REGULATION

It would be a waste of effort to look in physiology textbooks for a continuous chapter on the regulation of all physiological functions. This does not of course mean that it is a chapter of little importance. On the contrary. It pervades the whole field and actually the whole of Medicine as one of the crucial subjects. In a short survey like this, the general principles of physiological regulations may only be outlined.

They have much in common with regulations in technical fields. They are based on ***negative feedback***: a change at the output of a regulated quantity will affect its input in reverse sense. The result is that a fluctuation detected as excess is suppressed and, on the contrary, a deficit is supplemented. Thus, regulations are a controlled reaction to loading and maintain the state of equilibrium.

Physiological regulations occur at all levels and have a manifold image. They control circulatory functions, the digestive tract, maintenance of constant body temperature, etc. They are ***systemic regulations***. In the first place they are effected by the vegetative (autonomic) nervous system. They ensure adequate adaptation of a whole complex of actions to the most diverse types of load as well as to external conditions. The increased demands of functions during load are taken into account by the ***adrenergic, sympathetic activation system. The cholinergic, parasympathetic system*** has an inverse, dampening function, i.e., calming down and a return to the original equilibrium. The result is that the organism does not waste its energy. In summary, we can say that these regulations are a reflex response to the information from the periphery, which comes from innumerable receptors, sensors. The well-known baroreflex may be given as an illustrative example.

A similar systemic regulation as the nervous one is represented by the humoral system. In the course of evolution it has developed on three levels: as autocrine, paracrine, and endocrine (formerly called hormonal). Instead of electric signals – action potentials – information is transferred materially, by humoral signal molecules. A relatively uncomplicated example of such regulation is the regulation of the level of glucose in the blood, glycaemia. It is understandable that such regulations are by several orders slower than nervous regulations. However, both control systems co-operate in harmony, complement and adjust each other in order to maintain the equilibrium of internal environment, homoeostasis.

The two above-mentioned systems are well known and studied in detail. The contemporary science has been turning its attention to more subtle control mechanisms, ones that occur on lower levels, tissular, cellular, and even subcellular. They are outspokenly ***local regulations*****.** They are of physical or chemical nature and are to a considerable extent autonomic, independent of both nervous and humoral regulation. An evidence for this autonomy is that they are demonstrable also on isolated (i.e. denervated) preparations of tissues and in artificial solution. Thus, generally they may be called ***autoregulations*****.** That known longest of them is myogenic autoregulation (Bayliss effect): increased pressure in the vessel automatically increases the tension of its wall and the flow of blood is locally adjusted. Another, functionally remarkably significant autoregulation, is vasoconstriction in the area of non-ventilated pulmonary alveoli. Also ranking in this category are two mechanisms of correction of cardiac contractility. Heterometric autoregulation (Starling's law, Starling's mechanism) consists in variable insertion of myofilaments; homoeometric autoregulation (Bowditch phenomenon) is the result of a complicated but flexible handling of cellular substructures with the activator of contraction, cytoplasmic calcium ("calcium handling").

Autoregulations on the molecular level include the recently discovered control of sensitivity of some membrane receptors. In the excess of the ligand, the receptor is immersed by endocytosis into the cell and, when in deficit, it returns by exocytosis to the surface; or, as the case may be, the deficit of the ligand triggers the synthesis of the receptor *de novo* and in this way the number of receptors per unit of membrane surface is increased. These mechanisms are designated as "up- and down-regulations". Also well-known have been regulations on the level of mitochondria, endoplasmic reticulum, and even on the level of genes ("enhancers" and "silencers").

I tis obvious that physiological regulations, both systemic and autoregulations, have with all their multiformity a common goal or sense: to comply with the organism's demands during load and, at the same time, to maintain the balance of the internal environment, with a maximum of economy. This is not a complex of coincidences, but rather the result of evolutionary improvement from unicellular forms of life up to man.

AUTOREGULATION OF CARDIAC CONTRACTILITY

When the volume of the heart chamber gets increased by higher filling, the contraction of the wall would, for purely physical reasons (Laplace's law), have to be weaker. But, on the contrary, the contraction will become stronger. This happens thanks to ***heterometric autoregulation*****,** long known as ***Starling's mechanism***.

The first interpretation of the mechanism of heterometric autoregulation was based on the evidenced enlargement of the active zone of overlapping of actin and myosin filaments when stretching the heart's sarcomeres. In the human myocardium, the maximum contraction force is reached at an initial sarcomere length of 2.2 micrometres. It is a length that is only rarely exceeded in the human heart under physiological situation. If the initial length of the sarcomere is higher, there occurs a smaller overlap of the thin and thick myofilaments and the contraction is weaker.

