. Strikingly, when the body temperature is too high, it inhibits the immune functions.

8.5.4. ANAPYREXIA

Anapyrexia is a regulatory abnormality, which is the opposite of fever (Fig. 8.16.). The main disorder of the central regulation is a shift in the "set-point" to a lower level within a short period of time. The patient senses a normal temperature as being relatively too hot, and the consequent vasodilation and sweating, along with the suppression of the metabolic rate to the possible minimum, all these serve to evoke a transient and moderate fall in body temperature. This is observed e.g. in women during menopausal hot flushes. Another idea is that the set range becomes narrower, consequently, a hot flush can develop far easier and it is followed by cold defensive steps.

In slowly developing regulatory disorders, the spectacular rise in heat loss may be absent, therefore only the reduced metabolism leads to the suppression of body temperature. This is characteristic in fasting, as seen in cases of hypometabolism or hypothyroidism. In this case, the body temperature is defended at a lower level, and upon cooling, the metabolic rate increases in order to maintain the standard lower body temperature.

On the basis of a central regulatory disorder, the permanently lower regulated body temperature has also been formerly described. Such may be the symptomless cooling, of which, is slowly developing, yet lasting hypothermia. The circadian temperature changes are maintained at a subnormal level. In such chronic hypothermia delusions, hallucinations and confusion are strikingly characteristic regarding the patient's behavior, not the hypothermia itself.

8.6. GERONTOLOGICAL ASPECTS OF ENERGY BALANCE

Essentially, two general changes of energy balance can be observed with increasing age. In middle-aged individuals, the energy balance is positive, in which the energy content and body weight correspondingly increase (the obesity of aging). After the age of 65-70 years, the body mass decreases, as seen in aging anorexia. Both aspects can be demonstrated among other mammals, and suggests that this is a regulated phenomenon. Change(s) in the regulation by the central nervous system are due to shifts in the balance among anabolic and catabolic mechanisms, in which the anabolic over-

weight of the middle-aged population is converted to a catabolic state in old age. This may explain the changes in caloric intake, in which the food intake exceeding the energy need (and tendency for obesity) in the earlier phase is later changed and anorexia develops. Throughout the process a standard feature of gradual but increasing change in body composition prevails, one in which the muscle mass begins decreasing, as seen in middle-aged individuals, however, later, the loss of muscle and other proteins speeds up (sarcopenia). Similarly, as seen in starvation, sarcopenia is a factor which limits human lifespan and makes the quality of life much worse. The relative or absolute mass of fat simultaneously increases, yet with increasing age, a part of the growing percentage of lipids is located not in the fat tissue, rather in other tissues and leads to lipotoxicity (ch. 9.2.2.4.2.; Fig. A14.3.).

Among the elderly, the body composition is shifted towards the metabolically less active tissues. This, and the accompanied diminished in levels of physical activity, may partially explain the falling BMR and smaller capacity to increase the metabolic rate. The decline of the metabolic rate is not parallel with the changes of food intake, and at later ages, the decrease of food intake is more pronounced, resembling more like a lasting partial starvation, and thus, explains the weight loss and particularly rapid loss of muscle (sarcopenia). If the metabolic rate must increase for any reason, such as seen in infections and/or surgery, the situation corresponds to accelerated starvation. The fat amount located outside the fat tissue is gradually increasing.

The parameters of thermoregulation also change with age. Among the aged, the capacity of heat production declines as well as the capacity of heat loss. This may be aggravated by a disorder of the thermal sensation. The defense against cold and heat is equally deficient, therefore both hypothermia and hyperthermia may develop far more easily. Young adult rats in a cold (ca. 0 ^{0}C) environment were able to maintain the normal body temperature for hours, while the body temperature of older specimens in the same environment decreased by several ^{0}C, yet, among the older specimens the defense against heat was also insufficient.

Symptomless cooling is typical: A senior whose diminished mobility does not really notice the cold environment, does not experience a metabolic response, therefore the body temperature gradually decreases and manifest hypothermia develops – eventually, this may be interrupted by massive shivering, what is not enough to regain the normal body temperature. In other cases, even this aspect is clearly missing, and as a result, only the hypothermia-induced confusion is obvious. The effector system of thermoregulation is complex. In addition to the metabolic rate, the circulation and salt- and water-balance is also involved, however, among seniors, all these characteristics prove defective (vasomotor changes and sweating are limited), therefore, severe thermoregulatory catastrophe situations (hypothermia and/or heat stroke) develop far more easily. Diseases in which fever is typical may often be different among seniors, they may appear without a trace of fever, or appear with uncertain thermal changes, yet eventually, hypothermia accompanies the disease. Environmental thermal changes may evoke pathological consequences even if the body temperature is maintained, as in the case of heat syncope, heat-induced decompensation of the heart and severe salt- and water-abnormalities. Interestingly, the (side)effects from prescription medication also undergo changes in temperature, as seen in the case in which antihypertensive drugs act less strongly in cold and have a more pronounced effect in a hot environment. While seniors often avoid colder environments, in the summer heat it is common to see seniors in public who are considerably overdressed. It should be promoted to seniors to avoid the hottest periods of the day and to remind them to always have a sufficient amount of drinkable water. However, in addition to water consumption, salt intake is also important, as during perspiration and sweating salt is also lost, and without the appropriate level of salt, hypotonicity, nausea, and inevitably, hypodipsia develops. The hyponatremia (ch. 6.1.4.1.) leads to a poor quality of life, one which may easily become a life-threatening situation.

Further readings:

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