Inorganic Salts in Biochemistry

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Almost eighty years ago, Lord Lister wrote in his studies on "Early Stages of Inflammation," "It appears to me, we have a sure though imperfect glimpse of the operation of mysterious but potent forces, peculiar to the tissue of living beings and capable of reversing the natural order of chemical affinities, forces which I suspect will never be fully comprehended and the study of which should always be approached with humility and reverence." We talk today of catalysis, hormones, and vitamines. Their nature and origin (1), still not entirely known, is based on the physico-chemical structure of the human body: i.e. (a) the colloid character of the medium (hydrophilic and hydrophobic colloids), (b) the solubility and distribution of the crystalloids in the colloids; their mutual influence and their influence on the dispersion, lysis, condensation, and hydration of the colloids, (c) the conduction of chemical and physico-chemical potential differences through the nervous system; the central nervous system and the autonomic nervous system (sympathetic and parasympathetic).

This paper deals only with one small section of the entire problem: the inorganic salts (ionized elements). The accumulation of certain physiological ions in different organs, even in different structures of the same organ, produces a chemical and physico-chemical tension which is fundamental for the function of the organ. The subject will be treated as follows:

I. Distribution of inorganic salts (ionized elements) in different organs
II. Functional value of cations and anions
III. Regulation and distribution of ions by hormones, and influence of ions on hormones
IV. Vitamines and ions.

I. Distribution

The distribution may be seen from Table I, which shows the ratio of cations and of anions computed from different sources (2). Whether their compounds are organic or inorganic is not of great importance as long as they act as ions. Even their insoluble stable compounds, such as calcium phosphate and calcium carbonate dissociate constantly, exchanging their ions with the blood and lymph streams which carry the acid phosphates and carbonates of sodium and potassium. There is a biological association of certain ions, which as a rule, prevails in the same tissues; e.g. Na^+ and Cl^-, K^+ and PO_4^{---}. The same is true between ions and colloids; e. g. K^+ and lecithin which coexist throughout the entire plant and animal structures, Na^+ and cholesterol which are frequently found together in one and the same organ or in body fluids, and Cu^{++} and vitamine B which are always associated (3).

II. Function

Extremely small quantities are often of high functional value; Cu^{++}, Mn^{++}, and I^-. Chemically related ions (K^+, Na^+, Ca^{++} and Mg^{++}) frequently function as antagonists, although they may replace each other or may have

TABLE I.—RATIO OF CATIONS AND OF ANIONS FROM VARIOUS SOURCES

	$Na^+:K^+$	$Ca^{++}:Mg^{++}$	Other Cations	$Cl^-:P_2O_3$	Other Anions	Cholesterol :Lecithin
Human body	1:2	30:1	Fe^{++}, Mn^{++}, Cu^{++}, NH_4^+	1:7	CO_3^{--}, S_2O_3, NO_3, I^-, Br^-, Fl^-	
Milk	1:4	5:1		1:1½	I^-	Fat
Blood						
Plasma	10:1	3:2		60:1	CO_3^{--}	>
Erythrocytes	1:4	/ /	$Fe^{++}>Cu^+$	0:+		<
Leucocytes (pus)	1:2	2:1	$Fe^{++}<Cu^+$	1:20	$S_2O_3^{--}$, NO_3	<
Brain		1:3	Fe^{++}		Br aggregated in pituitary	
White substance	+:0 }1:2½			>}1:2		>Cerebrin
Gray substance	0:+ }			<}		<
Nerve cells	+:0		} NH_4^+			
Axis cylinder	0:+		}			
Sciatic nerve	1:2½		Fe^{++}	<		
Retina	+:0			+:0		
Cerebrospinal fluid	30:1					
Skeleton		80:1		1:400	CO_3^{--}	< Fat
Bone marrow	<		Fe^{++}, Cu^+	<		
Teeth				1:30	CO_3^{--}	
Dentine		<				
Enamel		>				
Skin	>	Ca^{++}	Fe^{++}	>	$S_2O_3^{--}$	
Nails, hair				700:1	$S_2O_3^{--}$	
Sweat	>			+:0		
Lacrymal secr.	+:0	Ca^{++}		P_2O_5		
Sebaceous secr.						
Muscle (Striated, heart and smooth)	1:24	1:4	Fe^{++}.NH_4^+	1:3	$S_2O_3^{--}$	
Lung	20:1	1:1	Fe^{++}	1:6	>	
Digestive tract					$S_2O_3^{--}$, Fl^-	
Saliva	1:5(1:1½)	33:1(6:1)		1:1		
Gastric juice	1:1	+:trace	Fe^{++}, NH_4^+	2½:1		
Pancreatic juice	300:1	1:1	Mn^{++}	22:1		
Pancreas	1½:1	10:1	Fe^{++}, Cu^+	18:1		1:1(1:3)
Bile	19:1	3:1		8:1		
Liver (child)	1:3	5:1	Fe^{++}, Mn^{++}	1:10	$S_2O_3^{--}$	
Liver (adult)	1:1½	15:1		1:20		
Spleen						
Male	4½:1	14:1	Fe^{++}, Cu^+	1:50		
Female	2:1	14:1	Fe^{++}, Cu^+	1:20		
Kidney	2½:1	4:1	Fe^{++}, Mn^{++}	1:2½	$S_2O_3^{--}$, etc.	
Urine		1½:1		3½:1		

