

# Inevitability of Balance Restoration

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Prolonged imbalance between input and output of any element in a living organism is incompatible with life. The duration of imbalance varies, but eventually balance is achieved. This rule applies to any quantifiable element in a compartment of finite capacity. Transient discrepancies occur regularly, but given sufficient time, balance is always achieved, because permanent imbalance is impossible, and the mechanism for eventual restoration of balance is foolproof. The kidney is a central player for balance restoration of fluid and electrolytes, but the smartness of the kidney is not the reason for perfect balance. The kidney merely accelerates the process. The most crucial element of the control system is that discrepancy between intake and output inevitably leads to a change in total content of the element in the system, and uncorrected balance has a cumulative effect on the overall content of the element. In a living organism, the speed of restoration of balance depends on the permissible duration of imbalance without death or severe disability. The three main factors that influence the speed of balance restoration are: magnitude of flux, basal store, and capacity for additional storage. For most electrolytes, total capacity is such that a substantial discrepancy is not possible for more than a week or two. Most control mechanisms correct abnormality partially. The infinite gain control mechanism is unique in that abnormality is completely corrected upon completion of compensation.

**Key Words:** acid-base equilibrium; water-electrolyte balance; body composition; infinite gain control; external balance

Prolonged imbalance between input and output of any quantifiable element in a living organism is incompatible with life. The duration of imbalance varies, but eventually balance must be achieved in order to survive. This rule applies to any quantifiable element. Red cell destruction equals red cell production. Oxygen uptake equals oxygen utilization. Sodium intake must equal sodium output, and water intake must match water loss. Transient discrepancies occur regularly between input and output, between production and metabolism, and between uptake and utilization of various substances in the body. Yet, given sufficient time, balance is almost always achieved, because

prolonged imbalance is incompatible with life<sup>1)</sup>.

## Why is balance always restored?

The underlying mechanism that allows eventual restoration of balance is perfect and foolproof. For the restoration and achievement of balance of fluid and electrolytes in living organisms, the kidney is a central player, but the smartness of the kidney is not the reason for perfect balance. The kidney merely accelerates the process by utilizing a principle ubiquitous in nature, but it does not determine its ultimate outcome. The most crucial element

of the control system that results in ultimate balance between input and output is that discrepancy between intake and output of an element inevitably leads to a change in total content of the element in the system, and the uncorrected balance leads to a cumulative effect on the overall content of the element. When input is greater than output, the content increases. When output is greater than input, the content decreases. In a system with a limited capacity, an increase in content increases concentration, which would ultimately result in an increased output<sup>2)</sup>.

Capacity of any system is always limited. We often say, the sky has no limit. Yet, there is a limit to the capacity of atmospheric air volume into which various gaseous elements are contained. Carbon-14 is a radioactive isotope of carbon 12 (98.9%) and carbon 13 (1.1%). The amount of carbon 14 in atmosphere is extremely minute, about one part in a trillion. The ratio of C-14 to C-12 is fairly constant, because the amount of C-12 produced is exactly equal to the amount disintegrated. C-14 has a half life of 5,730 years. Incorporation of atmospheric carbon into an organic molecule by biosynthetic mechanisms incorporates C-14 and C-12 at the same ratio in the atmosphere. Once the organic matter stops exchanging with the atmospheric CO<sub>2</sub>, the ratio of C-14 to C-12 decreases progressively with time because of decay of the radioactive C-14<sup>3)</sup>. Using this principle, C-14 has been widely used to determine the age of organic matters of ancient past. One can, for example, determine, by C-14 dating analysis of the sample of the mummy of Ramses II, whether the pharaoh really died some 3,200 years ago. A famous example of C-14 dating was the determination of the real age of the Shroud of Turin (claimed to be the burial shroud of Jesus) to be about 600 to 700 years old.

