CHAPTER I

"LA FIXITÉ DU MILIEU INTÉRIEUR EST LA CONDITION DE LA VIE LIBRE." (CLAUDE BERNARD)

INTRODUCTORY

Of the principles which govern the physiological processes of the human body, that of the fixity of its internal environment has been as thoroughly established as any. Within the last twenty years works of first-rate importance by Haldane, Henderson and Cannon have all dealt with the subject. Great progress has been made in our understanding both of the mechanisms which secure the constancy of the internal medium and of the exactness with which these mechanisms operate.

The principle enunciated by Claude Bernard, if dressed up in modern language, seems to me just a little grotesque. To say that the temperature of the body is adjusted to the tenth part of 1 per cent. on the absolute scale, or the hydrogen-ion concentration of the blood to the hundredth part of a *p*H so that the organism may obtain a free life, is surely to make a very ill-balanced statement. The accuracy of the first clause contrasts almost comically with the vagueness of the second.

Indeed this "up-to-date" version of Claude Bernard's statement constitutes almost a challenge. In general, the "end" is more important that the "means", therefore it seems at least desirable to make some effort towards arriving at a conception of the liberty of life to be attained by the fixity of the *milieu intérieur*.

There are two obvious avenues of approach to the problem.

It is instructive to study the efficiency attained in forms of life humbler than those endowed with a circulating medium of constant properties, to see how nature has ensured some degree of efficiency up to that point, ascertaining if possible the mechanism which ensures constancy and from what that mechanism is developed.

The second avenue of attack is that of breaking down the constancy of the internal "environment", preferably in that form of

life—man—in which it is most highly developed, and noting the nature and degree of impairment which takes place.

To commence with, then, we may select certain physical and chemical properties of the blood which are maintained at an approximately constant value; we may endeavour to ascertain how this constancy was attained; we may then proceed to consider at what disadvantage, if any, the organism was, while as yet the internal circulating medium was variable.

Lastly, a word as regards the phrase "milieu intérieur": I do not regard the specialised hormones, such as adrenaline, as part of the general environment, nor do I include drugs. I have included sugar, possibly illogically, but it is very interesting.

HYDROGEN-ION CONCENTRATION

Every process of the living aerobic cell tends to alter the chemical composition of the medium in which the cell is situated in at least two ways. The mere fact of life tends to deprive the environment of oxygen and, if that environment be fluid, to increase its hydrogen-ion concentration. Not only is every cell in the body putting carbonic acid into the blood, but also the reaction of the circulating medium may be affected by special circumstances proper to the specialised activities of certain cells. Those of the pancreas when thrown into activity abstract alkali, and the oxyntic cells of the stomach abstract acid.

There is therefore every opportunity for the hydrogen-ion concentration of the internal environment to be inconstant. Yet in man it remains remarkably constant. The variation given in current books and taken from van Slyke's figure (1921) is 7·0–7·8 *p*H, *i.e.* roughly 1–5 gm. in 10^8 litres—about a fivefold variation. It is unnecessary to stress the smallness of the absolute quantity, it is equivalent to 1–5 gm. of hydrogen spread over the total volume of plasma of all the people in the United Kingdom, or about half the people in the United States. Yet that is the variation for the extreme limits of human life, the variation as between fatal coma and fatal convulsions. The concentration of hydrogen ions in the plasma of a healthy person is regulated about five times as exactly.

The data are given graphically (Fig. 1) by Arborelius and Liljestrand (1923).

From rest up to work involving 50 litres per min. oxygen intake (945 kg. metres per min.), the alteration in hydrogen-ion concentration of the blood is given as from *p*H 7·33 ($cH = 4{\cdot}8 \times 10^{-8}$) to *p*H 7·26 ($cH = 5{\cdot}5 \times 10^{-8}$) for the average value obtained from determinations of the two authors.

Similar figures are given by Dill, Talbott and Edwards (1930) in Table I.