a synergistic function in other respects. Certain units (Na^+, Cl^-; Na^+, cholesterol) are often aggregated in organs side by side, but separated from their antagonists (K^+, lecithin; K^+, phosphate), which results in a high potential difference (white and grey substance of brain; organ cells and body fluids; brain and spinal fluid). The importance of the equilibrium between ions can easily be demonstrated.

a. the respiration quotient, $\frac{CO_2}{O} = 1$, is increased by feeding dextrose, but much less by feeding dextrose with mono- or disodium phosphate (Fig. 1). This is explained (Fig. 2) by a deficiency of glycogen formation (4).

b. the proportions, $(Na^+ + K^+) : (Ca^{++}, Mg^{++} :: 50:1$, and $K^+ : Ca^{++} :: 1:2$ are essential in the maintenance of the heart beat and the irritability of cellular elements in general (5).

c. the ratio, $(K_2HPO + KH_2PO_4) : (Ca^{++} + Mg^{++})$, is a stimulus for the respiratory center, the irritability of which is increased by an increase in the quotient and is decreased by a decrease in the quotient. This ratio can be influenced either by X-ray treatment (6), by adrenalin injection (7), by splenectomy or sympathectomy, or by resection of the pancreatic duct (8).

The functional significance of the presence and of the prevalence of certain ions in the different structures will be shown in a few examples. A study of Table I and more detailed analyses would furnish much more material. The purpose of this paper is to initiate these studies. A brief survey of the tabulation will, however, aid in making the study a little easier.

Milk, the simplest food, may be compared with the needs of the human body (Table I), and we see a parallel occurrence and prevalence of ions. More detailed studies reveal that human milk contains iodine during the first five days of lactation (9). This fact, as a rule, is entirely overlooked when cow's milk is given (Fig. 3) during the first days of lactation. This may account, in part, for the high mortality of children not fed with mother's milk during the first week.

The erythrocyte contains, closely aggregated into a cell nine micra in diameter, all the ions necessary for, and favorable to oxidation-reduction; Fe^{+++}, K^+, PO_4^{---}, with oxygen attached to the hemoglobin, and with lecithin as the vehicle. The nuclei of the leucocytes are relatively rich in copper; the plasma is rich in NaCl, Ca^{++} (blood coagulation), cholesterol, with phosphates and carbonates as buffers. For further details, see Pribram (10).