The amount of C-14 in the atmosphere remains constant by the same mechanism to achieve the external balance of other quantifiable elements in nature as well as in the living organism. C-14 is produced by cosmic rays interacting with nitrogen-14 in the upper troposphere and stratosphere by substitution of one neutron for a proton, the nuclear reaction made possible by the enormous energy level of

cosmic rays. Once produced, C-14 must be contained in a system of a limited capacity, i.e., atmospheric air space, and the amount of C-14 determines the amount of disintegration. As explained earlier, the effective air volume into which C-14 or any air molecule will be contained is finite, because gravity prevents distribution into a larger volume; the air volume is about  $3.83 \times 10^{21}$  L (3.83 zetta L). C-14 contained in this air disintegrates at a constant rate with a half life of 5,730 years<sup>3)</sup>.

The amount of C-14 production has been fairly constant, because the amount of cosmic rays entering the earth is fairly constant. The amount converted back to nitrogen-14 by radioactive decay depends on the total amount of C-14. The amount created at the beginning of the creation of solar system was probably not the same as the amount decaying. If the amount created exceeded the amount decaying, the amount would be increasing steadily until the amount decaying equaled the amount created. What would happen if the amount of the cosmic ray radiation doubled, resulting in a two fold increase in the production of C-14? Initially, C-14 content in the atmosphere would increase. However, the increase would not be indefinite; the increased C-14 content would automatically increase the amount destroyed. When the C-14 content is doubled, the amount destroyed would eventually double, and a new equilibrium would be struck. A reduction in cosmic ray radiation would reduce the C-14 production, but again a new equilibrium would be struck at a reduced level of C-14.

For the past 10 to 20 years, a great deal of public concern has been voiced on the rising CO<sub>2</sub> content of the atmosphere and its impact on global warming. The rising CO<sub>2</sub> content implies that the amount of CO<sub>2</sub> added to the atmosphere is more than the amount eliminated from the atmosphere. Again, the discrepancy cannot and will not remain permanent, because the CO<sub>2</sub> content in the atmosphere has a positive influence on the rate of its removal from the atmosphere. The main source of CO<sub>2</sub> addition to the air is burning of fossil fuels (oil, gas, and coal). The total amount of CO<sub>2</sub> added is about 30 billion t/year. When this amount is added to the air volume of

$3.83 \times 10^{21}$  L, the  $\text{CO}_2$  concentration should increase at the rate of 3.98 ppm/year. The actual rise in  $\text{CO}_2$  content has been about 2 ppm/year in recent years<sup>4</sup>. The difference is what is removed from the atmosphere by diffusion into the ocean, and some washed by rain water again to enter the ocean. In the ocean  $\text{CO}_2$  is in equilibrium with bicarbonate and carbonate. As atmospheric  $\text{CO}_2$  content increases, the amount entering the ocean will increase progressively. When the amount removed equals the amount produced, again a new balance is reached, and  $\text{CO}_2$  content will be steady again. Of course, it is quite likely that by the time a new balance is achieved, the earth could be much warmer, with major ecological changes. Nevertheless, imbalance does not last forever.

Many substances in the human body utilize the same principles to reach the state of balance. For example, if creatinine production doubled in the absence of any change in glomerular filtration rate (GFR), serum creatinine would exactly double at which point, the renal excretion of creatinine would be twice the usual value. At this point a new balance is reached between production and excretion. For some substances, new balance is accelerated by various control mechanisms. For example, if sodium ( $\text{Na}^+$ ) intake is doubled, renal  $\text{Na}^+$  excretion will also double quite promptly, but this doubling of renal  $\text{Na}^+$  excretion does not require serum  $\text{Na}^+$  or total body  $\text{Na}^+$  content to double. Doubling of renal  $\text{Na}^+$  excretion requires only a slight increase in  $\text{Na}^+$  content of the body, less than 5% of total content, because of the excellent control mechanisms<sup>5,6</sup>. By the same token, a reduction in  $\text{Na}^+$  intake to 1/10 of the usual amount does not require  $\text{Na}^+$  content of the body to decrease 1/10 of normal in order to restore the balance<sup>1</sup>.

In the human body, the capacity for most substances is quite limited, and daily variations for most electrolytes are quite large in relation to the total body content. Furthermore, there is a limit to which the organism can tolerate the deviation in the content of elements. Survival of the organism demands existence of certain physiological mechanisms to accelerate the compensation processes to prevent deviation from occurring to a lethal level.