The amount of work done was of the same order. The extreme case was that of W. C., who did work corresponding to a total ventilation of 82 litres per min. The alteration in the hydrogen-ion concentration of his blood was from $cH = 3{\cdot}6 \times 10^{-8}$ to $cH = 5{\cdot}2 \times 10^{-8}$, a proportional increase of 1 : 1·45.

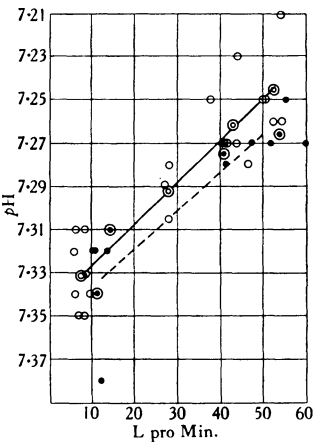

Fig. 1. Ordinate = reaction of blood, abscissa = ventilation in litres per minute; ○, individual observations on M. A.; ⊙, average of observations on M. A.; ●, individual observations on G. L.; ⊙, average of observations on G. L.

Table I

Subject	*p*H		Change of *p*H	Ventilation per kg. of body weight (litres)
	Rest	Work (running 20 min.)		
D. B. D.	7·42	7·39	−0·03	0·58
P. F. P.	7·44	7·32	−0·12	0·80
A. A. McC.	7·42	7·37	−0·05	0·72
J. H. T.	7·40	7·44	+0·04	0·67
W. C.	7·44	7·29	−0·15	1·19
O. S. L.	7·41	7·31	−0·10	0·67
J. L. S.	7·39	7·37	−0·02	0·72
H. T. E.	7·39	7·30	−0·09	0·59
A. V. B.	7·40	7·40	0·0	0·70
W. J. G.	7·36	7·38	+0·02	0·81
Average	7·41	7·36	−0·05	0·75

Instead then of a possible alteration of 500 per cent. in the viable limits, the variation even in heavy exercise is only 45 per cent.

A very interesting point in the estimations of Dill, Talbott and Edwards is the range of normals. They lie between pH = 7·36 (cH = $4{\cdot}4 \times 10^{-8}$) and pH = 7·44 (cH = $3{\cdot}6 \times 10^{-8}$), a variation of range of only 22 per cent. This range is scarcely greater than that of the maximal daily variation in a single individual as found by Cullen and Earle (1929). The blood may become more alkaline towards evening to the extent of seven-hundredths of a pH.

Comparison of the Constancy in Man with that in Lower Animals

With these figures let us contrast those from the fish. Determinations, kindly given me by Dr Hall and Dr Gray of Duke University from the blood of the scup, taken at rest, showed a variation in the hydrogen-ion concentration of the blood between cH of 3×10^{-8} and of $2{\cdot}5 \times 10^{-7}$, *i.e.* 100 : 833, a variation not of 22 per cent. but of 800 per cent. The extreme limits of hydrogen-ion concentration in the blood of sub-mammalian forms are given differently by different authors and are quite obscure. Rohde (1920) believes that frogs normally have a pH which varies from 6·32 to 7·13, and that if fed on boric acid it may fall within 10 minutes to 4·2, while if fed on soda it will rise to 8, *i.e.* a ten-thousandfold variation. These figures, however, have not been substantiated by Mrs Hertwig-Hondru (1927), who placed the variation within much narrower limits (7·36 to 7·59). Even these are much larger variations than for man when at rest normally.

The following figures (Table II) are given for the hydrogen-ion concentration in the insects cited (Glaser, 1925):

Table II

	pH	
Grasshopper	7·2	7·6
House-fly	7·2	7·6
Cockroach	7·5	8·0
Malacosoma	6·4	7·4
Bombyx mori	6·4	7·2
General range	6·4	8·0

The evolution of the whole mechanism which participates in the regulation of the hydrogen-ion concentration of the blood is a matter of extraordinary interest. It concerns primarily the kidney, the blood itself, and the respiratory centre.

