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ORGANIZATION FOR PHYSIOLOGICAL HOMEOSTASIS

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Biologists have long been impressed by the ability of living beings to maintain their own stability. The idea that disease is cured by natural powers, by a *vis medicatrix naturae*, an idea which was held by Hippocrates, implies the existence of agencies ready to operate correctively when the normal state of the organism is upset. More precise modern references to self-regulatory arrangements are found in the writings of prominent physiologists. Pflüger (1877) recognized the natural adjustments leading toward the maintenance of a steady state of organisms when he laid down the dictum, "The cause of every need of a living being is also the cause of the satisfaction of the need." Similarly Fredericq (1885) declared, "The living being is an agency of such sort that each disturbing influence induces by itself the calling forth of compensatory activity to neutralize or repair the disturbance. The higher in the scale of living beings, the more numerous, the more perfect and the more complicated do these regulatory agencies become. They tend to free the organism completely from the unfavorable influences and changes occurring in the environment." Further, Richet (1900) emphasized the general phenomenon,—"The living being is stable. It must be in order not to be destroyed, dissolved or disintegrated by the colossal forces, often adverse, which surround it. By an apparent contradiction it maintains its stability only if it is excitable and capable of modifying itself according to external stimuli and adjusting its response to the stimulation. In a sense it is stable because it is modifiable—the slight instability is the necessary condition for the true stability of the organism."

To Claude Bernard (1878) belongs the credit of first giving to these general ideas a more precise analysis. He pointed out that in animals with complex organization the living parts exist in the fluids which bathe them, i.e., in the blood and lymph, which constitute the "milieu interne"

or "intérieur"—the internal environment, or what we may call the *fluid matrix* of the body. This fluid matrix is made and controlled by the organism itself. And as organisms become more independent, more free from changes in the outer world, they do so by preserving uniform their own inner world in spite of shifts of outer circumstances. "It is the fixity of the 'milieu intérieur' which is the condition of free and independent life," wrote Bernard (1878, i, pp. 113 and 121), "all the vital mechanisms, however varied they may be, have only one object, that of preserving constant the conditions of life in the internal environment." "No more pregnant sentence," in Haldane's (1922) opinion, "was ever framed by a physiologist."

DEFINITION OF HOMEOSTASIS. The general concept suggested in the foregoing quotations may be summarized as follows. The highly developed living being is an open system having many relations to its surroundings—in the respiratory and alimentary tracts and through surface receptors, neuromuscular organs and bony levers. Changes in the surroundings excite reactions in this system, or affect it directly, so that internal disturbances of the system are produced. Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action, and thereby wide oscillations are prevented and the internal conditions are held fairly constant. The term "equilibrium" might be used to designate these constant conditions. That term, however, has come to have exact meaning as applied to relatively simple physico-chemical states in closed systems where known forces are balanced. In an exhaustive monograph L. J. Henderson (1928) has recently treated the blood from this point of view, i.e., he has defined, in relation to circumstances which affect the blood, the nice arrangements within the blood itself, which operate to keep its respiratory functions stable. Besides these arrangements, however, is the integrated coöperation of a wide range of organs—brain and nerves, heart, lungs, kidneys, spleen—which are promptly brought into action when conditions arise which might alter the blood in its respiratory services. The present discussion is concerned with the physiological rather than the physical arrangements for attaining constancy. The coördinated physiological reactions which maintain most of the steady states in the body are so complex, and are so peculiar to the living organism, that it has been suggested (Cannon, 1926) that a specific designation for these states be employed—*homeostasis*.

Objection might be offered to the use of the term *stasis*, as implying something set and immobile, a stagnation. Stasis means, however,

not only that, but also a condition; it is in this sense that the term is employed. *Homeo,* the abbreviated form of *homoio,* is prefixed instead of *homo,* because the former indicates "like" or "similar" and admits some variation, whereas the latter, meaning the "same," indicates a fixed and rigid constancy. As in the branch of mechanics called "statics," the central concept is that of a steady state produced by the action of forces; *homeostatics* might therefore be regarded as preferable to homeostasis. The factors which operate in the body to maintain uniformity are often so peculiarly physiological that any hint of immediate explanation in terms of relatively simple mechanics seems misleading. For these various reasons the term homeostasis was selected. Of course, the adjectival form, *homeostatic,* would apply to the physiological reactions or agencies or to the circumstances which relate to steady states in the organism.

CLASSIFICATION OF HOMEOSTATIC CONDITIONS. According to Bernard (1878, ii, p. 7), the conditions which must be maintained constant in the fluid matrix of the body in order to favor freedom from external limitations are water, oxygen, temperature and nutriment (including salts, fat and sugar).

Naturally during the past fifty years new insight has been acquired and therefore a more ample classification than that just given should be possible. Any classification offered now, however, will probably be found to be incomplete; other materials and environmental states, whose homeostasis is essentially important for optimal activity of the organisms, are likely to be discovered in the future. Moreover, in any classification there will be cross-relations among the homeostatic states; a uniform osmotic pressure in the body fluids, for example, is dependent on constancy within them of the proportions of water, salts and protein. The classification suggested below, therefore, should not be regarded as more than a serviceable grouping of homeostatic categories; it may claim only the merit of having served as a basis for studying the means by which the organism achieves stability:

A. Material supplies for cellular needs.
   1. Material serving for the exhibition of energy, and for growth and repair—glucose, protein, fat.
   2. Water.
   3. Sodium chloride and other inorganic constituents except calcium.
   4. Calcium.
   5. Oxygen.
   6. Internal secretions having general and continuous effects.

B. Environmental factors affecting cellular activity.
   1. Osmotic pressure.
   2. Temperature.
   3. Hydrogen-ion concentration.

Each item in the foregoing list exists in a relatively uniform condition of the fluid matrix in which the living cells of the organism exist. There are variations of these conditions, but normally the variations are within narrow limits. If these limits are exceeded serious consequences may result or there may be losses from the body. A few examples will make clear these relations:

A reduction of the glucose in the blood to about 70 mgm. per cent (e.g., by insulin) induces the "hypoglycemic reaction" (Fletcher and Campbell, 1922), and a reduction below 45 mgm. per cent brings on convulsions and possibly coma and death; an increase of the percentage above 170 to 180 mgm. results in loss via the kidneys. Too much water in the body fluids results in "water intoxication," characterized by headache, nausea, dizziness, asthenia, incoördination (Rowntree, 1922); on the other hand, too little water results in lessened blood volume, greater viscosity, and the appearance of fever (Keith, 1922; Crandall, 1899). Sodium (with the attendant chloride ion) is especially important in maintaining constant the osmotic properties of the plasma; if the percentage concentration rises from 0.3 to 0.6 per cent, water is drawn from the lymph and cells, and fever may result (Freund, 1913; Cushny, 1926, p. 19); on the other hand, if the concentration is reduced, toxic symptoms appear—marked reflex irritability, followed by weakness, shivering, paresis and death (see Grünwald, 1909). The normal level of calcium in the blood is about 10 mgm. per cent; if it falls to half that concentration, twitchings and convulsions are likely to occur (MacCallum and Voegtlin, 1909); if it rises to twice that concentration, profound changes take place in the blood, which may cause death (Collip, 1926). The normal daily variations of body temperature in man range between 36.3°C. and 37.3°C.; though it may fall to 24°C. and not be fatal (Reincke, 1875), that level is much lower than is compatible with activity; and if the temperature persists at 42–43°C., it is dangerous because of the coagulation of certain proteins in nerve cells (Halliburton, 1904). The hydrogen-ion concentration of the blood may vary between approximately pH 6.95 and pH 7.7; at a pH of about 6.95 the blood becomes so acid that coma and death result (Hasselbalch and Lundsgaard, 1912); above pH 7.7 it becomes so alkaline that tetany appears (Grant and Goldman, 1920). The heart rate (of the dog) has

been seen to decrease from 75 beats per minute to 50 when the pH fell from 7.4 to 7.0; and to increase from 30 per minute to about 85 when the pH rose from 7.0 to 7.8 (Andrus and Carter, 1924). The foregoing instances illustrate the importance of homeostasis in the body fluids. Ordinarily the shifts away from the mean position do not reach extremes which impair the activities of the organism or endanger its existence. Before those extremes are reached agencies are automatically called into service which act to bring back towards the mean position the disturbed state. The interest now turns to an enquiry into the character of these agencies.