The following is the sequence of events in the control system. A certain amount of an element is contained in a compartment. If input of the element into the compartment exceeds its output, the content will increase. The higher content now affects to reduce input and increase output. As long as the discrepancy remains, the content will keep increasing, because the effect of discrepancy is cumulative. The higher content will have greater effects on input and output. The cumulative change stops only when input equals output. When input is less than output, the opposite sequence of events will ultimately restore the balance<sup>1</sup>.

Restoration of salt balance will be used as an example. A person in a state of  $\text{Na}^+$  balance ingests 10 g and excretes 10 g/day. Now, assume that a diuretic is started on this person. On the first day of diuretic therapy, salt output is 20 g/day, with net loss of 10 g of salt. The next day, although on the same diuretic dosage, salt excretion decreases to 15 g a day because the reduction in effective vascular volume caused by the previous day's net salt loss activates salt-retaining mechanisms such as the renin-angiotensin-aldosterone system and reduction of salt losing hormones. Still, the overall result is an additional negative balance of 5 g of salt. Although the negative balance is less on the second day, the cumulative loss standing now at 15 g is greater on the second day than on the first, and the effective vascular volume is lower. The lower effective volume reduces salt output further to 12 g/day on the third day, with an additional negative balance of 2 g. The overall cumulative loss is 17 g. As long as the salt output remains greater than salt intake, cumulative salt loss becomes larger and larger, albeit less steeply than before. Cumulative salt loss stops only when salt output equals salt intake. Indefinite salt loss is theoretically impossible, because the continued salt loss will ultimately cause such severe volume depletion that the person will become hypotensive, and salt excretion would stop completely<sup>7</sup>. Of course, before reaching such an extreme state, renal excretion of salt would decrease to a level equaling intake. In the example given, what causes restoration of balance is not the smartness of kidney or cleverness of humoral mechanisms.

For example, the  $\text{Na}^+$  balance would still be restored in the absence of aldosterone, in which case the person could be quite sick with dehydration when the balance is finally attained.

The same control mechanism explains why urinary excretion of potassium ( $\text{K}^+$ ) does not remain greater than intake in patients with primary hyperaldosteronism. With increased aldosterone,  $\text{K}^+$  output will initially exceed  $\text{K}^+$  intake. The resulting negative  $\text{K}^+$  balance causes hypokalemia, which in turn tends to reduce urine  $\text{K}^+$  excretion. As long as  $\text{K}^+$  excretion exceeds  $\text{K}^+$  intake, serum  $\text{K}^+$  will decrease progressively until  $\text{K}^+$  excretion equals  $\text{K}^+$  intake. Rarely, a patient dies of a cardiac arrhythmia before balance is attained. In vast majority of cases, however, balance is achieved before the patient succumbs to ventricular fibrillation.

### Speed of balance restoration

In a living organism, the speed of restoration of balance is teleologically determined. If an organism can tolerate protracted imbalance of a particular element without death or severe disability, balance need not be restored promptly. If quick restoration of balance is vital for survival, a mechanism for rapid restoration of balance is necessarily acquired in the process of evolution. Thus, the acceptable duration of discrepancy, or alternatively, rapidity with which restoration of balance is achieved, depends on importance of maintaining the content of an element within a narrow range in order to prevent the demise or serious disability of the organism<sup>1)</sup>. Four main factors influence the speed of balance restoration (Table 1):

- Magnitude of flux.
- Basal store.
- Capacity for additional storage.
- The physiological limit for deviation of the body content.