The blood. The evolution of the blood has been such that in general the more highly developed the form of life the less does the addition of a given quantity of acid or alkali alter the hydrogen-ion concentration, that is to say the more perfectly is the blood buffered. This is only true in a very rough sense. For this purpose the animal kingdom may be divided into great blocks: (1) the sub-vertebrate forms, (2) the cold-blooded vertebrates, and (3) the warm-blooded vertebrates, the birds and mammals.

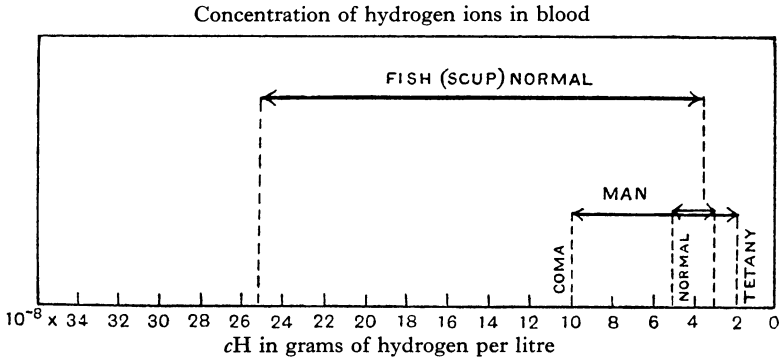

Fig. 2

Moreover, there are three principal ways in which the addition of acid to the circulating fluid is prevented from suddenly and unduly altering the hydrogen-ion concentration of the same:

(1) By the buffering of the fluid and the tissues in contact therewith.

(2) By the excretion of acid or retention of alkali by the kidney (and the production of ammonia).

(3) By the excretion of carbonic acid by the lung.

It will at once strike the reader that the first method is not quite "on all fours" with the second and third; the first is rather a method for the mitigation or "evasion" of the effects of the

addition of acid and alkali, than for the regulation of the number of hydrogen ions present. This distinction is one which I will refer to; here it is not of great importance, but please note it for future reference.

In the circulating fluid in such situations as the water vascular system of the sea urchin there can be very little buffering (see Fig. 3). In many of the sub-mammalian forms the blood is buffered to quite an appreciable extent. This buffering is associated with the acquisition of some sort of pigment for the purpose of carrying oxygen, the two chief of which are haemoglobin and haemocyanin. Haemoglobin is of course found in considerable quantities in the blood of many worms, while haemocyanin is the prevalent respiratory pigment in the arthropods and molluscs.

It is not to be supposed that these pigments had originally any function in the blood other than that of carrying oxygen, if indeed they had any respiratory purpose whatever. But in each case it was desirable, in order that the pigment should be as useful as possible, that the oxygen should be capable of the most easy detachment in the situations in which it was most badly needed. Such situations would in the main be those in which carbonic acid or some other acid was likely to accumulate, and therefore it has come to pass that these two pigments have survived. The buffering action appears to be purely incidental, and indeed it is doubtful whether in such low forms of life there is any particular object in having the blood very highly buffered.

So far then as haemoglobin is concerned (and the evolution of the principal buffer is the evolution of haemoglobin), the consideration of buffering appears to have been somewhat of an afterthought, for recently Redfield and Florkin (1931) have discovered in a worm, *Urechis caupo*, a form of haemoglobin in which carbonic acid has no effect on the affinity of the pigment for oxygen.

Similarly, the most primitive form of haemocyanin, like its counterpart in the haemoglobin series, does not appear to have any value as a buffer. The oxygen affinity of the more complicated forms is affected by carbonic and other acids.

