

## HOMEOSTASIS AND HETEROSTATIS

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Claude Bernard [1] was the first to point out clearly that the internal medium of living organisms is not merely a vehicle for carrying nourishment to cells but that "it is the fixity of the 'milieu interieur' which is the condition of free and independent life" (vol. 1, p. 404). W. B. Cannon [2] suggested the designation "homeostasis" for "the coordinated physiological processes which maintain most of the steady states in the organism" (p. 91).

When faced with stressful situations that require systemic adaptation, the organism can respond through three essentially distinct mechanisms: (1) nervous-by conscious planning of defense, innate or conditioned reflexes and autonomic "emergency reactions" (partly mediated through neurohormones); (2) immunologic and phagocytic antibody formation, activation of the reticuloendothelial system; hormonal-through the syntoxic hormones which permit, tolerance of the pathogen without attacking it (e.g., glucocorticoids preventing inflammation, without destroying its cause) or catatoxic substances that eliminate the aggressor (e.g., certain steroids and drugs which accelerate the biodegradation of toxicants without inducing tissue resistance to them) [3].

In recent years, the discovery of the important role played by hepatic microsomal enzyme induction in defense against certain toxicants led to the development of a new field of pharmacology designated "xenobiochemistry" and defined as the "biochemistry of foreign organic compounds" [4, p. v]. This science is concerned with the fate of "xenobiotics" (from the Greek "xenos" and "bios" for "stranger to life"), that is, compounds which are foreign to the metabolic network of the organism [5].

At first, the term xenobiochemistry appeared to be a particularly suitable label for the new approach, because both the toxicants and the inducers of their biodegradation were foreign to the body. (Most of the initial work was performed with barbiturates, polycyclic hydrocarbons, insecticides, etc.) Indeed, Brodie and his co-workers [6], who probably did more for the development of this field than any other group of investigators, came to the conclusion that presumably the defensive enzyme systems "are not essential to the normal economy of the body, but operate primarily against the toxic influences of foreign compounds that gain access to the body from the alimentary tract" (p. 604).

The large number of investigators and the fast-growing literature dealing with problems in this field have recently prompted the founding of a special journal under the name *Xenobiotics*. Yet, nowadays, hardly anyone doubts that, neither the substrates nor the inducers of such defensive enzymes need be foreign to the body's economy [7]. Of course, in the case of poisons completely foreign to the organism, any amount in the body is excessive and hence "foreign" only if their concentration greatly exceeds physiological level. Thus, various hormones and hormone derivatives can protect against both exogenous and endogenous damage inducing enzymes capable of accelerating their biodegradation, or syntoxically by increasing tissue resistance to them

[3]. Among the most important natural compounds amenable to catatoxic or syntoxic defense are: steroid hormones, bile acids, bile pigments, fat-soluble vitamins, inflammatory mediators (histamine, serotonin, prostaglandins), and so forth, all of which are either made within the body or absorbed from the diet as essential physiologic ingredients of living matter.

The salient feature of these adaptive mechanisms is therefore not that they attack only substances foreign to the body but that they establish a new equilibrium between the body and an unusually high level of the potential pathogen, either by destroying the excess (catatoxic action) or by making tissues tolerant to it (syntoxic action).

When such an abnormal equilibrium must be established to protect against potential pathogens, I propose to speak of heterostasis (heteros = other; stasis = fixity) as the establishment of a new steady state by exogenous (pharmacologic) stimulation of adaptive mechanisms through the development and maintenance of dormant defensive tissue reactions. In a sense this would be the counterpart of homeostasis (homoios =like) which has been defined as the maintenance of a normal steady state by means of endogenous (physiologic) responses. In heterostasis, as in homeostasis, the fixity of the "milieu interieur" is not absolute. Both Bernard [1] and Cannon [2] have clearly realized that in order to maintain a state of relative stability the body cannot remain completely inert but must answer each stimulus with an appropriate counter stimulus to maintain equilibrium. However, in homeostasis, this equilibrium is maintained with small fluctuations near the physiologic level, whereas in heterostasis unusual defense reactions are mobilized to permit resistance to unusual aggression. Furthermore, in general, homeostasis, unlike heterostasis, depends upon rapidly developing and vanishing readjustments, although-as in all biologic classifications-tranitional types are common.

Of course, both homeostatic and heterostatic reactions, though usually of defensive value may be worthless or even harmful under certain circumstances. This can be illustrated by the following examples: (1) In predisposed individuals, excessive neuroendocrine "emergency reactions" may precipitate a cardiovascular accident. (2) Antibody formation can result in anaphylaxis or allergy; indeed, even phagocytosis can offer a suitable milieu to certain organisms and protect them against blood-borne antimicrobials (e.g., in a tubercle). (3) Defensive syntoxic hormones can interfere with the encapsulation and destruction of microorganism by suppressing useful inflammatory or immunologic reactions. Similarly, by accelerating the biotransformation of relatively innocuous compounds, catatoxic steroids, can enhance the production of highly pathogenic metabolites.

The most salient difference between homeostasis and heterostasis is that the former maintains the normal steady state by physiologic reactions, whereas the latter "resets the thermostat" to maintain a higher state of defense by artificial exogenous intervention. Heterostasis can be accomplished by exogenous administration of natural (e.g., hormones) or artificial (e.g., barbiturates) substance inducing responses of this kind. Furthermore, the heterostatic reactions may be syntoxic (e.g., corticoids, anti-inflammatory drug permitting coexistence with potential pathogens by evoking

responses which make our tissues indifferent to certain potentially pathogenic stimuli. Thus, they suppress excessive inflammatory reactions which represent the very essence of some diseases. However, they may also be catatoxic (e.g., some anabolic hormones, barbiturates, insecticides) if they enhance drug-metabolizing enzyme activity and thereby accelerate the biodegradation of potential pathogens. The most potent catatoxic substance known to date is pregnenolone-16 $\alpha$ -carbon e (PCN); this is a close relative of the naturally occurring pregnenolone and yet an artificial compound in that it is produced synthetically by the introduction of, a carbonitrile group into its natural congener.

Thus, the concept of heterostasis includes both syntoxic and catatoxic reactions induced by natural or artificial exogenous compounds. On the other hand, it excludes all therapeutic measures directly (or "passively") not by stimulating the body's own adaptive capacities. For example, (1) Antidotes, which act directly upon potential pathogens (e.g., buffers that neutralize acids, chemicals which inactivate poisons by directly combining with them, antimicrobial agents). (2) All forms of substitution therapy (e.g., vitamin C for scurvy, corticoids for Addison's disease, transplanted or artificial kidneys for renal failure) which merely represent chemical or mechanical prostheses. (3) The ablation of diseased tissues (infected parts, tumors). (4) Passive "shielding" (e.g., by lead screens against X rays, receptor blockade against drugs, competition for a substrate).

Thus, the types of adaptation, which depend upon active participation of the body, are: homeostatic-(a) syntoxic, (b) catatoxic; heterostatic-(a) syntoxic, (b) catatoxic.

This list comprises all active defense reactions irrespective of their nervous, immunologic, phagocytic, or hormonal mediation., It can be incorporated into a general classification of adaptive mechanisms, whether the "milieu interieur" participates actively or passively, as summarized in figure 1.

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