FEEDBACK CONTROLS IN PHYSIOLOGY AND MEDICINE

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FEEDBACK CONTROLS IN PHYSIOLOGY AND MEDICINE

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FEEDBACK CONTROLS IN PHYSIOLOGY AND MEDICINE

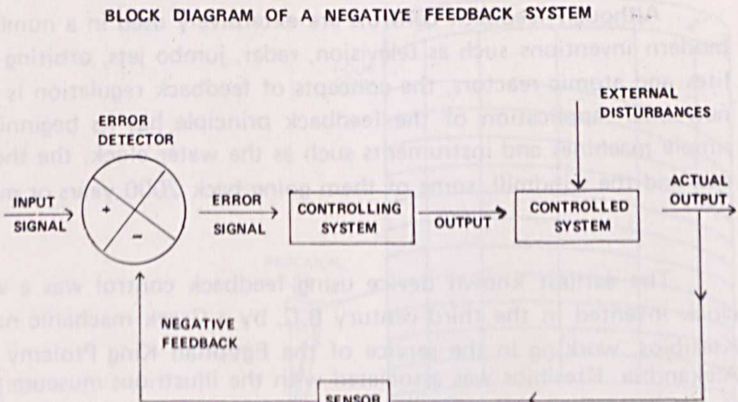
The cells, tissues and organs of living organisms are not random collections of physical and chemical elements, but intricately organised arrangements of systems of interacting parts and processes. The performance of a living organism is not that of its elements, but that of its systems such as the nervous, cardiovascular, respiratory, endocrine and so on. The study of living organisms begins with an analysis, in isolation, of the component parts that make up the systems, but it must proceed to synthesis in which the emergent behaviour of the whole animal is examined. Since living things are mostly self-regulating and self-maintaining, it is obvious that there must be controls of the various systems to regulate and counteract any changes that may occur within the animal. The study of physiology is therefore nothing more than a study of the various systems in the body and the feedback controls that are involved in the regulation of these systems.

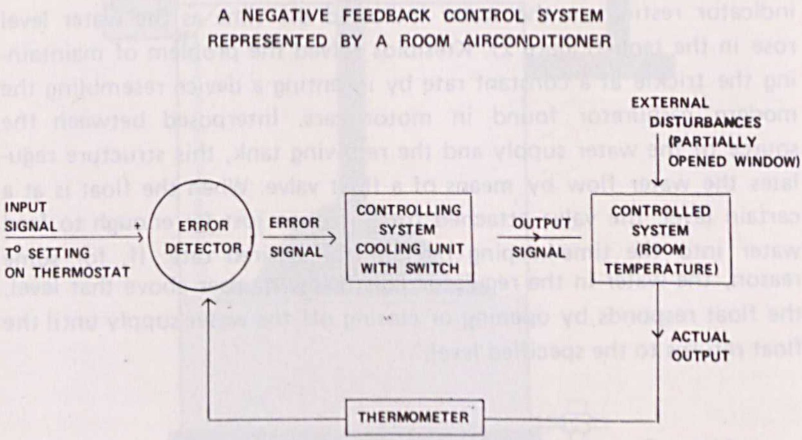
What is a feedback control system? Weiner (1948) defines it as 'a method of controlling a system by reinserting into it the results of its past performance'. The purpose of such a system is to carry out a command automatically and it functions by maintaining the controlled variable (output signal) at the same level as the command variable (input signal) despite external disturbances. Since control systems in animals are exceedingly complex and interrelated, the approach used by engineers has been introduced to study these biological phenomena. This is called control theory or systems analysis and it uses mathematical equations and models to illustrate the different concepts involved. This recent development is very useful because it opens up new fields of physiological experimentation and new possibilities of analysing physiological control mechanisms. Further, the use of mathematical equations enables one to check for internal consistency and for agreement with available experimental data. Since systematic operation is so inherent to biologic functions, it would be useful to point out some important features of feedback control systems by using a familar analogy, an air-conditioner in a room.

As can be seen from Figure 1, the main characteristic feature of a feedback control system is its closed-loop structure. The temperature of the room is the controlled variable (output signal) and the temperature setting on the thermostate is the input signal. The temperature of the room is sensed by the thermometer and this temperature is compared with the desired temperature at the error detector (in the thermostat). If there is a difference between the room temperature and the desired temperature, the error detector detects this and actuates the controlling system (cooling unit). For example, if the room temperature is increased because of a partially opened window (a disturbance), there will be an error between the desired and actual temperature. This is detected by the error detector and results in activation of the controlling system. More cool air is then pumped into the room and the room temperature falls. When it has reached the desired temperature, there will be no more error and the cooling unit is automatically cut off

Feedback systems may be negative or positive. The above example is a system employing negative feedback control. In these systems, any disturbance is counteracted and the original state is restored. Thus negative feedback systems oppose change and maintain stability. Positive feedback systems, on the other hand, amplify the effects of a dusturbance and this results in instability. Although both