With the transition from the lower to the vertebrate forms came the next and indeed the final stage in the evolution of a highly

buffered internal medium for the body. That stage was the enclosure of the haemoglobin in corpuscles. It is not that corpuscles

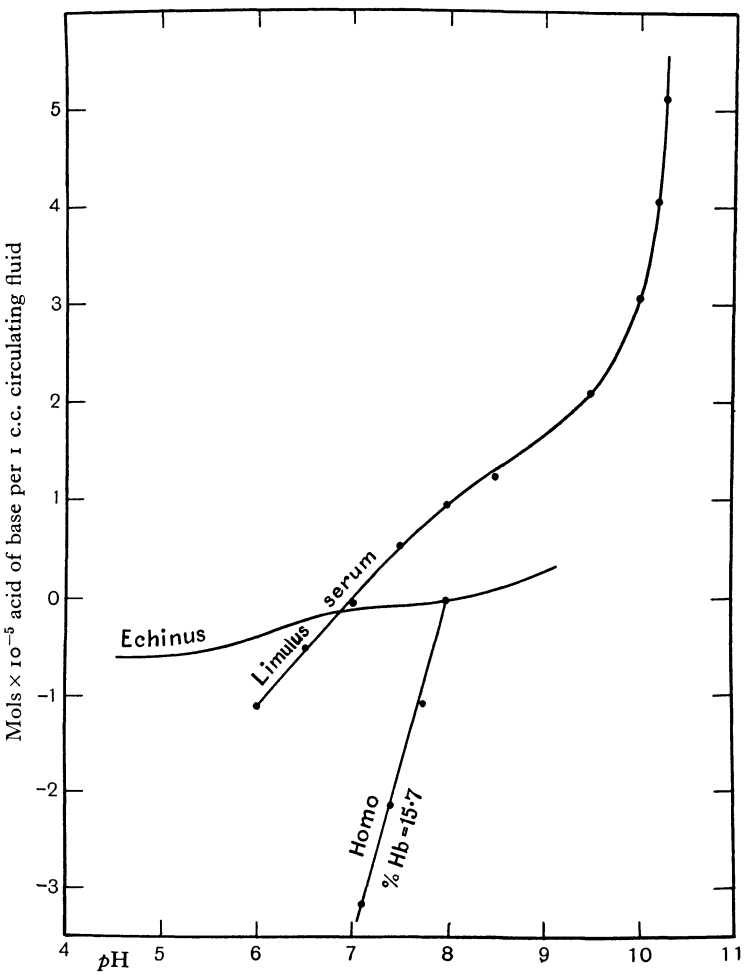

Fig. 3. Titration curves of blood of Man (after Terroux), of *Limulus* (after Redfield) and of *Echinus* (after Pantin).

which contain haemoglobin are unknown in lower forms of life, but putting on one side the exact phylogenetic status of *Amphioxus*

—the vertebrate does, as the invertebrate did not, systematically and extensively use intracorpuscular haemoglobin as its oxygen carrier, and in so doing it "amplifies" the value of that pigment to a remarkable degree. The merit of corpuscles as amplifiers has been pointed out with such emphasis and explained with such thoroughness, that it would be superfluous for me to say much. Commencing with Hamburger and ending with the exposition given in the Henderson nomograms, the mechanism is set out. The corpuscle wall is permeable to acid and impermeable, or according to J. Mellanby less permeable, to base; therefore when acid is added to the plasma, it or its equivalent passes in large measure into the corpuscle, there to be dealt with by the haemoglobin-bicarbonate system; in so doing it leaves the reaction of the plasma relatively unchanged.

There is no record of haemocyanin in vertebrate blood, nor is there any record of its being contained in corpuscles. Why, we do not know. The mechanism by which haemoglobin is held in corpuscles is as yet unexplained. Possibly haemocyanin does not possess the chemical qualities which form the basis of such a system. It is known for instance that if the corpuscles of many animals be centrifuged until the mass becomes transparent, and if then any haemolytic agent be added to the jelly, the haemoglobin will separate out at once in crystals. Yet it is clear from the nature of the dissociation curves that the haemoglobin behaves in the corpuscle as though it were in solution. According to Svedberg (1926) the molecular weight of haemocyanin is about 2,000,000, which would be about thirty times as great as that of haemoglobin. It appears to differ in different forms, being about 2,000,000 for *Limulus* and 5,000,000 for the snail. A molecule so gross may well be incapable of masquerading as a solution in concentrations in which it would ordinarily crystallise.