An inductive unfolding of the devices employed in maintaining homeostatic conditions—an examination of each of the conditions with the object of learning how it is kept constant—would require more space than is permitted here. It will be possible, however, to define in broad terms the agencies of homeostasis and to illustrate the operation of some of those agencies by reference to the specific cases. Thus the account may be much abbreviated.

Two general types of homeostatic regulation can be distinguished dependent on whether the steady state involves *supplies* or *processes*.

HOMEOSTASIS BY REGULATING SUPPLIES. The characteristic feature of the homeostasis of supplies is provision for A, storage as a means of adjustment between occasional abundance and later privation and need, and for B, overflow or discharge from the body when there is intolerable excess. Two types of storage can be distinguished: a temporary flooding of interstices of areolar tissue by the plenteously ingested material, which may be designated *storage by inundation*; and an inclusion of the material in cells or in other relatively fixed and permanent structures—*storage by segregation*. We shall consider illustrations of these two types.

STORAGE BY INUNDATION. The analogy implied in this phrase is that of a bog or swamp into which water soaks when the supply is bountiful and from which the water seeps back into the distributing system when the supply is meager. There appears to be such an arrangement in the loose areolar connective tissue found under the skin and around and between muscles and muscle bundles, and also in other parts of the body. Connective tissue is distinguished from other kinds in being richest in extracellular colloid, in having a close relation to blood vessels—indeed, it serves as a support for the blood vessels—and in exposing an enormous surface area. In such structures chiefly do the agencies rule which hold not only mobile water but also substances

dissolved in it, i.e., electrolytes and glucose. Here there are few cells, but instead "a spongy cobweb of delicate filaments," each of which is composed of minute fibrils bound together by a small amount of "cement substance" (Lewis and Bremer, 1927). Within the fine mesh of these collagenous fibres occur mucoid and small amounts of albumin and globulin. In this mesh and bound by it in some manner water and its dissolved substances appear to be held. Probably the proportions of stored water, electrolytes and glucose do not vary beyond a fairly limited range. Because there is evidence, however, that water and electrolytes, at least, may be affected somewhat independently with regard to their retention and elimination, they will be considered separately.

Water. The evidence for water storage is best demonstrated in experiments which withdraw water from its reservoirs and which permit an examination of the amount held in them. After hemorrhage all tissues lose water. By comparing one side of the body with the other in the same animal (the cat) Skelton (1927) found that most of the water which leaves the tissues after bleeding comes from the muscles and the skin—i.e., where loose areolar tissue is most abundant; the amount per 100 grams of tissue, however, is much less from the muscles than from the skin. The observations by Engels (1904) on dogs are in harmony with those of Skelton. Engels found that though 48 per cent of the total body water is in muscles, as might be expected from the great bulk of muscle tissue, about 12 per cent is in the skin, nearly half again as much as is in the fluid blood. And after injecting 0.6–0.9 per cent sodium chloride solution into a vein for an hour, he discovered that 690 grams had been retained and that the muscles and the skin had taken up the solution to almost the same per cent.

That the water stored in the tissues passes out from them as it is needed is shown by the studies of Wettendorf (1901) on the state of the blood during water deprivation. His dogs were, of course, continually losing water through respiratory surfaces and kidneys. Yet one of his animals thirsted for 3 days with no change in the freezing point of the blood, and another for 4 days with a depression of only 0.01°C. Clearly this constancy must be due to the seepage of water from the reservoirs to the blood as fast as it is lost from the body.

Just how the water is brought to the reservoirs, how it is held there, and how it is released as required for preserving the osmotic homeostasis of the blood, is not yet satisfactorily explained. Doubtless a change in the balance between filtration pressure through the capillary walls and

osmotic pressure of the proteins, as expounded by Starling (1909), plays an important rôle. And naturally, conditions affecting the capillary wall (e.g., increasing its permeability), raising or lowering intracapillary blood pressure, or altering the concentration of the plasma proteins would affect the water content of the tissues. Diffusion pressure would likewise take part in the complex of active factors. Furthermore, as Adolph (1921) and Baird and Haldane (1922) have shown, the taking of sodium chloride can markedly influence the retention of water in the body. Probably other electrolytes likewise play a rôle. There is evidence also that the H- and OH-ion concentration may be important—a shift towards an alkaline reaction causing imbibition of water by connective tissue and an opposite shift resulting in release (Schade, 1925). That the thyroid gland is a determinative agent is indicated by the great increase of protein in the plasma and of albumin in the tissues in myxedema, and the disappearance of these conditions, together with a large release of water and sodium chloride, when thyroxin is administered (see Thompson, 1926). How these various factors coöperate when water and sodium chloride are needed in the circulation—after hemorrhage, for example—is not clear, and urgently calls for investigation. Krogh (1922) has written concerning the arrangement of water mobilization, "The nature of such a mechanism is entirely unknown and I should not like to venture even a guess regarding it"—and yet it is of primary significance for the organism.

Sodium chloride. There is good evidence that the sodium and chloride ions in the plasma may vary independently, and that of the two the base is much the more constant element (see Gamble and Ross, 1925; Gamble and McIver, 1925, 1928). In a study of steady conditions in the fluid matrix, therefore, the emphasis might properly be laid on the homeostasis of the fixed base. Since most of the facts now available, however, have come from experiments in which the behavior of sodium chloride has been examined, the present treatment of the subject must be concerned with that salt. The evidence for storage of sodium chloride in the body is found in retention under different conditions. With a fairly constant chloride intake abundant sweating and attendant loss of chloride through the skin are accompanied by a great reduction of the chloride output in the urine—a condition which continues although thereafter a diet rich in salt is taken; by this method of study a compensatory retention of 10 to 14 grams of sodium chloride has been observed (Cohnheim, Kreglinger, and Kreglinger, 1909). Further, the taking of concentrated sodium chloride by mouth results in the appear-

ance in the urine of only a part of the amount ingested—most of it is retained in storage in the body; and even if thereupon enough water is drunk to produce a diuresis the urine has a low salt content, i.e., the salt is not given up readily from its storage place (Baird and Haldane, 1922).

When a search is made for the sodium chloride reserve in the body the highest percentage of chloride is found in the skin and the lowest in the muscles—indeed, on a chloride-rich diet one-third of the chloride of the body may be in the skin, and after an intravenous infusion of a sodium-chloride solution the skin may hold the stored chloride to an amount varying in different experiments between 28 and 77 per cent of the amount injected. This evidence is supported by observations on animals fed a chloride-poor diet. Under these circumstances between one and two-tenths of the chloride content of the body is lost, and of this amount between 60 and 90 per cent comes from the skin, though the skin is only 16 per cent of the total body weight (Padtberg, 1910). It is noteworthy that the blood gives up relatively little of its chloride content; again the circulating fluid is kept constant by supplies from tissue storage.

It is well to recognize that the way in which sodium chloride is held in the skin, whether by adsorption on surfaces in areolar tissue or by solution in the interstitial fluid of the areolar spaces, is not known. Probably it is osmotically inactive. That sodium chloride and water are closely related in storage, however, seems to be well established (see Adolph, 1921).