The high functional differentiation between brain and nervous substance is characterized by the absence of Na^+ in the grey substance and in the axis cylinder, and the absence of K^+ in the nerve cell and in the white substance of the brain. The prevalence of Cl^- and PO_4^{---} corresponds, as a rule, to that of Na^+ and K^+ respectively. There is, however, an exception. The retina contains Na^+ and Fe^{++} instead of K^+, and is rich in PO_4^{---} which plays a role in the activation of retinoflavin.

The stable chemical structure of the bone and the unstable structure of the bone marrow with its high functional (reproductive) activity, are striking examples of the significance of the distribution of ions in the body. The teeth show a prevalence of calcium in the enamel and of magnesium in the dentine. Further work is needed to find the functional significance of this fact.

The skin has the most complicated structure of all organs; each layer responds differently to ions, and each layer aggregates different ions. Even different concentrations influence the closely related fibres of the skin differently. Connective tissue responds to diluted NaCl with hydration; collagene fibres to concentrated NaCl. The most potent hydrator of the skin is iodine; the most potent dehydrators are SO_4^{--} and CO_3^{--}. The anions, therefore, regulate the water content of the skin. Sweat glands and lachrymal glands aggregate NaCl while hair and sebaceous glands aggregate calcium.

INFLUENCE OF PHOSPHATE ON R.Q.

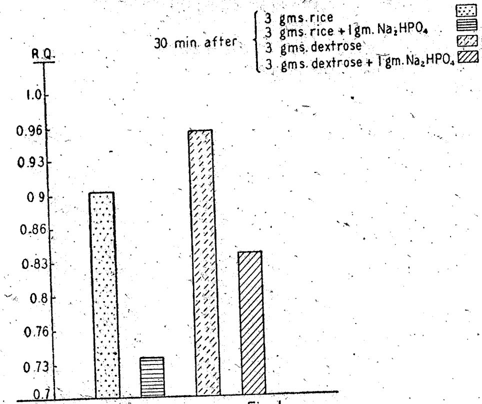

Fig. 1

INFLUENCE OF PHOSPHATE ON LIVER GLYCOGEN

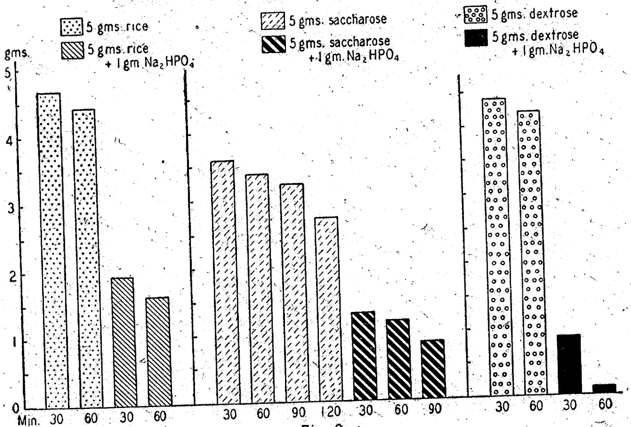

Fig. 2

IODINE CONTENT
(in gammas per 100 cc.)