Figure 1   Components of a negative feedback control system





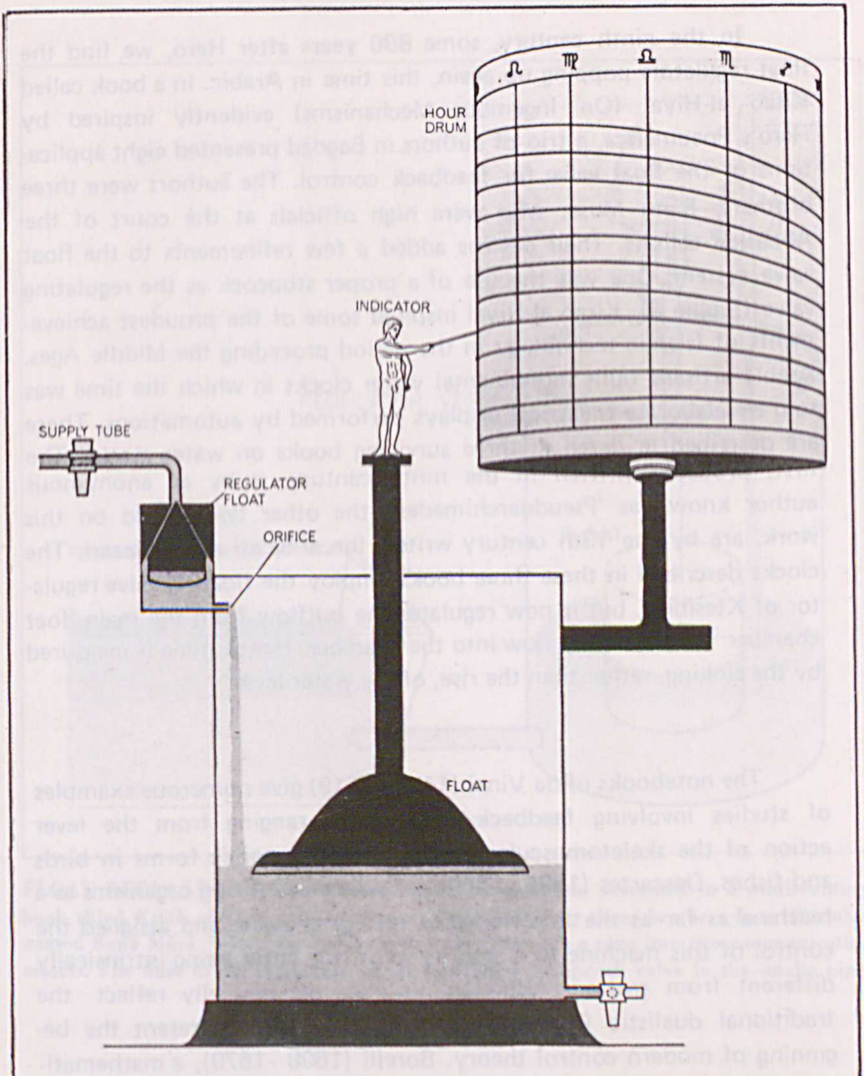
types of feedback controls are found in the human body, the negative feedback controls are more common and play an important part in many of our everyday physiological functions.

Although feedback controls are extensively used in a number of modern inventions such as television, radar, jumbo jets, orbiting satellites and atomic reactors, the concepts of feedback regulation is not a new one. Application of the feedback principle has its beginning in simple machines and instruments such as the water clock, the thermostat and the windmill, some of them going back 2000 years or more.

The earliest known device using feedback control was a water clock invented in the third century B.C. by a Greek machanic named Ktesibios, working in the service of the Egyptian King Ptolemy II in Alexandria. Ktesibios was associated with the illustrious museum there that was then the principal cultural centre of the Mediterranean world and attracted many of Greece's foremost scholars. The water clock invented by Ktesibios measures the passage of time by means of a slow trickle of water, flowing at a constant rate into a tank. An indicator resting on the water indicated the time as the water level rose in the tank (Figure 2). Ktesibios solved the problem of maintaining the trickle at a constant rate by inventing a device resembling the modern carburetor found in motor cars. Interposed between the source of the water supply and the receiving tank, this structure regulates the water flow by means of a float valve. When the float is at a certain level, the valve attached to it is open just far enough to feed water into the time-keeping tank at the desired rate. If, for some reason, the water in the regulator falls below or rises above that level, the float responds by opening or closing off the water supply until the float returns to the specified level.

About 3 centuries after Ktesibios, we again encounter automatic regulators of the float type in a book called Pneumatica by Hero of Alexandria. Hero was a prolific author and inventor and his book contains a number of amazing anticipations of modern inventions. Among

Figure 2   Water clock of Ktesibios (for details see main text)

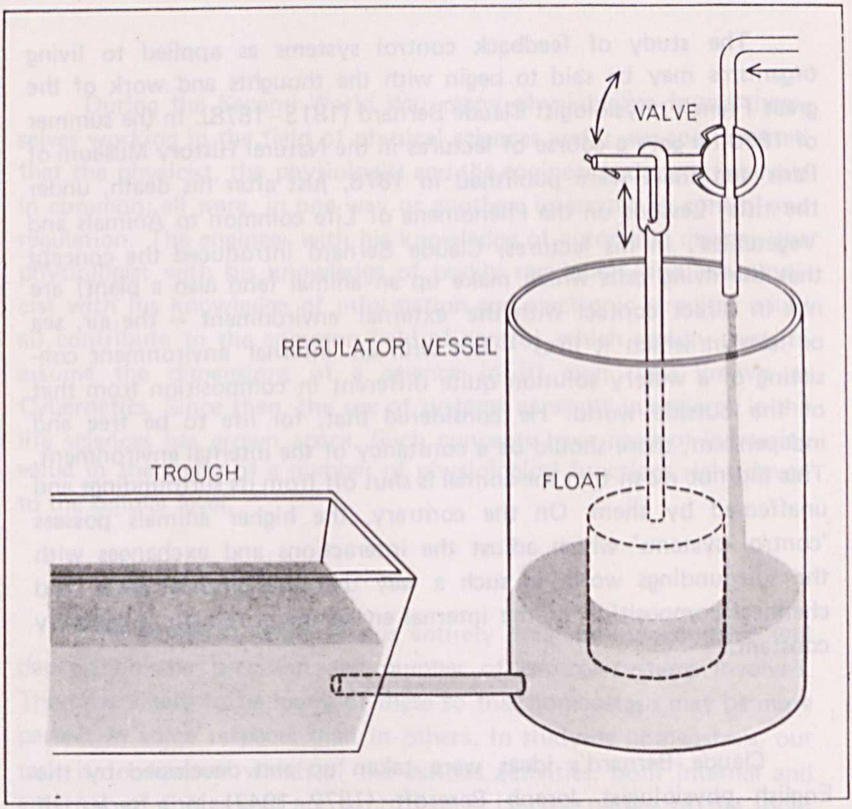


other things, it describes several float regulators considerably more refined than that of Ktesibios.