Glucose. The first, temporary depository for excessive blood sugar, as for excessive sodium chloride, is the skin. When sugar or other readily digestible carbohydrate is a large constituent of the diet the glycemic concentration rises commonly from about 100 to 170 mgm. per cent (Hansen, 1923). During this period of high percentage of sugar in the blood there is also a high percentage in the skin (Folin, Trimble and Newman, 1927). This appears to be again an example of storage by inundation. No chemical change occurs in the sugar. No special device is required either to deposit it in the temporary reservoir or to remove it therefrom. As the circulating sugar is utilized or placed in more permanent storage in the liver and in muscle cells, the glycemic level falls. Thereupon the more concentrated glucose, which has overflowed into the spaces of the skin and possibly into other regions where alveolar tissue is abundant, gradually runs back into the blood again and then follows the usual courses of the blood glucose into use or into the fixed reserves.

STORAGE BY SEGREGATION. As previously stated, this mode of storage, commonly within cells, is stable and lasting. It is seen, for example, in carbohydrate reserves as glycogen, in protein reserves as irregular masses in liver cells, in fat reserves as adipose tissue, and in calcium reserves as the trabeculae of the long bones. It differs from storage by inundation in being subject to much more complicated control. Storage by inundation may be regarded as a process of outflow from the blood stream and backflow into it according to the degree of abundance—a relatively simple process. Storage by segregation commonly involves changes of physical state or of molecular configuration and appears to be subject to nervous or neuro-endocrine government. This rather tentative statement is used because of the large gaps in our knowledge, which further consideration will reveal. We shall consider the segregated storage of carbohydrate, protein, fat and calcium.

Carbohydrate. The best example of homeostasis by means of segregation is offered by the arrangements for storage and release of carbohydrate. As is well known, when carbohydrate food is plentiful the glycogen reserves in the liver are large; in prolonged muscular work these reserves may be almost wholly discharged (Kulz, 1880); and yet, while they are being discharged, the blood sugar is maintained at concentrations which neither result in the possibility of sugar loss through the kidneys, nor in the possibility of disturbance from hypoglycemia (Campos, Cannon, Lundin and Walker, 1929). A mechanism must exist, therefore, to release sugar from the liver as it is needed.

An insight into the action of factors which prevent the fall of the blood sugar to a seriously low level may be obtained by a study of the effects of insulin. As stated above, the reduction of the glycemic concentration to about 70 mgm. per 100 cc. by insulin induces the "hypoglycemic reaction," characterized by pallor, rapid pulse, dilated pupils and profuse sweating. These are signs of sympathetic innervation. That this is part of a general display of activity by the sympathetic division of the autonomic system is shown by the involvement of the adrenal medulla. Using the denervated heart as an indicator, Cannon, McIver and Bliss (1923, 1924) found that as the blood sugar fell a critical point was reached at about 70 mgm. per cent, when the heart began to beat faster—a phenomenon which failed to appear if the adrenal glands had been inactivated. If the blood sugar continued to fall the heart rate became faster, thus indicating a greater output of adrenin; and if the blood sugar rose, either because of intravenous injection of

glucose or because of a physiological reaction, the heart beat returned to its original slow rate, thus indicating a subsidence of the extra discharge of adrenin. Since medulliadrenal secretion is controlled by splanchnic impulses, and since such impulses in coöperation with secreted adrenin are highly effective in causing an increase of blood sugar (Bulatao and Cannon, 1925; Britton, 1928), it is clear that the reduction of the glycemic percentage below a critical level calls forth an agency—the sympathico-adrenal system—to correct the condition. These observations have been confirmed by Abe (1924) who used the denervated iris to signal a greater output of adrenin, and by Houssay, Lewis and Molinelli (1924) who used for that purpose an adrenal-jugular anastomosis between two dogs. If, in spite of the increasingly active service of this agency as the blood sugar falls, the fall is not checked, convulsions occur (at about 45 mgm. per cent) and each convulsion is associated with a maximal display of sympathico-adrenal activity. If the liver is well supplied with glycogen such activity can restore the blood sugar to the normal level and thus abolish the conditions which brought on the convulsive attacks (McCormick, Macleod, Noble and O'Brien, 1923).

The importance of this agency has been demonstrated by experiments on healthy non-anesthetized animals in which the adrenal glands had been inactivated. The fall of blood sugar after insulin was less retarded at the critical level in cats thus altered, and the convulsive seizures were induced sooner and with smaller doses than in animals with active glands (Cannon, McIver and Bliss, 1924). This increased sensitiveness to insulin after medulliadrenal inactivation has also been proved true of rats (Lewis, 1923), of rabbits (Sundberg, 1923) and of dogs (Lewis and Magenta, 1925; Hallion and Gayet, 1925). The evidence that a small dose of insulin, mildly effective in a normal animal, causes in an animal treated with ergotamine profound hypoglycemia, with convulsions and collapse (Burn, 1923), is in harmony with this testimony, for the drug, though without influence on the action of insulin, paralyzes the protective sympathico-adrenal mechanism. Section of the splanchnic nerves, according to Lewis and Magenta, renders animals more sensitive than does removal of one adrenal and denervation of the other by splanchnic section; under the latter circumstances, it should be noted, one splanchnic is still innervating the liver.

Operation of agencies opposed to those just considered occurs when the blood sugar tends to rise. The efficacy of these agencies is revealed when an excess of glucose is ingested. The blood sugar rises to a level

close to that at which it escapes through the kidneys, but normally it does not often surpass that level (Hansen, 1923). The excess sugar, apart from that set aside by inundation, is either stored in the liver or in muscles, or is converted to fat, or is promptly utilized. There is evidence that the process of storage by segregation in hepatic and muscle cells is dependent on secretion of insulin: 1. Removal of the pancreas results in prompt appearance of hyperglycemia and a great reduction of the hepatic glycogen reserves. 2 .The administration of insulin to sugar-fed *depancreatized* dogs reduces the blood sugar to the normal percentage and causes glycogen to accumulate again in large amounts in the liver (Banting, Best, Collip and Noble, 1922). 3. Insulin in small doses causes a deposit of glycogen in the liver of phlorizinized rabbits and cats, even though no sugar is provided (Cori, 1925). 4. Insulin injected into decapitated, eviscerated cats causes a decided increase in the glycogen deposit in the muscles, especially when extra blood sugar is provided (Best, Hoet and Marks, 1926). 5. Islet cells in a remnant of the pancreas degenerate, showing signs of overwork (Allen, 1920; Homans, 1914), when carbohydrate is fed; from this evidence it appears that hyperglycemia stimulates the islet cells to secrete. This stimulation may be direct, as proved by absence of diabetes if a portion of the pancreas is transplanted under the skin and the rest of the gland is then removed and by the appearance of the disease when the engrafted piece is extirpated (Minkowski, 1908), by prompt reduction of hyperglycemia from injected glucose although the vagi have been severed (Banting and Gairns, 1924), or by reduction of diabetic hyperglycemia when a pancreas is connected with blood vessels in the neck (Gayet and Guillaumie, 1928). There is evidence also of a nerve control of insulin secretion, for stimulation of the right vagus reduces blood sugar, but not if the vessels of the pancreas are tied (Britton, 1925); and, according to Zunz and La Barre (1927), after union of the pancreatic vein of dog A to the jugular of dog B injection of glucose into A causes the blood sugar to fall in B—an effect that does not occur if the vagi of A have been cut or atropine given. That this nervous control is not necessary does not prove that it is useless when present—for example, the heart after denervation will continue beating and will maintain the circulation! It may be that the vagus provides a fine adjustment for insulin secretion as the sympathetic does for secretion of adrenin.