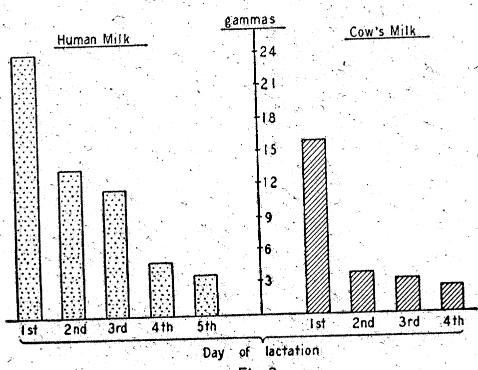

Fig. 3

The influence exercised by each of the constituents of the blood on the function of the heart muscle has been thoroughly studied by Ringer (11). See also Langendorff (12). Inorganic salts play the main role here. The antagonisms of K^+ and Ca^{++}, K^+ and Na^+, Ca^{++} and NH_4^+ are striking. The importance of the K^+ for diastole and of the Ca^{++} for systolic contraction are well established. K^+ acts as a radioactive substance and can only be replaced by radioactive substances or by beta-rays. The primary stimulus for the contraction of muscles is NH_4^+ (13). Charles Darwin (14) observed that 1/20,000 of a grain (= 3.3 grammas) of $(NH_4)_3PO_4$ causes flection of almost all the tentacles of drosera. Prawdicz-Neminski showed that relaxation of the muscle, after contraction by the ammonium salt, is caused by the formation of the double salt with Mg^{++}. Twenty mg of $MgCl_2$ (6 H_2O) and 0.25 mg of NH_4OH to 100 cc. of Ringer's solution are sufficient to counteract exhaustion of the heart muscle. The salt is soluble in lactic acid, and is removed from the muscle after contraction. The periodic contractions of striated muscle find here their explanation. All the ions are present in the muscle fibre; phospho-creatine being the source of NH_4^+ and PO_4^{---}, Mg^{++} also being present in relatively large quantities ($Ca^{++}:Mg^{++}::1:4$). NH_4^+ is present in the intestinal tract, and preponderant in the vena cava superior since its blood does not pass the liver. The blood of the vena cava inferior, after having passed the liver, contains less NH_4^+. A high potential difference between the two venae cavae arises from this fact. In addition, the blood of the vena cava superior is emptied at the most sensitive spot of the heart, the Keith-Flack node (15). The vagus nerve likewise enters the heart at this area. Ammonium salts are accumulated by nerve tissue, which is thirteen times richer in NH_4^+ than muscle tissue, and, in the active state, even fourteen times (16).

The importance of the exchange of K^+ against Na^+ for the distribution of water (shifting to the inner organs) during fever has been emphasized by the author (17).

The lung tissue, different from all the other organs, is very rich in Na^+. The prevalence of phosphates over chlorides is remarkable in this connection. It may be due to the Ca^{++} and Mg^{++} content. The ventilation of the blood by the lung governs the CO_2 balance and, indirectly, the acid-base balance of the blood.

In the digestive tract we have the saliva, very rich in K^+, especially if undiluted and the urea, containing the balanced CO_2-NH_3 compound, a potent solvent. In the gastric juice we find HCl, unique in living tissue. It is formed by a relatively simple chemical process: $H_2CO_3 + NaCl = HCl + Na_2CO_3$ (18). This reaction involves an automatic regulation of the CO_2 tension in the blood, which tension is the stimulus for the respiratory center.

The liver, extremely rich in K^+, harbors the bile which is rich in Na^+ and cholesterol. The importance of the ratio ($K^+ + Mg^{++}$)$:Na^+$ in the liver may be learned from Fig. 4 in which the Na^+, K^+ and Mg^{++} contents of the normal liver, of the liver in pregnancy, and in eclampsia are compared (19).

The spleen is rich in Na^+ and in phosphates, especially in the male, less in the female. The kidney takes care of the removal of all ions from the body.

III. Regulation and Distribution of Ions by Hormones, and Influence of Ions on Hormones

Fig. 5, in which the cations and the anions are combined with those organs in which they prevail and in the function of which they play an important role, shows the coordination of certain groups of organs and the interrelation of their ionic function. Fig. 6, in which the physiological cations and anions are connected with the endocrine glands (hormones) and with the vitamines (A, B, C, and D) to which they have relation, shows the coordination of hormones, vitamines and ions. It is evident from these diagrams that each ion has a specific projection in certain organs and endocrines, such as the I^- in the thyroid, the NH_4^+, Ca^{++}, Mg^{++}, CO_3^{--}, and PO_4^{---}