By the time we have reached the level of the lower vertebrates all the elements in the buffering of blood have been laid down. As regards buffering there is little difference in kind between frog's blood and that of an anaemic human being. The transition from the cold-blooded to the warm-blooded vertebrate is a matter of degree.

The preliminary step is that of producing an internal medium into which acid and alkali can be put with but a disproportionately small alteration in reaction; the finer points as regards the regulation of the hydrogen-ion concentration depend not upon the blood itself but upon the organs of excretion. As the excretion involves both substances in aqueous solution and carbonic acid gas the organs in question are the kidneys and the lungs respectively.

The kidney. The primitive organ for the regulation of hydrogen-ion concentration as of other things in the blood is the kidney.

I suppose the great problem which the kidney presents is: How can it regulate the blood concentration of so many substances simultaneously? Whatever the answer to this question may be, it would *a priori* not be surprising if in the effort to do a great many things at the same time, the kidney did each one of them a little less perfectly than would otherwise be the case. That may be the reason why, if the composition of the blood is altered by the injection of acid or alkali, a long time elapses before the previous *status quo* is entirely re-established.

Suppose there are 4·8 litres of blood in the body, and that the volume of blood which traverses the kidney is 2 c.c. per gm. per min., and the weight of the kidneys 320 gm., 640 c.c. of blood per minute will pass through these organs, or 13 per cent. of the blood in the body. Suppose (1) that a gram of some foreign substance, such as bicarbonate, is injected into the blood and only escapes therefrom in the kidney, and (2) that the blood leaving the kidney is entirely freed from this material, in 5 min. the amount in the blood will be halved, and in 20 min. there will only be about one-tenth of a gram remaining.

In point of fact the above assumptions do not hold. In general, material which can be eliminated by the kidney can also pass into the tissues, to be returned later to blood flow.

We may, however, "bracket" by making an assumption equally extravagant, namely that the alkali immediately diffuses all over the body, so that the whole body gets into equilibrium before any alkali is secreted; but let us retain the assumption that the kidney is as efficient as possible and that the blood emerged in the renal vein normal. On the above assumption, as the flow through the

kidney per minute represents about 1 per cent. of the body weight (the water in that blood will be rather more than 1 per cent. of the water in the body) the excess of bicarbonate should be reduced to half in about an hour and to 10 per cent. of its amount in something of the order of 4 hours. One might expect then that the actual time for the elimination of alkali would be somewhere between that given by the assumption that all the alkali stayed in the blood and that all diffuses at once into the tissues and that in a time which was not less than 20 min. nor more than 4 hours the excess of alkali would be reduced to one-tenth of its original amount.

But in point of fact nothing of the kind occurs. Davies, Haldane and Kennaway (1920) showed that when a considerable amount of alkali (57½ gm. of sodium carbonate, within about 20 min.) was ingested, after 9 hours the kidney was still eliminating sodium carbonate in large quantities; after about 12 hours the elimination ceased.

It would seem that our second assumption must go too, as the kidney does not reduce the venous blood to normality and is therefore not as efficient as it might conceivably be.

The kidney apparently works—so far as alkali is concerned—on quite different principles. The authors quoted made the illuminating observation that at best the kidney produces (presumably because it can do no more) urine of a certain limiting concentration of alkali (about 2·5–2·8 per cent.). Any further increase in the elimination of alkali beyond that obtained by raising the content of the normal volume to 2·8 per cent. must be effected by increasing the elimination of water. In that case either the concentration or the amount of every soluble substance in the body becomes affected indirectly. Short of knowing that the kidney cannot eliminate urine of more than a certain alkaline content we are very much in the dark as to any quantitative statement regarding the factors which regulate the elimination of alkali by the kidney. There seems, however, to be good reason for supposing that the influence of the nervous system does not figure prominently as one of them.

Many researches have of course been made upon the effect of the nervous system upon renal secretion, but none of them gives information as to the rate at which a given excess of alkali or acid is