The general scheme which has been presented above is represented diagrammatically in figure 1. As Hansen (1923) has pointed out, there are normal oscillations in blood sugar occurring within a relatively

narrow range. Possibly these ups and downs result from action of the opposing factors, depressing or elevating the glycemic level. If known elevating agencies (normally and primarily the sympathico-adrenal apparatus) are unable to bring forth sugar from storage in the liver, the glycemic level falls from about 70 to about 45 mgm. per cent, whereupon serious symptoms (convulsions and coma) may supervene. The range between 70 and 45 mgm. per cent may be regarded as the *margin of safety*. On the other hand, if the depressing agency (the insular or vago-

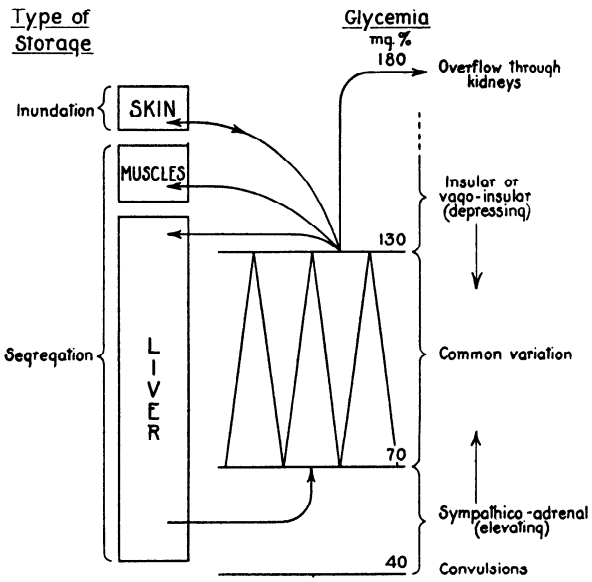

Fig. 1

insular apparatus) is ineffective, the glycemic level rises to about 180 mgm. per cent and then sugar begins to be lost through the kidneys. The range from 100 or 120 to 180 mgm. per cent may be regarded as the *margin of economy*—beyond that, homeostasis is dependent on wasting the energy contained in the sugar and the energy possibly employed by the body to bring it as glucose into the blood.[1]

[1] Evidence opposed to the foregoing views has been brought forward recently by Cori and Cori (1928). They state that "the most prominent effect of epinephrin is observed in the peripheral tissues and consists in a mobilization of muscle glycogen and in a decreased utilization of blood sugar"; and that insulin causes a rapid disappearance of the hepatic stores, due to increased use of blood

Protein. The homeostasis of protein is perhaps widely manifested in the constancy of body structure. That would include the blood, however, and since we are concerned with the conditions which keep uniform the fluid matrix of the body, we shall pay particular attention only to that.

The importance of constancy of the plasma proteins need not be

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sugar in peripheral tissues and to "compensatory mobilization of liver glycogen." These declarations, so contrary to evidence long accepted, call for comment. First, they gave doses of adrenalin (0.2 mgm. per k.) and of insulin (7.5 units per k.) far beyond physiological limits (equivalent to 14 cc. of adrenin and 525 units of insulin in a man of 70 k.!). Pronounced physiological effects have been obtained in white rats (which they used) with a dose of adrenin *one-twentieth* of their dose. Although they argue that their adrenin doses were slowly and fairly evenly absorbed, they present no actual evidence; and the fact that the highest blood sugar in their experiments came early and was associated with the lowest glycosuria indicates both that their argument is ill-based and that the huge doses disturbed the circulation. Further, "mobilization of muscle glycogen" consists, they explain, in a change of the glycogen to lactic acid, and from this circulating lactic acid a reconstruction of glycogen by the liver. But the glycogen in muscle is there for use; to "mobilize" it without use is like withdrawing forces from the firing line and settling them in barracks! Again, in declaring that adrenin causes hyperglycemia "because the utilization of blood sugar is diminished" they neglect the evidence: 1, that intravenous injection of adrenin raises blood sugar with almost no latent period (Tatum, 1921); 2, that emotional excitement can raise blood sugar 30 per cent or more in a few minutes, but not after adrenalectomy (Britton, 1928), and that the same phenomena are seen when the splanchnics are stimulated (Macleod, 1913), and 3, that after an adrenin injection the blood sugar rises quickly in the liver veins and only later is equaled in the portal or femoral vein (Vosburgh and Richards, 1903)—all evidence against their views, because the hyperglycemia comes too soon and is too clearly of hepatic origin to be ascribed to failure of use of glucose by peripheral tissues. Moreover, their belief that adrenin causes "decreased utilization of blood sugar" is contradicted by the observation that when glucose and adrenin are supplied to the heart-lung preparation sugar consumption rises to about four times the former amount (Patterson and Starling, 1913), and that dogs exhausted by running can be made to continue (i.e., using sugar in their muscles) and will put forth from 17 to 44 per cent additional energy if they are given subcutaneously small doses of adrenin (0.02–0.04 mgm. per k., sometimes repeated) but not if a large dose (0.17 mgm. per k.—n.b., *less* than that used by the Coris) is given (Campos, Cannon, Lundin and Walker, 1929). Finally, although they mention a "compensatory mobilization of liver glycogen" as the cause of depleted hepatic stores after their enormous doses of insulin, they do not hint at the nature of the compensatory process, though they report low blood-sugar levels which would set in action the sympathico-adrenal apparatus. For these various reasons the views advanced by Cori and Cori seem not to warrant a surrender of the well established conceptions of the action of adrenin and insulin.

emphasized. Because they exert osmotic pressure and do not ordinarily escape through capillary walls, they prevent the salts dissolved in the blood from passing freely into perivascular spaces and out from the body through the renal glomeruli (Starling, 1909). When Barcroft and Straub (1910) removed much of the blood from a rabbit, separated the corpuscles, and reinjected them suspended in an equal volume of Ringer's solution instead of plasma, so that the difference was merely a reduction of the colloid, urine secretion was increased *forty times*. The development of "shock"—engorgement of liver, spleen, kidneys, intestinal mucosa and lungs, with accumulation of fluid in the intestine—noted by Whipple, Smith and Belt (1920) when the plasma proteins were reduced to 1 per cent, tells the same story. But not only does homeostasis of the plasma proteins provide for homeostasis of the blood volume; at least one of them (fibrinogen) is, in case of hemorrhage, essential for preservation of the blood itself. The very existence of the fluid matrix of the body is dependent, therefore, on constancy of the proteins in the plasma—and usually they are remarkably constant in various conditions of health and disease.

Blood is the one tissue in the body from which protein can be quantitatively removed and its restoration then studied. When by plasmapharesis the plasma proteins are reduced from about 6 to about 2 per cent there is a prompt rise in their concentration within fifteen minutes, a more gradual restoration thereafter during the first twenty-four hours to about 40 per cent, and full recovery in two to seven days. It may be that the prompt rise is relative, due to escape of salt solution from the blood vessels, although arguments have been advanced that it results from emergency discharge of the proteins from storage (Kerr, Hurwitz and Whipple, 1918). The slower recovery seems certainly dependent on the liver, for the following reasons: 1. If the liver has been injured by phosphorus or chloroform, restoration of the plasma proteins is delayed. 2. Dogs with an Eck fistula may have no restoration for the first three days after plasmapharesis. And 3, fibrinogen, which usually is completely restored within twenty-four hours, is not thus restored if the liver is unable to act (Foster and Whipple, 1922, Meek, 1912).

The evidence that the liver is important for homeostasis of proteins in the blood plasma raises the question whether protein is stored there. Results obtained by histological and biochemical methods have agreed in supporting the conclusion that hepatic cells can carry reserve protein as well as reserve carbohydrate. The early observations of Afanassiew

(1883) that the liver cells of dogs given an abundance of "albuminates" increase in size and contain protein granules between the structural strands, have been confirmed by Berg (1914, 1922), by Cahn-Bronner (1914), by Stübel (1920) and by Noël (1923). In sum, these recent histological studies show that when animals are fed protein there appear in the hepatic cells fine droplets or masses, which react to Millon's reagent, which yield the ninhydrin reaction of a simple protein, which disappear on fasting, and which reappear on feeding protein or amino acids. The biochemical analyses by Seitz (1906), who found that in fed animals the total nitrogen of the liver in relation to that in the rest of the body is from two to three times as great as in fasting animals, have been supported by the results obtained by Tichmeneff (1914). He starved mice for two days, then killed half of them and after giving the others an abundance of cooked meat killed them and compared the livers of the two groups. Expressed in percentage of body weight, the livers of the meat-fed animals increased about 20 per cent, with the hepatic nitrogen content augmented between 53 and 78 per cent.