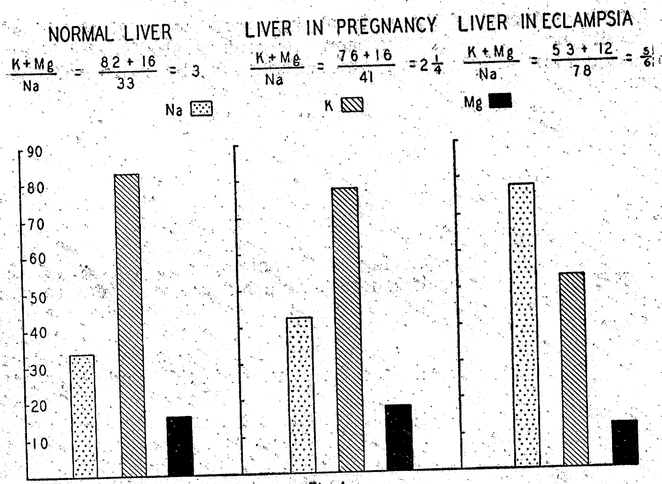

Fig. 4

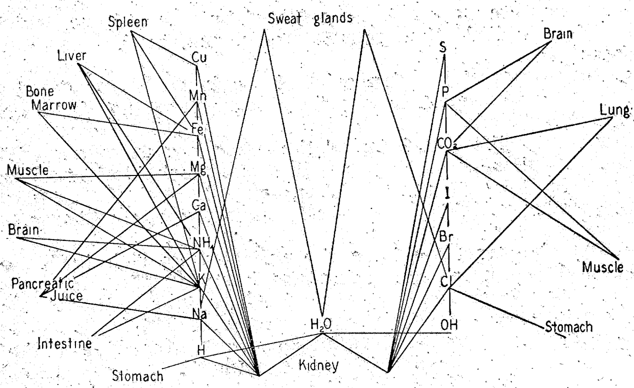

Fig. 5

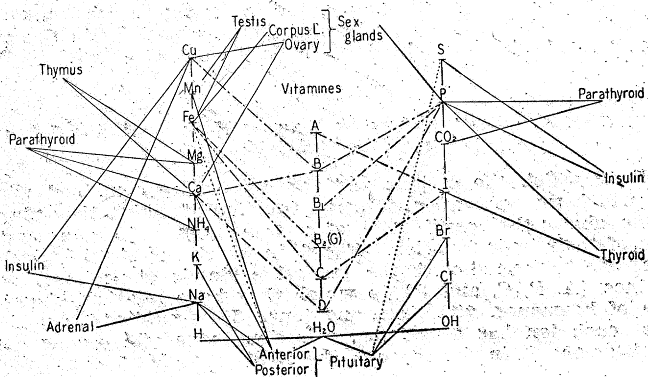

Fig. 6

in the parathyroid. Synergistic hormones and ions are to be found. Examples are: Na^+ and insulin (20), Na^+ and adrenalin (21). This means that the simultaneous administration of Na^+ and the hormone is equivalent to a larger quantity of the hormone.

The distribution of certain ions is controlled by hormones, such as that of Na^+ and of Ca^{++} by the anterior pituitary gland; that of K^+ and of Na^+ by the posterior pituitary gland, which shifts the ions to skin, liver, and circulation. The Mn^{++}, likewise controlled by the pituitary gland, has a fundamental importance in the development of the testis (22). Complete lack of Mn^{++} in the food causes degeneration of the testes in male rats. After 100 days the rapidly progressive degeneration leads to a complete atrophy of testes. Five mg. of Mn^{++}, added to the same diet, are sufficient to prevent the testicular atrophy (23). In the female, Mn^{++} and dextrose are necessary to maintain the normal oestrus cycle. The anterior lobe of the pituitary gland evidently needs Mn^{++} as a stimulus for the production of its hormone.

IV. Vitamines and Ions

Vitamines (dotted lines) have definite affinities to certain ions, such as vitamine D to Ca^{++} and PO_4^{+++}, vitamines C and B_2 to Fe^{++}, and vitamine A to I. The two diagrams, Figs. 5 and 6, combined, in three dimensions would give a model of the simultaneous cooperation and interrelation between organs, including the ductless glands (hormones), vitamines, and ions. This would offer "an imperfect glimpse of the operation of some of the potent forces peculiar to the tissue of living beings."

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