In the ninth century, some 800 years after Hero, we find the float regulators popping up again, this time in Arabic. In a book called Kitab al-Hiyal (On Ingenious Mechanisms) evidently inspired by Hero's Pneumatica, a trio of authors in Bagdad presented eight applications of the float valve for feedback control. The authors were three brothers, Banu Musa, who were high officials at the court of the Abbaside caliphs. Their devices added a few refinements to the float valve system. One was the use of a proper stopcock as the regulating valve (Figure 3). Kitab al-Hiyal inspired some of the proudest achievements of Islamic technology in the period proceding the Middle Ages. Arabic artisans built monumental water clocks in which the time was told by elaborate theatrical displays performed by automations. These are described in detail in three surviving books on water clocks. The first, probably written in the ninth century, is by an anonymous author known as 'Pseudoarchimedes'; the other two, based on this work, are by the 13th century writers Ibn al-Sa'ati and al-Jazari. The clocks described in these three books employ the floating valve regulator of Ktesibios, but it now regulates the outflow from the main float chamber instead of the flow into the chamber. Hence, time is measured by the sinking, rather than the rise, of the water level.

The notebooks of da Vinci (1452–1519) give numerous examples of studies involving feedback mechanisms ranging from the lever action of the skeletomuscular system to aerodynamic forms in birds and fishes. Descartes (1596–1650) considered the living organisms as a machine as far as the knowledge of his age allowed, and assigned the control of this machine to a soul or spirit, the latter being intrinsically different from matter. Although his concepts basically reflect the traditional dualistic Christian doctrine, they also represent the beginning of modern control theory. Borelli (1608–1679), a mathematician who acquired a solid knowledge of anatomy from Malpighi in Pisa, studied locomotion in man and animals as well as the pressures in

Figure 3   Float regulator incorporating a stopcock valve



FLOAT REGULATOR for an animal drinking trough was described in a ninth-century book titled *Kitāb al-Ḥiyal* (*On Ingenious Mechanisms*) by three brothers from Baghdad named Banū Mūsā. Water was drawn from a river through a pipe into two communicating vessels. The float in the regulating vessel controlled a stopcock valve in the intake pipe.

the cardiovascular and respiratory systems. Through his extraordinarily fertile imagination, he anticipated a large number of inventions using the concept of feedback including self-contained underwater breathing apparatus, submarines and diving bells.

The study of feedback control systems as applied to living organisms may be said to begin with the thoughts and work of the great French physiologist Claude Bernard (1813–1878). In the summer of 1870 he gave a course of lectures in the Natural History Museum of Paris and these were published in 1878, just after his death, under the title *'Lessons on the Phenomena of Life common to Animals and Vegetables'*. In his lectures, Claude Bernard *introduced the concept* that the living cells which make up an animal (and also a plant) are not in direct contact with the 'external' environment – the air, sea or *lake in which it lives* – but with an 'internal' environment consisting of a watery solution quite different in composition from that of the outside world. He considered that, for life to be free and independent, there should be a constancy of the internal environment. This did not mean that the animal is shut off from its surroundings and unaffected by them. On the contrary, the higher animals possess 'control systems' which adjust the interactions and exchanges with the surroundings world in such a way that the physical state and chemical composition of the internal environment remain remarkably constant.

Claude Bernard's ideas were taken up and developed by the English physiologist Joseph Barcroft (1872–1947) in a series of lectures delivered at Harvard University in 1929 and published in 1934 under the title 'Features in the Architecture of Physiological Function'. Also, in 1929, the great American physiologist Walter Cannon (1871–1945) introduced the term 'homeostasis' (from Greek, meaning literally 'similar standing') to describe all the processes concerned in controlling the physical and chemical properties of the internal environment of an animal. He developed an extended his ideas in a book 'The Wisdom of the Body' published in 1932. The titles of the above two books emphasise the fact that control of the internal environment is essential to the whole design and organisation of an animal so as to enable its component parts to work in cooperation with one another.

During the Second World War many physiologists found themselves working in the field of physical sciences and it was soon realised that the physicist, the physiologist and the engineer had many interests in common; all were, in one way or another, interested in control and regulation. The engineer with his knowledge of automatic devices, the physiologist with his knowledge of bodily regulation, and the physicist with his knowledge of information and electronic circuitry could all contribute to the common field of control, which rapidly came to assume the dimensions of a science in its own right known as Cybernetics. Since then, the use of systems concepts in research in the life sciences has grown apace. Such concepts have been of increasing value in the study of a number of physiological functions right down to the cellular level.

The extent to which life is entirely 'free and independent' will depend on the precision and number of control systems involved. There are likely to be many of these so that homeostasis may be more perfect in some respects than in others. In studying homeostasis, our task is to discover which of the various activities, both internal and external, of the animal are controlled – i.e. the nature of the input and output of each of the controlling systems concerned, how the misalignment between them is detected and corrected, and how accurately the system works. This is done chiefly by applying the method of experimental physiology together with some aspects of biochemistry and biophysics. But a proper interpretation of the results require, also, a sound knowledge of the fundamental theory of control systems.

Feedback Mechanisms In Biological Systems

Control systems, man made and biological, attempt to maintain the value of some output as close to the desired value as possible. Most of the regulations in the human body involve negative feedback controls and these enable a number of physiological variables to be maintained fairly constant. Some of these are:

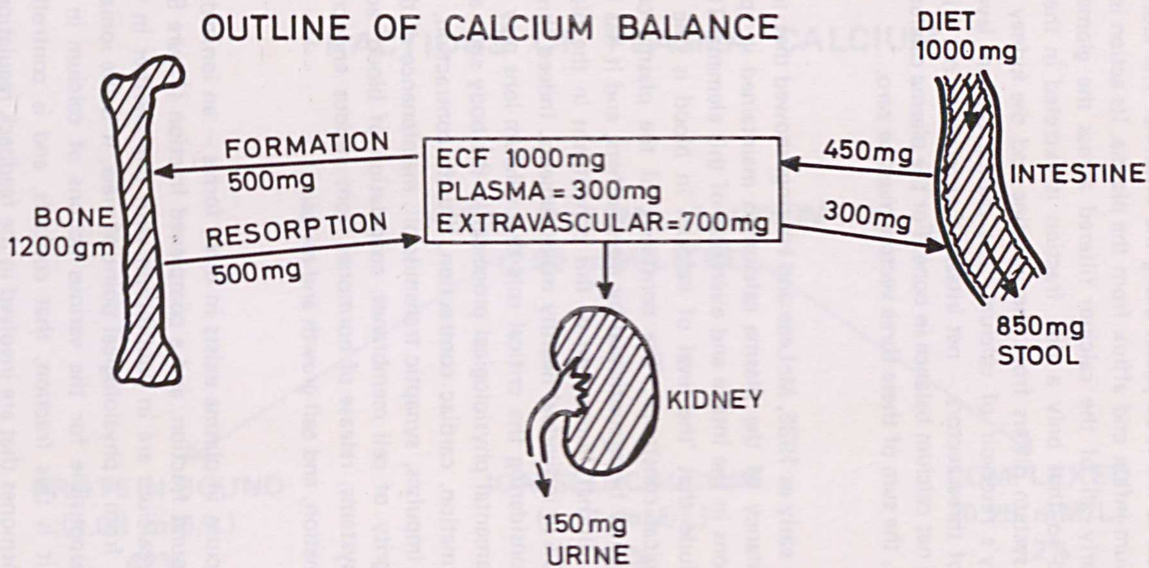
1. Regulation of body temperature
2. Regulation of breathing
3. Regulation of cardiac output
4. Regulation of blood pressure
5. Regulation of body water and osmolarity
6. Regulation of the concentrations of hormones in blood
7. Regulation of muscle length and tension
8. Regulation of blood glucose levels
9. Regulation of plasma calcium levels
10. Learning and memory
11. Regulation of hunger and satiety

Because of the importance of calcium in the body, the regulation of plasma calcium involves more than one feedback mechanism. I shall therefore discuss certain aspects of the regulation of calcium in plasma with special reference to the feedback controls involved.

The human body contains more calcium than any other inorganic ion. About 99 percent of this is present in the bones. A human adult of average size has approximately 1200 to 1400 grams of calcium in his body. Of this, less than one gram is found in the blood and extracellular fluid. The calcium in the blood is confined mainly to the plasma with negligible quantities in the cells.

Plasma calcium regulation in mammals is effected by the interaction of three systems — the gastrointestinal, renal and skeletal systems (Figure 4). Calcium from the diet is absorbed into the

Figure 4 Outline of calcium balance



circulation as the food passes along the intestine. The kidney regulates the calcium influx and efflux from the plasma. Its action is so efficient that nearly all of the calcium filtered across the glomerulus is re-absorbed so that only a tiny fraction is excreted in the urine. The skeletal system differs from the intestine and the kidney in that it is the body's reservoir of calcium. The plasma calcium level is the resultant of three vectors – net intestinal absorption, net urinary excretion and net calcium balance in bone. For the plasma calcium to remain constant, the sum of these three vectors must be zero.

As early as 1935, McLean and Hastings showed that, in mammals, the constancy of the plasma calcium is maintained in spite of wide fluctuations in the intake and excretion of this element. This led them to conclude that 'the level of calcium in blood is one of nature's physiological constants'. The constancy of the plasma calcium has more recently been confirmed by many others, and it has been shown that the diurnal fluctuation of this constituent in the plasma is less than $\pm$ 3% in individual healthy make subjects. Indeed this is not surprising considering the critical role that calcium ions play in many of the fundamental physiological processes in the body such as bone and teeth formation, cardiac contraction, muscle contraction, conduction of nerve impulses, synaptic transmission, maintenance of the stability and integrity of cell membranes, coagulation of blood, activation of enzyme systems, release of hormones from various endocrine glands, milk formation, and cell growth and mitosis.

Calcium in plasma exists in three forms – an ionized fraction, a protein-bound fraction, and a complexed fraction (Figure 5). All these forms of calcium are in equilibrium with one another in the plasma. However, from a physiological point of view, it is the ionized calcium that is responsible for the various actions of calcium in the body. Further, it is this fraction, that controls, and is controlled by, the various hormones that are involved in the feedback regulation of plasma calcium.

Figure 5 Plasma calcium fractions in man

FRACTIONS OF PLASMA CALCIUM

TOTAL PLASMA CALCIUM
(2.50 mM/LITRE)

PROTEIN-BOUND
(1.08 mM/L)
42%

IONISED CALCIUM
(1.17 mM/L)
46%

COMPLEXED
(0.25 mM/L)
12%

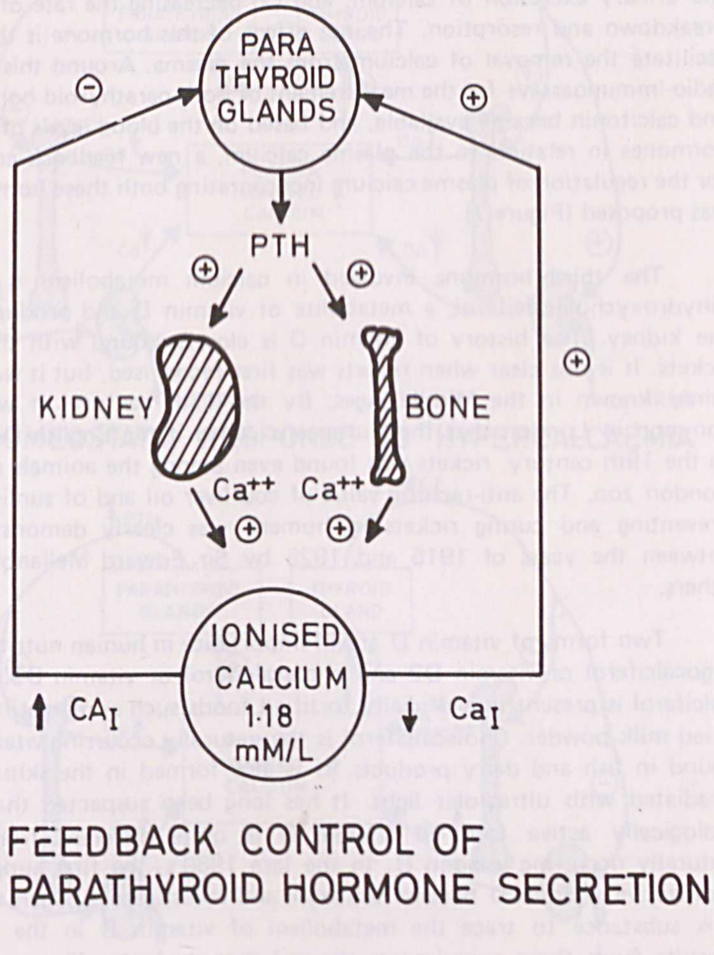
Three hormones are directly involved in the regulation of a constant concentration of ionized calcium in the plasma. These are (1) parathyroid hormone from the parathyroid glands, (2) calcitonin from the C cells of the thyroid glands, and (3) 1,25-dihydroxycholecalciferol, a metabolite of vitamin D and produced in the kidney.