Although the experiments on homeostasis of plasma proteins indicate that the liver is an important source of these materials in case of need, and although the testimony cited above would justify consideration of the liver as a storage place for protein, the modes of storage and release are almost wholly unknown. Stübel (1920) did, indeed, observe that the small protein droplets or masses in the hepatic cells could be greatly reduced by injecting adrenin subcutaneously. If these masses help to supply essential protein elements for blood clotting, as the dependence of fibrinogen on the liver would imply, their liberation by adrenin and by conditions which would excite the sympathico-adrenal apparatus might account for certain phenomena of faster clotting. Coagulation is more rapid after adrenin injections (see Cannon and Gray, 1914; La Barre, 1925; Hirayama, 1925), after splanchnic stimulation (Cannon and Mendenhall, 1914), or after large hemorrhage which calls the sympathetic into action (Gray and Lunt, 1914), but only if the blood is allowed to flow through the liver and intestines. In this category also is the very rapid clotting of blood taken at the height of the hypoglycemic reaction (Macleod, 1924), when sympathico-adrenal activity is maximal.

It is quite possible that protein is stored in other places than the liver, and also that the thyroid gland is an important agency for controlling both storage and release. Boothby, Sandiford and Slosse (1925) have reported that with a uniform nitrogen intake a negative nitrogen balance

exists while thyroxin is establishing a new higher metabolic level. After its establishment there is a smaller deposit of nitrogen in the body. Now if thyroid dosage is stopped (while the uniform nitrogen intake continues), a positive balance obtains until a new lower metabolic level is reached, i.e., more nitrogen is deposited. These effects are much more marked in a person afflicted with myxedema than in a normal person. Indeed, as Boothby has suggested, the "edema" of myxedema may be an abnormal amount of deposit protein in and beneath the skin. The efficacy of thyroid therapy, previously noted, in reducing the increased proteins of the plasma and the albumin of the tissues, in cases of myxedema, supports the view that the thyroid gland is somehow associated with protein regulation and metabolism.

Although the foregoing review has brought out the primary importance of homeostasis of the proteins of the plasma for maintaining the volume and character of both the intravascular and extravascular fluid matrix of the organism, and for protecting the organism against loss of the essential part of the matrix—the blood—, it has revealed also how much still needs to be learned. Here, as with other useful material, constancy is attained by storage, which stands between plenty and need, and in this respect the liver plays an important rôle. The sympathico-adrenal apparatus seems to influence release from storage, and also varying activity of the thyroid gland may be determinative. Are special agencies required to manage the laying by of the reserves? We do not know.

Fat. According to Bloor (1922) the concentration of fat, cholesterol and lecithin in the blood is fairly constant in the same species of animals, but may differ greatly in different species. As is well known, ingestion of fat produces an "alimentary lipemia" which may cause the fat content of the blood to rise as high as 3 per cent in the dog and 2 per cent in man. A relatively large increase in the fat content of the blood appears to be without serious consequence. In pathological states —e.g., in diabetes—the lipemic percentage may rise to 10, 15 and even to 20 per cent without producing obvious symptoms. On the other hand the normal blood fat is remarkably persistent. Carbohydrate and protein alone may be fed for considerable periods without reduction of the lipemic level, and fasting for short periods may actually be accompanied by a rise (Schulz, 1896), although after two weeks of fasting the level may undergo a slow fall. Whether total absence of fat from the blood could be produced, and if so, whether that condition would be attended by disturbances, are questions yet to be answered.

The constancy of the lipemic level for many days in spite of relative or complete starvation implies that there is a governing agency which brings the fat from storage into the blood stream. As Lusk (1928, p. 107) has remarked, "The length of life under the condition of starvation generally depends upon the quantity of fat present in the organism at the start." Fat is stored in the liver, if carbohydrate is not fed (Rosenfeld, 1903); it is also stored under the skin, beneath serous coats (e.g., around the kidneys), in the omentum, and between and in the muscle fibres. What leads to fat storage in some individuals to a greater extent than in others is unknown. In hypothyroidism there may be a generally diffused obesity, an obesity which rapidly disappears under thyroid therapy. A slight scratch in the surface of the brain stem between the infundibular process and a mammillary body produces adiposity (Bailey and Bremer, 1921), as does a tumor or other lesion of this region. Grafe (1927) cites instances of unilateral hypertrophy or atrophy of fatty tissues and suggests that the disposal of fat is under a sympathetic control managed from the hypothalamic region. It is pertinent to note that kittens allowed to live after unilateral sympathectomy until they have doubled their weight, have no demonstrable differences in the amount or distribution of the fat on the two sides of the body (Cannon, Newton, Bright, Menkin and Moore, 1929).

If the regulation of fat storage is obscure, the regulation of its release is even more so. When fat is needed for maintaining the energies of the body it is removed from adipose tissue until the fat cells are practically empty. Yet, even when death from starvation occurs, the fat content of other tissues may not be very different from normal (Terroine, 1914). What causes the fat to move from the adipose stores is not known. Lusk's remark, that "the fasting organs attract fat from the fat deposits of the body, and it is brought to them in the circulating blood," was probably not intended to be explanatory, and it is not. Possibly the reversible reaction mediated by lipase, as described by Kastle and Loevenhart (see Loevenhart, 1902), may be an important factor in maintaining homeostasis of the lipemic level—the enzyme favoring storage when the level is raised and favoring release when the level falls. But on these points more information is desirable.

Calcium. The special and diverse uses of calcium—for the growth of the skeleton and teeth, for the repair of broken bone, for the maintenance of proper conditions of irritability of nervous and muscular tissues, for the coagulation of blood, and for the production of serviceable milk—render it a highly important element in the bodily economy. Like

sugar and protein and fat, calcium may be in great demand on exceptional occasions. Under such circumstances, however, the amount in the blood must not be much reduced, for serious consequences ensue. As previously noted, there is normally a homeostasis of calcium in the blood at approximately 10 mgm. per cent. If the blood calcium is lowered to less than 7 mgm. per cent, as may be done by removal of the parathyroid glands (without change in the percentage of sodium and potassium), or by injection of sodium citrate, twitchings and tetanic convulsions occur, with a severity measured by the degree of deficit of available calcium; and these symptoms are quickly relieved by injecting a soluble calcium salt sufficient to restore the normal percentage (MacCallum and Voegtlin, 1909; MacCallum and Vogel, 1913; Trendelenburg and Goebel, 1921). On the other hand, if the blood calcium is raised above approximately 20 mgm. per cent, by injection of parathyroid extract, profound changes are produced in the blood—the viscosity is greatly increased, the osmotic pressure rises, the blood phosphates are doubled, and there are four times the normal amount of non-protein and urea nitrogen—conditions associated with vomiting, coma, and a failing circulation (Collip, 1926). Obviously homeostasis of blood calcium is of capital importance.

As in the homeostasis of other materials, that of calcium is made possible by storage, built up in times of abundance and utilized in time of need. The recent studies of Bauer, Aub and Albright (1929) have demonstrated that the trabeculae of the long bones are easily made to disappear by a persistent diet deficient in calcium and by growth, and that they are readily restored by feeding a calcium-rich diet. The trabeculae serve, therefore, as a storehouse of conveniently available calcium.