However, later it was shown that the variable sensitivity of troponin C to calcium is also applied here. With a shorter initial length of the sarcomere the force of contraction is reduced, also because the sensitivity of troponin C to calcium is reduced.

And, most recently, yet another possible mechanism was shown: by protracting the sarcomere the fibrils of titin are stretched and, due to this change, the actin and myosin fibres get closer to one another. This points to the fact that an apparently definitive interpretation of a phenomenon only becomes one out of many in the course of time.

At first it was thought that heterometric autoregulation is a compensatory mechanism in the dilatation of a failing heart. However, it is only its help in need and ranks among several other mechanisms by which the organism, in case of insufficient pumping of blood by the heart, tries to equalise the declining perfusion of peripheral tissues.

Primarily, heterometric autoregulation serves for immediate equilibrating of the natural deflections in the filling of the left and right ventricle. It has been calculated that without this mechanism the permanent difference in the filling of the right and left ventricle by 1 % (caused by the differing venous return due to physiological "short circuit" via aa. bronchiales and vv. cordis minimae) would lead to a complete breakdown of circulation within one minute. Heterometric autoregulation of the contraction force plays an important role also in the equalisation of the consequences of different venous return to the left and right ventricle due to changes in breathing (a slightly raised venous return and, consequently, filling of the ventricles at inhalation; the reverse at exhalation). Starling's mechanism is naturally

also applied in the increased filling of ventricles at body load in harmony with the positively inotropic effect of the sympathetic system and in changes of body position. On summing up the physiological importance of heterometric autoregulation, we obtain the following survey:

1) Maintenance of cardiac output equilibrium in greater and lesser circulations;
2) Equilibration of contraction of individual regions of the cardiac wall;
3) Equilibration of the force of successive muscular fibres;
4) Equilibration of contraction of the consecutively connected sarcomeres;
5) Compensation for the unfavourable effect of Laplace's law;
6) Control of cardiac output in venous return alterations (breathing, changes of body position, Valsalva manoeuvre, Müller manoeuvre, and the like).

The other regulatory mechanism, formerly known under the descriptive eponym ***Bowditch staircase phenomenon***, now preferentially as ***homoeometric autoregulation***, is associated with heart rate (therefore it is also called ***heart rate effect*** or ***heart rate phenomenon***). An increase in the heart rate during load (whether physical or emotional) means shortening of the filling time and thus a decrease in the end-diastolic volume of the ventricles. If nothing happened with the duration and force of contraction, circulation would stop completely at a heart rate of about 100 per minute. The mechanism of this necessary compensation for the chronotropic effect of the sympathetic system is very complicated. It is connected with the complicated co-ordination of the electric signal (action potential), the cellular balance of calcium controlled by it, and moreover the sensitivity of troponin C to calcium. Thus, this autoregulation serves to maintain the contraction force even with the increasing heart rate, where the above-mentioned mechanism would bring about a weakening of the contraction.

When heart rate is increased, an increase in the contraction force takes place thanks to homoeometric autoregulation. One interpretation of this phenomenon is the inability of Na^+/K^+-ATPase to retain the sodium gradient at higher heart rates. In such a situation, for example during stimulation by the sympathetic system, the L-subtype of the calcium channel exhibits increased activity. The Na^+/Ca^{++} exchanger (three sodium ions enter the cell down the gradient and one calcium ion leaves the cell) tries to draw the excess of calcium from the cell. Upon increasing heart rate the diastole is shortened and Na^+/K^+-ATPase does no longer manage to remove the sodium which enters the cardiomyocyte via the Na^+/Ca^{++} exchanger. The gradient for sodium is reduced and calcium at increased concentration remains in the cardiomyocyte. The result is a positively inotropic effect.

The same process may also be regarded in the way that, thanks to the considerable shortening of the diastole, the Na^{+}/Ca^{++} exchanger does not have enough time to eliminate calcium from the cardiomyocyte, which leads to a positively inotropic effect (the ratio between intracellular and extracellular calcium increases).

Thus, both autoregulations of the force of heart contraction have one common denominator - **calcium**.

Recently, increased attention has been given in cardiology to the area of heart rate problems from the most varied points of view. A revival of the view of physiological autoregulations is also to be expected.