For example, an adult of average size has about 40 L of total body water, and daily intake and output of water

are about 2 L. Obviously, water output exceeding water intake by 1 L a day would lead to fatal dehydration within 10 days to 2 weeks. Conversely, water intake exceeding water output by the same magnitude would lead to water intoxication and death. An opposite example is calcium ( $\text{Ca}^{2+}$ ) balance. The total body  $\text{Ca}^{2+}$  content of an average adult man is 1,200,000 mg (60,000 mEq), and net daily external flux is about 150 mg (7.5 mEq). A daily negative balance of  $\text{Ca}^{2+}$  of 100 mg for 1 year would reduce total body  $\text{Ca}^{2+}$  by 36,500 mg, only 3% of the total body  $\text{Ca}^{2+}$  content. Obviously, a negative  $\text{Ca}^{2+}$  balance of such a magnitude, even for a protracted period, is not incompatible with life. Indeed during the period of development of osteoporosis, a substantial negative balance of  $\text{Ca}^{2+}$  for 10 years or longer is a common occurrence. Similarly, a positive caloric balance of 500 calories a day for a year will result in a total positive balance of 182,500 calories ( $500 \times 365 = 182,500$ ). This amount would result in an increase in adipose tissue weight of about 50 lbs, a situation not desirable but with no immediate effect on survival.

A large storage capacity doesn't mean a protracted imbalance is always possible. If possible, quantitative analysis must be applied. For example it has been stated that bone has a large store of alkali, and therefore can be a source of additional alkali for buffering purposes for many years in chronic renal failure without a change in serum bicarbonate concentration. The conclusion was reached without exact quantification. The bone content of alkali is

**Table 1.** Total Body Contents of Main Elements in the Body and Their Daily Turnover

Body elements	Total body content	Daily turnover	Days for 50% turnover
$\text{Na}^+$	3,500 mEq	4%	12
$\text{K}^+$	3,000 mEq	2.3%	22
$\text{Ca}^{2+}$	60,000 mEq	0.01%	2,700
$\text{Mg}^{2+}$	2,000 mEq	0.5%	100
Phosphate	557 g	0.17%	290
Water	40 L	5%	10
Alkali	28,000	0.2%	250
Calories	130,000	1.5%	33
Creatinine	400 mg	400%	0.12
Urea-nitrogen	4,000 mg	250%	0.2

indeed very large, but it is not sufficiently large to provide 19 mEq of alkali per day for 6 years in chronic renal failure, a claim that had been accepted for a long time. A quick calculation would indicate that at the rate of loss of 19 mEq/day, entire bone would melt away in about 3.6 years<sup>8)</sup>. Clearly, uremic patients with metabolic acidosis are in states of acid-base balance, i.e., acid production equals acid excretion.

### Infinite gain control mechanism

The purpose of feed-back control is to correct the abnormality caused by introduction of a new variable. Most control mechanisms correct the abnormality partially. The infinite gain control mechanism is unique in that the abnormality is completely corrected. This concept was introduced first by Guyton in his discussion of regulation of arterial blood pressure (BP)<sup>9)</sup>. He boldly predicted that in the absence of an altered renal function for salt excretion, no abnormality can maintain hypertension permanently. Normally, a minute change in arterial BP changes the quantity of renal salt excretion greatly. Suppose hypertension develops as a result of increased vascular resistance. Even a small increase in BP would greatly increase renal salt output. Increased salt output in the absence of commensurate increase in salt intake would lead to a net negative salt balance. The negative salt balance would reduce effective vascular volume, circulating blood volume, and eventually cardiac output. A lower cardiac output will reduce BP, but as long as the BP is still higher than the baseline, salt output will remain greater than the basal salt output. Only when the BP returns to the baseline value, the salt output will return to the baseline value. At this point, new balance is reached between the salt intake and salt output, and BP is back to the original level<sup>9)</sup>.

In Guyton's use, the term "gain" is defined as the fraction of abnormality that has been corrected divided by the fraction yet to be corrected. For example, if an abnormality causes an increase in BP, and a control system brings it back halfway to the original value, the feedback gain is one.

Gain is zero if a control system does not correct at all, and gain is infinite if the abnormality is almost all corrected with virtually nothing left to be corrected. Division of a number with an infinitely small number would result in number that is infinitely large.

The general characteristics of the infinite gain control mechanism can be described in the following way. Initially a new influence in a system affects either input or output of the element. The imbalance between input and output leads to either gain or loss of the element to be controlled. Gain or loss of the element partially corrects the abnormality induced by introduction of the new influence. But as long as any abnormality remains, imbalance remains. The corrective process continues until the abnormality is completely corrected; at this point and only at this point, balance between input and output is restored. In the infinite gain control mechanism, the system is set up in such a way that balance is restored only when the abnormality disappears completely. Since restoration of balance is inevitable, correction of the abnormality always is complete. An example will clarify the concept better than an abstract description as given above<sup>9)</sup>.