How the homeostasis of calcium is regulated has not been determined. The following evidence associates the parathyroid glands with the regulation: 1. Partial or complete removal of these glands results in a lowering of the calcium content of the blood, as mentioned above, and in a defective deposit of dentine in growing teeth and in a defective development of the callus about a bone fracture (Erdheim, 1911). 2. A diet poor in calcium induces parathyroid hyperplasia (Marine, 1913; Luce, 1923); pregnancy and lactation do likewise, without, however, reduction of the calcium percentage in the blood. 3. Diseases characterized by defects in calcification of bone—e.g., rickets and osteomalacia—are attended by hypertrophy of the parathyroid glands (see Strada, 1909; Weichselbaum, 1914). And 4, implantation of parathyroids in a parathyroidectomized

rat restores the power to deposit dentine having a normal calcium content (Erdheim, 1911). But *how* the parathyroids control calcium homeostasis—whether they act directly or are stimulated by nerves, whether they act alone and by increased or decreased activity effect storage or release, or whether they coöperate with other agencies perhaps antagonistic—all this still needs investigation.

The pharmacodynamic action of thyroxin seems to involve the thyroid as well as the parathyroid glands in calcium metabolism (Aub, Bauer, Heath and Ropes, 1929). Administration of thyroxin greatly increases the calcium losses in urine and feces whether persons are normal or myxedematous. There is evidence also that in hyperthyroidism the bones show osteoporosis and that calcium excretion is much augmented. Possibly the parathyroids serve for deposit and the thyroids for release of calcium—thyroxin raises the blood calcium in a low-calcium tetany. Such hints, however, must be regarded with suspicion until put to test, for, as shown in the experiments on the action of adrenin and insulin, mentioned above, powerful pharmacodynamic agents given in doses exceeding the physiological range can produce complicated and indirect effects.

The homeostatic functions of hunger and thirst. In the foregoing discussions storage has been emphasized as a regulatory mediation between supply and demand. Back of storage, however, and assuring provisions which can be stored, are powerful motivating agencies—appetites and hunger and thirst. Because of pleasurable previous experiences with food and drink appetites invite to renewal of these experiences; thereby material for the reserves is taken in. If the reserves are not thus provided for, hunger and thirst appear as imperious stimuli. Hunger is characterized by highly disagreeable pangs which result from strong contractions of the empty stomach—pangs which disappear when food is taken (Cannon and Washburn, 1912; Carlson, 1916). Thirst is an uncomfortable sensation of dryness and stickiness in the mouth, which can be explained as due to failure of the salivary glands (which need water to make saliva) to keep the mouth moist; when water is swallowed and absorbed they, as well as the rest of the body, are provided with it and since they can consequently moisten the mouth, the thirst disappears (Cannon, 1918). By these automatic mechanisms the necessary materials for storage of food and water are assured.

Overflow. Previously, in relation to the homeostasis of blood sugar, the use of overflow as a means of checking an upward variation of constituents of the blood has been mentioned. Not only excessive sugar,

but excessive water, excessive sodium and potassium and chloride ions are discharged by the kidneys. In accordance with the modern theory of urine formation (Cushny, 1926), these are all "threshold substances." They are resorbed by the kidney tubules only in such relations to one another as to preserve the normal status in the blood. All in excess of that is allowed to escape from the body.

It is interesting to note that these substances are primarily stored by flooding or inundation. When these reserve supplies are adequate, however, the ability of the overflow factor to maintain homeostasis is marvelous. The feat reported by Haldane and Priestley (1915) of drinking 5.5 liters of water in six hours—an amount exceeding by one-third the estimated volume of the blood—which was passed through the kidneys with such nicety that at no time was there appreciable reduction of the hemoglobin percentage, is a revelation not only of the efficacy of the kidney as a spillway but also of the provision in the body for maintaining a constancy of its fluid matrix.

The lungs as well as the kidneys serve for overflow. As is well known, a slight excess of carbonic acid in the arterial blood is followed by greatly increased pulmonary ventilation. Thus the extra carbon dioxide is so promptly and effectively eliminated that the alveolar air is kept nearly constant (Haldane, 1922). By this means provision is made for extra carbon dioxide to flow out from the blood over a dam set at a fixed level. In consequence, in usual circumstances, the hydrogen-ion concentration of the blood is fairly evenly maintained, and the harmful effects of an excessive shift in the alkaline or acid direction is avoided.

HOMEOSTASIS BY REGULATING PROCESSES. There are steady states in the body which do, indeed, involve the utilization of materials, but which are so much more notably dependent on altering the rate of a continuous process that they can reasonably be placed in a separate category. We shall consider two of them, the maintenance of neutrality, and the maintenance of a uniform temperature (in homeothermic animals). The physiological adjustments involved in these processes are so commonly known that a mere outline of them, without detailed description or many references, will be sufficient to illustrate the mode of regulation.

Maintenance of neutrality. The importance of confining the changes in the hydrogen-ion concentration of the blood to a narrow range has already been emphasized. This concentration is determined by the ratio, H_2CO_3:$NaHCO_3$, in the blood. On going to a high altitude the tension of carbonic acid is lessened, the ratio is lowered and the pH rises.

Under these circumstances the blood alkali also is lessened until the pH is restored. And on returning to sea level the opposite process occurs and continues until there is a normal adjustment again, due, according to Y. Henderson (1925), to "calling an increased amount of alkali into the blood," a result probably attained, however, by the passage of acid elements from the blood into the tissues or the urine.

Back of these adjustments between the blood and the tissues, however, are the preventive measures which protect the blood from danger by anticipatory action. Acid metabolites are continuously being produced in the living cells and if allowed to accumulate in them these substances interfere with or prevent further action. Elaborate arrangements are ready in the organism to forestall that contingency. To be sure, the facilities for controlling non-volatile acid are limited. But it can be dealt with in a variety of ways. The lactic acid, for example, which is developed in muscular contraction, is in part promptly neutralized—the phosphocreatine recently discovered by Fiske and Subbarow (1929) appears to be capable of functioning in an extraordinarily effective manner in neutralizing lactic acid within the muscle cells. Another part of the acid is soon oxidized; and the rest is rebuilt into neutral glycogen. For continued effectiveness of all three of these methods of disposal there must be provided an adequate supply of oxygen. Although muscles, and probably other tissues as well, go into "oxygen debt" by acting in spite of accumulating lactic acid, that state is characterized by a diminished capacity to do work, great according to the debt, by a prescription on the amount of debt allowable, and by the definite requirement of ultimate payment. When non-volatile acid is burned to volatile carbonic acid, however, it is in a form which can be carried away and disposed of to an almost unlimited amount, with only slight change in the reaction of the blood. During vigorous muscular work as much oxygen as possible must be delivered. There is practically no storage of oxygen in the body. Air-breathing animals are surrounded by an ocean of oxygen—the problem is solely that of conveyance from the boundless external supply to the exigent tissues. For that purpose circulatory and respiratory processes must be greatly accelerated. Fortunately these adjustments, required to get rid of the volatile acid, are precisely those required to bring to the tissues the oxygen which serves to make the acid volatile and readily discharged.