The relation of the parathyroids to calcium metabolism was first recognised by MacCallum and Voegtlin (1909) when they showed that the removal of all the four parathyroid glands from dogs lowered their plasma calcium concentration and led to tetany which could be temporarily relieved by injections of calcium salts. Subsequently, Collip and his collaborators (1925) reported that extracts made from the parathyroid glands could restore the plasma calcium in parathyroidectomized dogs and raise it in normal dogs.

Parathyroid hormone acts on two sites in the body to contribute to calcium homeostasis – it acts on the kidney to enhance the reabsorption of calcium from the glomerular filtrate, and it acts on bone, increasing its breakdown, and thus resorption of calcium from this location. Thus, the primary action of the parathyroid hormone is to increase the plasma calcium levels. Based on these, McLean (1957) postulated a negative feedback hypothesis for the regulation of plasma calcium. According to this concept, the parathyroid glands respond to a fall in plasma calcium by increasing the secretion of parathyroid hormone. The hormone, in turn, increases the plasma calcium by (1) increasing the reabsorption of calcium from the kidney and (2) increasing the breakdown of bone. A rise in plasma calcium, on the other hand, results is suppression of secretion of parathyroid hormone so that there is increased urinary loss of calcium as well as less mobilisation from bone (Figure 6).

The discovery of calcitonin was a consequence of a reinvestigation of the McLean hypothesis. To test this concept, Copp and his colleagues (1961) perfused the thyroparathyroid complex of dogs with blood high in calcium. The resulting fall in plasma calcium proved to be more rapid than that produced by removal of the parathyroid glands themselves. It was then assumed that the fall in plasma calcium provoked by hypercalcaemia was not due to suppression of the secretion of parathyroid hormone alone. To account for their findings, Copp proposed that a second calcium regulating hormone must exist

Figure 6   Feedback control of Parathyroid hormone secretion



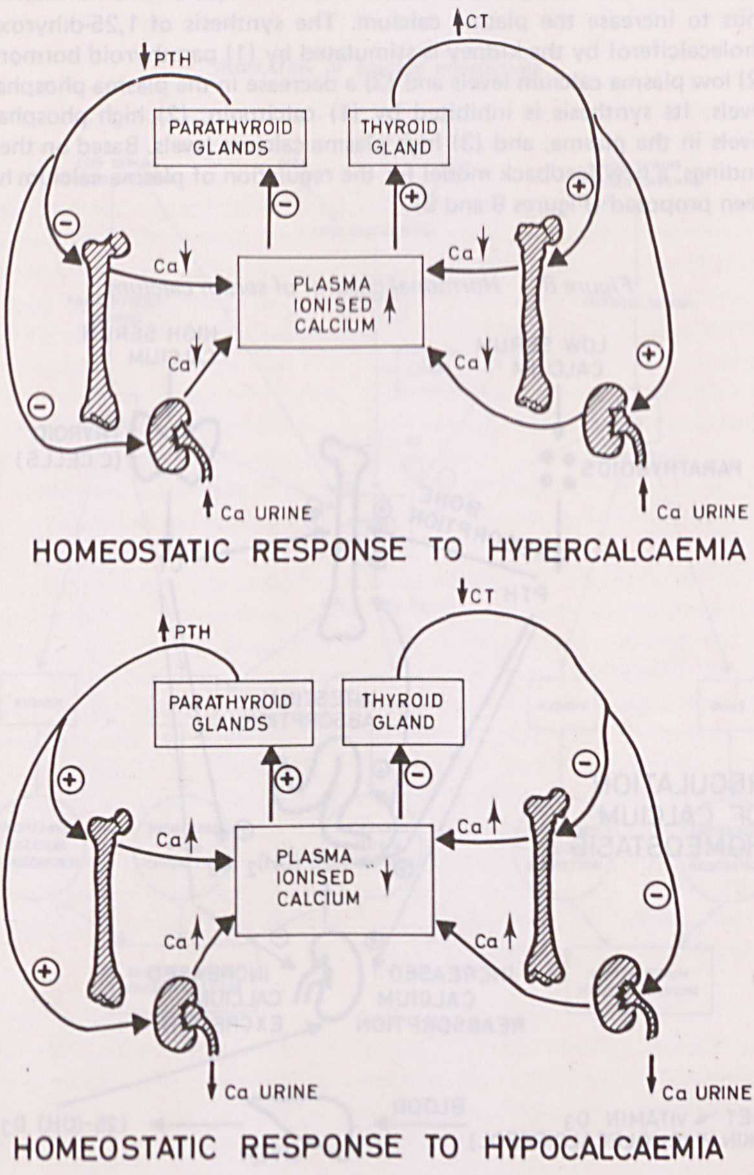
and he called it calcitonin. Although he believed that it was the parathyroid glands that were responsible for the secretion of calcitonin, later experiments in other animal species conclusively proved that the source of calcitonin was the C cells of the thyroid gland.

Calcitonin has actions that are opposite to those of parathyroid hormone. Calcitonin decreases the plasma calcium by (1) increasing the urinary excretion of calcium, and (2) decreasing the rate of bone breakdown and resorption. The net effect of this hormone is thus to facilitate the removal of calcium from the plasma. Around this time, radio-immunoassays for the measurement of both parathyroid hormone and calcitonin became available, and based on the blood levels of these hormones in relation to the plasma calcium, a new feedback control for the regulation of plasma calcium incorporating both these hormones was proposed (Figure 7).