Assume that a person produces 10 g of urea daily, and has urea clearance of 100 L/24 hours. Serum urea concentration would be stable if urea excretion is equal to urea production. At urea production of 10 g/day, urea excretion would have to be 10 g/day at equilibrium. In a person with plasma urea concentration of 10 mg/dL (100 mg/L), a urea clearance would be 100 L/day. At this point we will introduce a disturbance, for example, by doubling the total body water, while both urea production and urea clearance are kept unchanged. Initially, dilution would reduce plasma urea concentration to 50 mg/L (5 mg/dL), and urea excretion would decrease to 5 g/day (50 mg/L  $\times$  100 = 5,000 mg = 5 g) because urea concentration is lower with the same clearance. Since urea production (10 g) exceeds urea excretion (5 g), plasma urea concentration would increase to a higher level. As plasma urea increases to, for example, 70 mg/L (7 mg/dL), urea excretion rate will be 7 g/day. Still urea excretion is less than production,

and urea accumulation continues and serum urea concentration rises higher. The process will continue, as long as serum urea is under 100 mg/L. Only when urea concentration reaches 100 mg/L, will urea excretion be 10 g/day, equaling urea production rate. When a new balance is achieved, no further increase in urea concentration occurs. At this point, urea concentration is exactly back to the original level although total body water is now at twice the usual value.

## Conclusion

In a system that is regulated by input and output of quantifiable elements, imbalance is only transient. The state of imbalance is an unstable situation, and the effect of imbalance is to achieve a new balance. The principle responsible for attainment of new balance is imbedded in nature, and operates in living organisms as well as in the inanimate world. Only when elements involved are non-quantifiable, sustained imbalance between input and output is possible. Love is such an example. Some person receives a lot more love than one gives, and vice versa. I will end this chapter with an example of the application of the principle of external balance to explain the mechanism of the typically acidic urine pH in type IV renal tubular acidosis (RTA).

In a state of acid-base balance, net acid production must equal net acid excretion. A patient with stable acidosis due to type IV RTA is likely to be in a state of acid-base balance. If the acid production is a usual normal value, then net acid excretion must also be restored to normal when balance between net acid excretion and net acid production is reestablished. Since net acid production is normal in type IV RTA, net acid excretion, expressed as ammonium +titratable acid–bicarbonate, must be normal also. Chronic hyperkalemia typical of type IV RTA suppresses ammonia production in the proximal tubule. Reduced ammonia excretion is thus the mechanism of metabolic acidosis in type IV RTA. If urine contains a low amount of ammonium, the only way to restore normal net excretion

to achieve a new balance between acid production and acid excretion would be to increase the concentration of titratable acid and minimize bicarbonate excretion. Both of these conditions are achieved when urine pH is very low. Consequently, as ammonium excretion falls, the initial response would be a decrease in serum bicarbonate concentration, resulting in metabolic acidosis. When the blood pH decreases to a sufficiently low level to normalize net acid excretion, serum bicarbonate stops falling; a new equilibrium is reached between acid production and excretion<sup>1)</sup>.

The essentially identical mechanism in reverse is responsible for chronically elevated urine pH in chronic potassium deficiency, which is accompanied by increased production of ammonium in the proximal tubule. Chronic hypokalemia increases proximal tubular ammonia production and hence urinary excretion. The resulting increase in net acid excretion would initially increase plasma bicarbonate resulting metabolic alkalosis because net acid excretion would exceed net acid production. The discrepancy between net acid excretion and acid production would not last forever. As plasma bicarbonate rises to a higher level, the kidney begins to spill bicarbonate in the urine, which increases urine pH. A higher urine pH reduces titratable acid excretion. The lower titratable acid and higher urine bicarbonate reduces net acid excretion, opposing the effect of higher urine ammonia excretion. When net acid excretion decreases to a level equaling net acid production, a new balance is struck, and serum bicarbonate stops rising.

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