In vigorous muscular effort the pulmonary ventilation may be increased from 6 liters per minute to 60 or 80 liters or more, due to the effects of acid in the respiratory center. Under these circumstances the

sympathico-adrenal system is active (Cannon and Britton, 1927) and it is altogether probable that thereby the bronchioles are dilated at a time when wider passageways would facilitate the to-and-fro movement of larger volumes of air. There is an ampler return of blood to the heart per minute, because of contraction of the splanchnic vessels, because of the pressures excited by the active muscles on capillaries and veins within them, and because of the pumping action of the diaphragm. Thus the heart receives a greater charge of blood and puts forth a greater amount per beat. And because of lessened vagal tone, increased tension on the venous side, and participation of the sympathetic accelerators, the heart, well charged, may beat twice as fast as it does at rest. With a much larger minute output from the heart and a constricted splanchnic area the arterial pressure is markedly raised. In the active muscles the arterioles are dilated and the closed capillaries are opened; and through these more numerous channels the high head of arterial pressure drives an abundant blood stream. Evidence indicates that the total circulation rate may be augmented as much as four times. But not only are the corpuscles utilized more effectively by being made to move faster, the *number* of corpuscles is increased by discharge from storage in the spleen (see Barcroft, 1926)—an effect which, like splanchnic constriction and cardiac acceleration, the sympathetic system helps to produce (see Izquierdo and Cannon, 1928). In the laboring muscles, where acid is being produced and where especially oxygen is needed, the excess carbon dioxide itself facilitates the unloading of oxygen from the corpuscles and also its own carriage away to the lungs. In these ways the local flow may be increased as much as 9 times and the oxygen delivery may be increased as much as 18 times what it is during rest (Bainbridge, 1923). Thus, in spite of the fact that in a short time more lactic acid by far can be produced by muscular work than could be neutralized by the buffers in the blood—a condition which must inevitably cause death—the reaction of the blood is altered to only a minor degree.

No more admirable example of homeostasis can be mentioned than that of the pH of the fluid matrix of the body. It is managed by accelerating and retarding the continuous processes of pulmonary ventilation and the flow of blood. The physico-chemical changes within the blood itself, which will not be considered in this article, greatly diminish the effects of slight variations in these physiological processes. The degree of respiration is largely influenced by the hydrogen-ion concentration in the cells of the respiratory center, but they in turn are

influenced by an increase of the concentration of carbonic acid in the blood. Again the disturbance brings its own cure, and as the concentration is lowered by the heavier breathing, the heavier breathing ceases. The adjustment of the circulation may be similarly managed. The faster heart, the vascular constriction (except in active areas), and the contracted spleen point to functioning of the sympathetic system. Even slight voluntary activity calls the system into service (Cannon and Britton, 1927), and asphyxia is a highly effective stimulus for it (Cannon and Carrasco-Formiguera, 1922). The centers for sympathetic control may be influenced like the respiratory center—acidity may develop in them as a consequence of oxygen-want or carbonic acid excess and the primary result may be stimulation. This suggestion is supported by the experiments of Mathison (1911), showing that asphyxia and also extra carbon dioxide in the respired air raise arterial blood pressure, and by the observation of Cannon, Linton and Linton (1924) that muscle metabolites bring into action the sympathico-adrenal system. In vigorous muscular work the remarkably close correlation between the adjustment of the respiratory and the circulatory apparatus to the needs of the organism might thus be explained,—though both systems are started into faster service by impulses incidental to a voluntary act, they might be maintained in the performance of their extra task by the increased hydrogen-ion concentration in the blood and later they would gradually return to their quiet routine functions because their extra activity had resulted in reducing the hydrogen-ion concentration to the resting level.

Maintenance of uniform temperature. The importance of uniform temperature in providing conditions favorable for a constant rate of the chemical changes in the body requires no emphasis. And the danger of a rise of temperature a relatively few degrees above the normal, as well as the depressant effect of a fall much below the normal, likewise is well recognized. For general considerations, to be discussed presently, it is pertinent, however, to mention briefly the changes which take place when the body temperature tends to rise or fall. If the change is in the direction of a rise, relaxation of peripheral vessels occurs, thus exposing warm blood to the surface where heat may escape to colder surroundings; or when that is ineffective, sweating takes place, the skin is cooled by evaporation, and the abundant blood flowing through the skin loses heat thereby. Polypnea plays a part similar to sweating, and is especially serviceable in animals not well provided with sweat glands. If, on the other hand, the change is in the direction of a fall, there is a constriction of peripheral vessels and an erection of hairs and feathers

which enmesh near the skin a layer of poorly conducting air; when these means of conserving heat do not check the fall of temperature, adrenin, capable of increasing heat production, is set free in the blood stream (Cannon, Querido, Britton and Bright, 1927); and when the heat thus produced does not suffice, shivering is resorted to as the final automatic protection against a temperature drop. This highly efficient arrangement for maintaining homeostasis of body temperature involves only an acceleration or retardation of the processes of heat production and heat loss which are constantly going on. The delicate thermostat which operates the regulation appears to be located in the subthalamus (Isenschmid, 1926; Rogers, 1920), and to be influenced directly by changes in the temperature of the blood (Kahn, 1904; O'Connor, 1919; Sherrington, 1924), and also reflexly (see Hill, 1921). The noteworthy features of the total arrangement, apart from its efficiency, are the varieties of the devices for homeostasis, their appearance in a sequence of defences against change, and the close involvement of the sympathetic system in the conservation, production and dissipation of heat.

THE RÔLE OF THE AUTONOMIC NERVOUS SYSTEM IN HOMEOSTASIS. The homeostatic regulators act automatically. Although skeletal muscles and the diaphragm are, of course, under control of the cerebral cortex, their functions in the regulation of temperature (shivering) and neutrality (faster breathing) are managed low in the brain stem. And for the most part the regulators are not under voluntary government. Commonly the autonomic system, or that system in coöperation with endocrine organs, is called into action. Illustrations of these facts are seen in the vago-insular and the sympathico-adrenal influences on the glycemic level, the vagal and sympathetic effects on the heart rate and the sympathetic effects on blood vessels during vigorous muscular effort, and the sympathico-adrenal function in accelerating heat production when the body temperature tends to fall.

The facts just mentioned emphasize a distinction long recognized between the "voluntary" and the "involuntary" or "vegetative" functions of the nervous system. It is desirable to remove from physiology terms having psychological and botanical implications. The two relations of the nervous system—towards the external and towards the internal environment—naturally suggest that distinctions should be based on these opposite functions. The "voluntary" or cerebrospinal system, elaborately outfitted with exteroceptors and with muscles which operate bony levers, is arranged for altering the external environment or the position of the organism in that environment by laboring,

running or fighting. These may appropriately be regarded as *exterofective* activities, and the "voluntary" system therefore as the exterofective system. The exterofective activities, however, must produce coincident changes in the internal environment—e.g., utilizing blood sugar and discharging into the blood acid waste and extra heat. Under these circumstances the "involuntary" nervous system plays its part by acting on the heart, smooth muscles and glands in such ways as will preserve the "fitness" of the internal environment for continued exterofective action. This interofective function of the "involuntary" nervous system justifies calling it the *interofective* system. Inactivity of the exterofective system establishes a basal state for the organism, because minimal functioning of that system is accompanied by minimal functioning also of the interofective system. Exterofective action is reflected in interofective action, which rises as the internal disturbance rises and subsides as the disturbance subsides.

The interofective system has been referred to thus far as if it were single instead of consisting of three divisions, with distinctive general functions. These functions were summarized by Cannon (1914) as follows—the sacral, a group of reflexes for emptying hollow organs which become filled; the cranial, a series of reflexes protective and conservative and upbuilding in their function; and the mid- or sympathetic division, a mobilizer of bodily forces for struggle. Similar views have been expressed by Hess (1926) who has recognized the "histotropic" function of the cranial division in promoting the welfare of the tissues, and the "ergotropic" function of the sympathetic division in operating to increase the facilities for doing work. The ideas developed in the foregoing discussion modify only slightly the views expressed in 1914. The emphasis is somewhat differently placed, to be sure, if the maintenance of conditions favorable for exterofective activity is regarded as the chief function of the autonomic system. Thus, although the sacral autonomic division has as one of its functions the perpetuation of the race, it is also serviceable in emptying the bladder and rectum of loads which might interfere with extreme physical effort—an interpretation which is consistent with the well-known effects of strong emotion (e.g., fear) in voiding these viscera as a preparation for struggle. Likewise, though the cranial division has other conservative functions it notably exhibits its conservative uses in providing and preserving the measures which are required to keep the fluid matrix constant when profound disturbance might occur: it gives the heart opportunity for rest and recuperation by checking its rate in quiet times, it promotes the gastro-intestinal move-