The third hormone involved in calcium metabolism is 1,25-dihydroxycholecalciferol, a metabolite of vitamin D and produced in the kidney. The history of vitamin D is closely bound with that of rickets. It is not clear when rickets was first recognised, but it was certainly known in the Middle Ages. By the 17th century, it was so common in London that the Europeans called it the English Disease. In the 19th century, rickets was found even among the animals of the London zoo. The anti-rachitic value of cod liver oil and of sunlight in preventing and curing rickets in humans was clearly demonstrated between the years of 1915 and 1925 by Sir Edward Mellanby and others.

Two forms of vitamin D are of importance in human nutrition — ergocalciferol or vitamin D2 and cholecalciferol or vitamin D3. Ergocalciferol is present in artificially fortified foods such as margarine and dried milk powder. Cholecalciferol is the naturally occurring vitamin D found in fish and dairy products. It is also formed in the skin when irradiated with ultraviolet light. It has long been suspected that the biologically active form of vitamin D is quite different from the naturally occurring vitamin D. In the late 1960's, the first supply of radioactive vitamin D became available and investigators began to use this substance to trace the metabolism of vitamin D in the body. Results from these experiments showed that the naturally occurring vitamin D is metabolically converted first in the liver and subsequently in the kidney to the biologically active hormone 1,25-dihydroxycholecalciferol.

Figure 7   Role of Parathyroid hormone and Calcitonin in regulation of serum calcium



The main actions of 1,25-dihyroxycholecalciferol are (1) to increase the intestinal absorption of calcium, and (2) to increase the breakdown and resorption of bone. The net effect of this hormone is thus to increase the plasma calcium. The synthesis of 1,25-dihyroxycholecalciferol by the kidney is stimulated by (1) parathyroid hormone, (2) low plasma calcium levels and (3) a decrease in the plasma phosphate levels. Its synthesis is inhibited by (1) calcitonin, (2) high phosphate levels in the plasma, and (3) high plasma calcium levels. Based on these findings, a new feedback model for the regulation of plasma calcium has been proposed (Figures 8 and 9).

Figure 8   Hormonal control of serum calcium

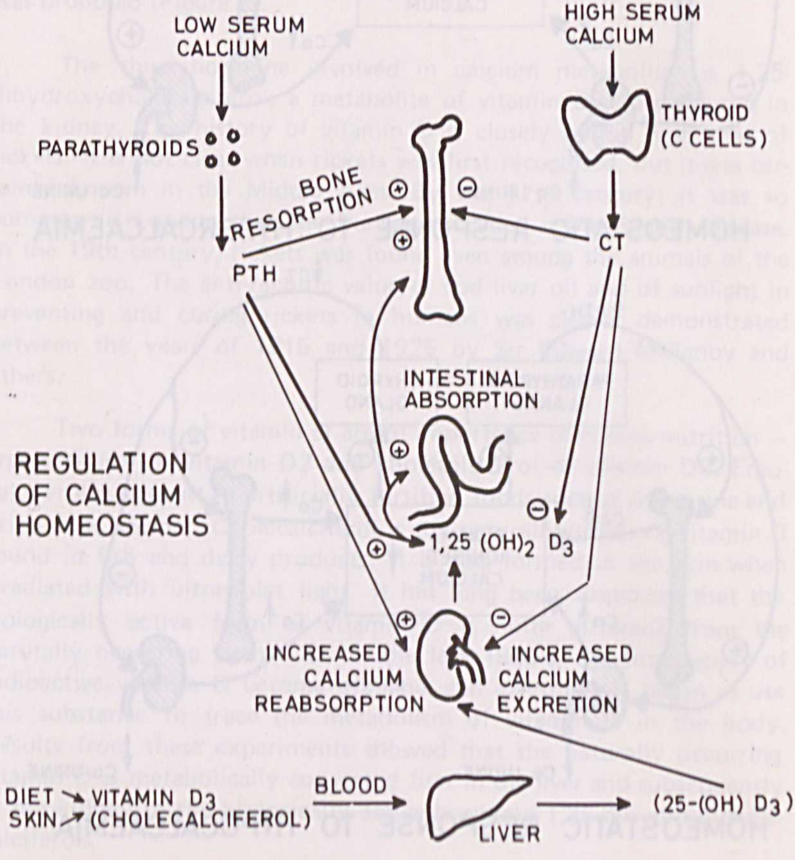
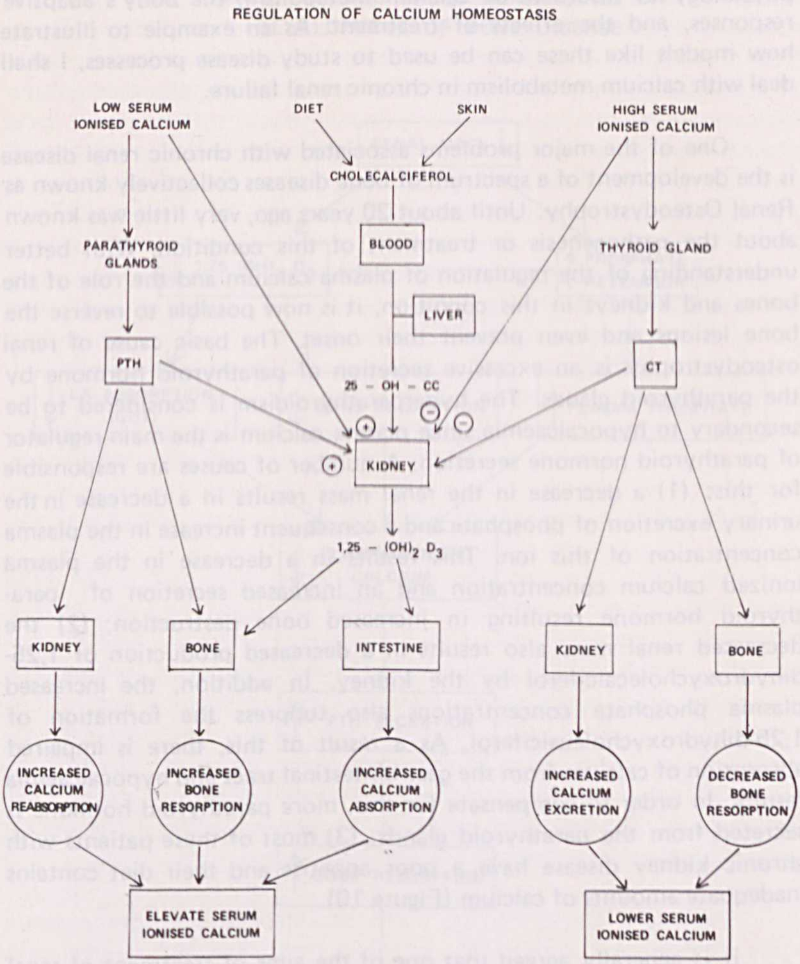


Figure 9   Regulation of calcium homeostasis

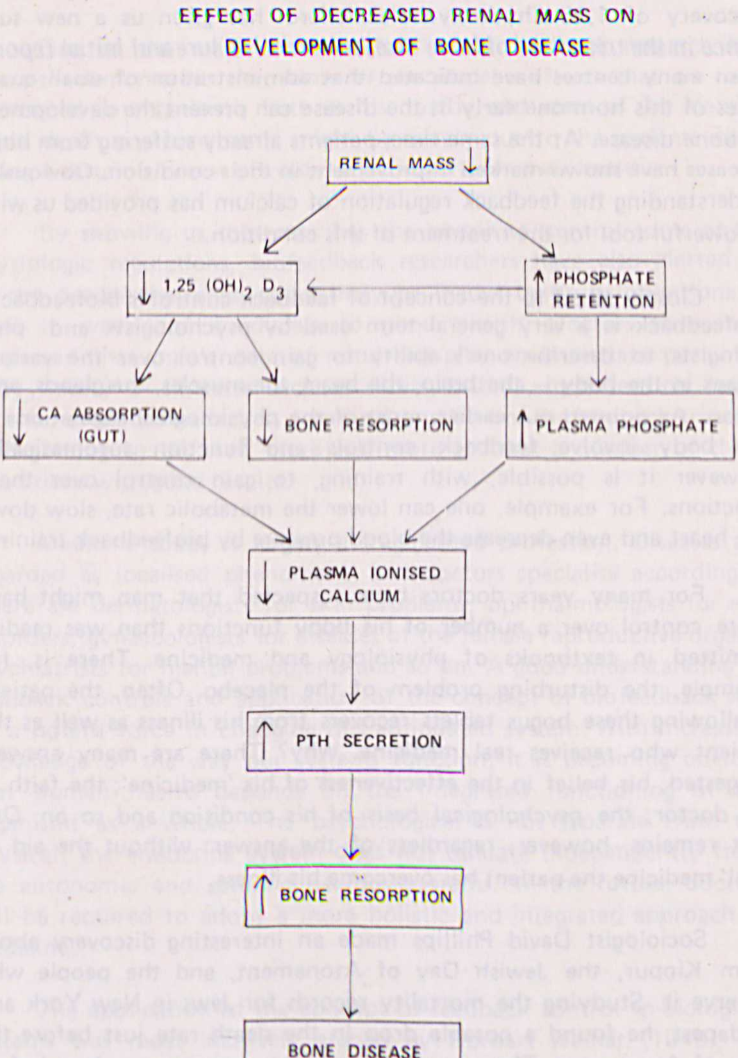


Models like these have several applications that are immediately apparent. Aside from providing control system analysts with a potentially new starting point in the construction of computer models of calcium homeostasis, it can also be used to understand the pathophysiology of disorders of calcium metabolism, the body's adaptive responses, and the effects of treatment. As an example to illustrate how models like these can be used to study disease processes, I shall deal with calcium metabolism in chronic renal failure.

One of the major problems associated with chronic renal disease is the development of a spectrum of bone diseases collectively known as Renal Osteodystrophy. Until about 20 years ago, very little was known about the pathogenesis or treatment of this condition. With better understanding of the regulation of plasma calcium and the role of the bones and kidneys in this condition, it is now possible to reverse the bone lesions and even prevent their onset. The basic cause of renal osteodystrophy is an excessive secretion of parathyroid hormone by the parathyroid glands. The hyperparathyroidism is considered to be secondary to hypocalcaemia since plasma calcium is the main regulator of parathyroid hormone secretion. A number of causes are responsible for this: (1) a decrease in the renal mass results in a decrease in the urinary excretion of phosphate and a consequent increase in the plasma concentration of this ion. This results in a decrease in the plasma ionized calcium concentration and an increased secretion of parathyroid hormone resulting in increased bone destruction; (2) the decreased renal mass also results in a decreased production of 1,25-dihydroxycholecalciferol by the kidney. In addition, the increased plasma phosphate concentrations also suppress the formation of 1,25-dihydroxycholecalciferol. As a result of this, there is impaired absorption of calcium from the gastrointestinal tract and hypocalcaemia results. In order to compensate for this, more parathyroid hormone is secreted from the parathyroid glands; (3) most of these patients with chronic kidney disease have a poor appetite and their diet contains inadequate amounts of calcium (Figure 10).

It is generally agreed that one of the aims of treatment of renal bone disease is suppression of parathyroid hormone secretion. This can be achieved by surgically removing the parathyroid glands. Apart from difficulties of the operation itself, total parathyroidectomy is often required to prevent recurrence of the condition. Consequently, attempts

Figure 10 Effects of renal disease on serum calcium and bone.



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have been made to treat the condition medically. These include regular haemodialysis, administration of calcium supplements and compounds such as aluminium hydroxide to decrease the plasma phosphate. Unfortunately many patients do not respond well to this regime. The discovery of 1,25-dihydroxycholecalciferol has given us a new substance in the treatment of bone disease in renal failure and initial reports from many centres have indicated that administration of small quantities of this hormone early in the disease can prevent the development of bone disease. At the same time, patients already suffering from bone diseases have shown marked improvement in their condition. Obviously, understanding the feedback regulation of calcium has provided us with a powerful tool for the treatment of this condition.