ments and excites secretion of the digestive juices and thereby assures the reserves of energy-yielding material, and it appears to be further useful through the vago-insular system in bringing into storage some of these reserves. These divisions, the sacral and the cranial, however, operate indirectly and somewhat remotely to protect homeostasis. It is the mid- or sympathetic division which acts directly and promptly to prevent changes in the internal environment; by mobilizing reserves and by altering the rate of continuous processes; as repeatedly noted in the foregoing pages, this division works to keep constant the fluid matrix of the body and therefore may properly be regarded as the special and immediate agent of homeostasis. The idea that the sympathetic division—or the sympathico-adrenal apparatus, for the nerve impulses and adrenin coöperate—serves to assure homeostasis, that for this purpose it functions reciprocally when the exteroceptive system functions, is not a fundamental modification of the "emergency theory" (Cannon, 1914a). Recent studies have shown that if emergencies do not arise, if marked changes in the outer world or vigorous reactions to it do not occur, the sympathico-adrenal apparatus is not a necessity and can be wholly removed without consequent disorder (Cannon, Newton, Bright, Menkin and Moore, 1929). Limitations appear when circumstances alter the internal environment; it is then that the importance of the sympathico-adrenal apparatus becomes evident. As has been shown above, however, this apparatus plays its rôle not only in preserving homeostasis during grave crises which demand supreme effort, but also in the minor exterofective adjustments which might change the fluid matrix of the body.

SOME POSTULATES REGARDING HOMEOSTATIC REGULATION. About four years ago Cannon (1925) advanced six tentative propositions concerned with physiological factors which maintain steady states in the body. It will be pertinent to consider them again now with reference to the foregoing discussion of homeostasis.

1. "In an open system such as our bodies represent, compounded of unstable material and subjected continually to disturbing conditions, constancy is in itself evidence that agencies are acting, or ready to act, to maintain this constancy." This is a confident inference—an inference based on some insight into the ways by which certain steady states (e.g., glycemia, body temperature, and neutrality of the blood) are regulated and a confidence that other steady states are similarly regulated. The instances cited in the previous pages have illustrated various agencies employed in the organism to that end. Although we do

not know how constancy of plasma proteins, lipemia and blood calcium, for example, is brought about, probably it results from as nice devices as those operating in the better known cases of homeostasis. Of course this realm of interest is full of problems—highly significant problems—inviting attempts at solution, and as they are solved the confidence expressed in the first postulate may be justified.

2. "If a state remains steady it does so because any tendency towards change is automatically met by increased effectiveness of the factor or factors which resist the change." Thirst, the hypoglycemic reaction, the respiratory and circulatory response to a blood shift towards acidity, the thermogenic functions, all become more intense as the disturbance of homeostasis is more pronounced, and they all subside promptly when the disturbance is relieved. Similar conditions probably prevail in other steady states. Of course, the state may not remain steady, as in pathological weakness or defect, and for that reason the postulate was made conditional. As Lotka (1925) has pointed out, this conditional statement, required for living beings and due to their lack of permanent stability, sharply distinguishes the proposal from the strict principle of Le Chatelier true for simple physical or chemical systems. Indeed, as Y. Henderson (1925) has remarked, the physiological and the chemical conceptions of equilibrium are quite different. "The one invokes energy to maintain itself, or if disturbed to recover . . . . the other in seeking balance only goes down hill dynamically."

3. "Any factor which operates to maintain a steady state by action in one direction does not also act at the same point in the opposite direction." This proposal, which should have been limited to *physiological* action, is related to the questions discussed in the footnote on p. 410. Does adrenin in physiological doses both discharge glycogen from the liver and increase glycogen storage there? Does insulin likewise act oppositely in relation to the hepatic glycogen reserves? In the footnote mentioned, reasons were given for not crediting the evidence for opposed action by a single one of these agents. An agent may exist which has an influence of a tonic type—a moderate activity—which can be varied up or down, and which can act at a given point in "high" concentration but not in a "low" concentration. The adrenal medulla, which is subject to control of opposed nervous influences (Cannon and Rapport, 1921), may be cited as an agent of that type.

4. "Homeostatic agents, antagonistic in one region of the body, may be coöperative in another region." The sympathico-adrenal and the vago-insular influences are opposed in action on the liver, but they

appear to be collaborators in their action on muscles, e.g., leading to effective use of sugar by muscle cells (Burn and Dale, 1924). Too little is known about the effects of these agents to permit this postulate to be of much significance at present.

5. "The regulating system which determines a homeostatic state may comprise a number of coöperating factors brought into action at the same time or successively." This statement is well illustrated in the arrangements for protection against a fall of temperature in which series of defences are used one after another, and also in the elaborate and complex arrangements for maintaining uniform reaction of the blood.

6. "When a factor is known which can shift a homeostatic state in one direction it is reasonable to look for automatic control of that factor or for a factor or factors having an opposing effect." This postulate is implied in earlier postulates. It is expressed as a reiteration of the confidence that homeostasis is not accidental but is a result of organized government, and that search for the governing agencies will result in their discovery.

The reader has had occasion to be impressed by the large gaps in our knowledge not only of homeostatic conditions but also of the arrangements which establish and maintain them. Repeatedly the phrase "is not known" has had to be employed. It is remarkable that features so characteristic of living beings as the steady states should have received so little attention. Innumerable questions remain to be answered. Little is known, for example, about the effective stimuli for such homeostatic reactions as are well recognized. Are there receptors which are affected in blood-sugar regulation or are the regulatory factors worked by direct action on cerebral centers? Again, there are homeostatic agencies which were not considered above, such as the extra erythrocytes produced in organisms living at high altitudes, the thicker hair growth during prolonged cold weather, and also steady states which have not been mentioned, such as the stabilization of phosphorus in relation to calcium, the evidence from constancy of basal metabolism that there is constancy in the thyroxin content of the blood, indeed the evidence from other steady states (as weight, and sex character) that other endocrine products are uniformly circulating—the questions presented by these and many other reactions which are serviceable in preserving uniformity in the fluid matrix offer a fascinating field for research.

In the two preceding sections the functions of the divisions of the autonomic system in relation to homeostasis were defined and some

postulates regarding homeostasis were presented, not with the idea that the statements should be taken as conclusive but rather that they might prove suggestive for further investigation. Indeed, that point of view should be recognized as prevailing throughout this review. It is the writer s belief that the study of the particular activities of the various organs of the body has progressed to a degree which will permit to a greater extent than is generally recognized an examination of the interplay of these organs in the organism as a whole. Their relations to their internal environment seemed to offer a suggestive approach to a survey of their possible integrative functions. In such a venture errors are sure to creep in which must later be corrected, and crude ideas are sure to be projected which must later be refined. Though the present account of agencies which regulate steady states in the body is likely to prove inadequate and provisional, there is no question of the great importance of the facts of homeostasis with which it deals. This account may at least serve to rouse interest in them and their importance. The facts are significant as outstanding features of biological organization and activity. They are significant also in understanding the complex disorders of the body, for in a state normally kept regular by a group of coöperating parts, full insight into irregularity is obtained only by learning their mode of coöperation. Again, effective methods of attaining homeostasis are significant in comparison with the methods in systems where steady states are not yet well developed; the regulation of homeostasis in higher animals is probably the result of innumerable evolutionary trials, and knowledge of the stability which has finally been achieved is suggestive in relation to the less efficient arrangements operating in lower animals and also in relation to attempts at securing stability in social and economic organizations. Finally, continued analysis of biological processes in physical and chemical terms must await a full understanding of the ways in which these processes are roused to perform their service and are then returned to inactivity. Indeed, regulation in the organism is the central problem of physiology. For all these reasons further research into the operation of agencies for maintaining biological homeostasis is desirable.

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