Closely allied to the concept of feedback control is biofeedback. Biofeedback is a very general term used by psychologists and physiologists to describe one's ability to gain control over the various organs in the body — the brain, the heart, the muscles, the glands, and so on. As pointed out earlier, most of the physiological regulations in the body involve feedback controls and function automatically. However it is possible, with training, to gain control over these functions. For example, one can lower the metabolic rate, slow down the heart and even decrease the blood pressure by biofeedback training.

For many years doctors have suspected that man might have more control over a number of his body functions than was readily admitted in textbooks of physiology and medicine. There is, for example, the disturbing problem of the placebo. Often, the patient swallowing these bogus tablets recovers from his illness as well as the patient who receives real medicine. Why? There are many answers suggested; his belief in the effectiveness of his 'medicine'; the faith in his doctor; the psychological basis of his condition and so on. One fact remains, however, regardless of the answer: without the aid of 'real' medicine the patient has overcome his illness.

Sociologist David Phillips made an interesting discovery about *Yom Kippur, the Jewish Day of Atonement, and the people who* observe it. Studying the mortality records for Jews in New York and Budapest, he found a notable drop in the death rate just before the *Day of Atonement. There was no such drop among non-Jews before* this religious holiday. Carrying his investigation further, Phillips also examined the mortality pattern at the time of people's birthdays. He found a significant drop in deaths before birthdays and a significant peak in deaths thereafter – which means, according to Phillips, that 'people look forward to witnessing certain important occasions and are able to put off dying in order to do so'.

One of the major contributions of biofeedback research has been to demonstrate that some of the placebo effects that we have attributed to a patient's faith in his doctor, and some of the inexplicable death postponements might be simply due to the patients exercising a certain amount of voluntary control over their health.

By showing us that man has the power to control some of his physiologic regulations, biofeedback researchers have also alerted us to the danger that such power may be inadvertently or intentionally used in ways not conducive to good health. Doctors have long suspected that man's state of mind can play an important part in a wide variety of illnesses such as ulcers, asthma, hypertension, heart attacks, anxiety headaches, insomnia and so on. Biofeedback training is beginning to be used more and more to treat a number of these conditions with good results.

Medicine today is largely a fragmented profession. Diseases are regarded as localised phenomena, and doctors specialise accordingly. There are dermatologists for skin problems, ophthalmologists for eye disorders, gynaecologists for diseases of the female reproductive organs, psychiatrists for mental problems and so on. A good understanding of feedback controls and application of the concept of biofeedback will be a potent force in changing this antiquated system. With increasing knowledge of the way our systems function, it is becoming obvious that human health depends on the integrated functioning of the organisms as a whole. The psychological is not separate from the physical; the endocrine system does not operate independently from the autonomic and somatic nervous systems. In the future, doctors will be required to adopt a more holistic and integrated approach to medicine.

The application of the concept of feedback control to biological systems was most incisively argued by Norbert Weiner (1949). He created a discipline to which he gave the name Cybernetics – from a Greek word meaning Helmsman. The science of cybernetics has not replaced anything in more conventional physiological language. On the contrary, it permits us to talk about phenomena for which we previously had no vocabulary. Cybernetics has offered us new ways of analysing physiological problems and provides a different kind of insight into their interrelationship. Further, it has stimulated the development of new instruments and appliances and research into the discovery of new drugs for the diagnosis and treatment of diseases. A modern example of the concept of feedback control in medicine is the artificial hand.

When an engineer designs the guidance system for a missile or sketches the circuit diagram for an orbiting satellite, he relies upon a variety of techniques that enable him to predict how some of the complicated array of individual components will behave in response to an external stimulus. Using analog and digital computers, the engineer is able to obtain rapid answers to his design problems whenever the complexity of the problem makes the search for analytical answers unhelpful. In living systems, the physiologists are also confronted by complicated array of interlinked components and they too would like to discover how such systems and their component parts will behave in response to an external disturbance – for example, a disease process. Unfortunately, in spite of a few notable successes, progress in the application of control theory to physiological and medical problems has been rather slow due to two main reasons. Firstly, physiologists and doctors have a poor mathematical background to appreciate and solve the equations that are involved in these models. Secondly, it is only in the last ten years or so that refined techniques such as radioimmunoassays and neutron analysis have been perfected to measure the minute amounts of hormones and other chemicals circulating in the body fluids.

One can now say that physiology has its foundations in three – just not two – fundamental sciences. The first is physics and the second is chemistry, both of which began to be applied to physiological and allied problems in the 19th century. The third is Systems analysis based upon control theory. Its usefulness in physiology and medicine is only just beginning to be appreciated. Although models and control theory cannot by themselves uncover new knowledge, they may provide new insights for the investigator who can, for the first time, see how the various system components in the human body interact dynamically to produce the whole organism and its response. To quote Vaihinger, 'It must be remembered that the object of the world of ideas and experimentation as a whole is not the portrayal of reality – this would be an utterly impossible task – but rather to provide us with an instrument for finding our way about in this world more easily'.

REFERENCES

Adolph, E.F. *Early concepts of Physiological Regulations. Physiol. Rev., 41: 737–770, 1961.*

Aurbach, G.D. *(Editor) Parathyroid Gland: Handbook of Physiology Section VII, Volume 7, American Physiological Society, Washington, D.C. 1976.*

Bayliss, L.E. *Living Control Systems. English Universities Press, London 1966.*

Karlins, M. and Andres, L.M. *Biofeedback. Garnstone Press, London 1973.*

Mayr, O. *The Origins of Feedback Control. Sci. Amer., 222: 110–118, 1970.*

Milhorn, H.T. *The Application of Control Theory to Physiological Systems. W.B. Saunders and Company, Philadelphia 1966.*

Riggs, D.S. *Control Theory and Physiological Feedback Systems. William and Wilkins, Baltimore 1970.*

Yamamoto, W.S. and Brobeck, J.R. *(Editors) Physiological Controls and Regulations. W.B. Saunders and Company, Philadelphia 1965.*