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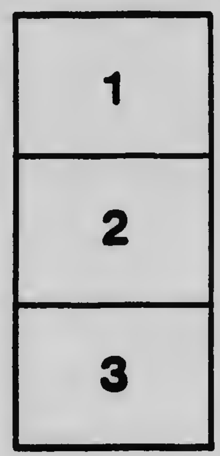
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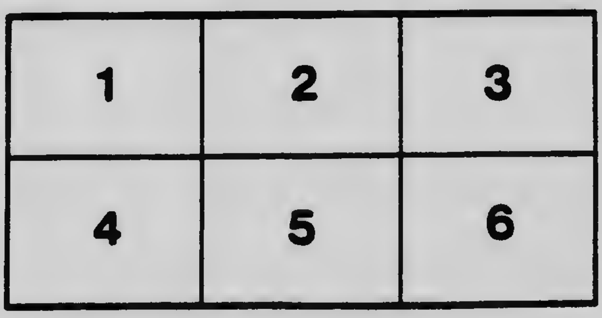
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Ancient Factors in the Relations between the Blood Plasma and the Kidneys

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THE ANCIENT FACTORS IN THE RELATIONS BETWEEN THE BLOOD PLASMA AND THE KIDNEYS.[1]

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The [illegible] organism, except that of the unicellular type, is a congeri[illegible] whose history, individually considered, as it is thus [illegible], constitutes the sciences we call comparative embry[illegible] comparative physiology and which we must know, not only [illegible] comprehend the full significance of the work they now perform, but also to recognize and interpret the possible variants from the normal in function and structure which they may manifest. This history, in invertebrates as in vertebrates, is one of change either in structure or in function, or, often, in both structure and function, and, accordingly, frequently confusing and difficult to follow in any attempt to gain a full comprehension of the conditions and forces that determined the character of each organ.

One needs but to scan the list of the organs of the vertebrate body to illustrate how true this is. The nervous system with its protean manifestations in the line of evolution, the thyroid, the thymus, the suprarenals, the pituitary body, the pineal gland, the gills, the lungs, the alimentary canal with its accessory structures and even the liver, all have a past in which the dominant feature has been changed in structure and function with the result that the final stage in each transcends the earlier ones and so obscures their characters that it is now difficult to determine the earlier history except in some cases from the structural side.

One thing is indeed certain. The change has never been of the *per saltum* type. But it has been unceasing, without pause, and it is progressing today as it has been in the long past. The Heracleitan flux therefore plays its part in organogenic evolution as distinctly as it does in the physical world.

Among all the organs with their varied history as to structure and their variations in function, there is, however, one whose function in one particular respect has not changed from the time

[1] The Hatfield Lecture delivered before the College of Physicians, Philadelphia, April 10, 1917.

when it first began to evolve in the very far past. This organ is the kidney and the function which it performs, as it has performed it far back in the very beginning of the history of vertebrate life, is the regulation of the inorganic composition of the internal medium of the body, which we know as the blood plasma.

This organ was among the very first to appear in the protovertebrate, or in the first invertebrate type which began to differentiate along the line of development which resulted in the appearance of the protovertebrate in the Cambrian, or it may be pre-Cambrian times. If we may rely on the order in which the organs appear in the embryological history of the vertebrate, the renal organ is as ancient as the neural canal, and its origin would appear to antedate by a long period the closure of this canal and the disappearance of the coelomic cavity into which the primitive nephric tubules opened. If the latter are, as has been claimed, derived by differentiation from the coxal glands of a crustacean-like form, they are of more ancient origin than the neural canal itself.

What the kidney of the protovertebrate was we may gather from the earliest form of the vertebrate kidney, which consisted of three divisions, arranged in order from before backward: the pronephros, the mesonephros and the metanephros. One of these, the mesonephros, becomes the adult kidney in fishes and amphibia; another, the metanephros, becomes the functional kidney in other vertebrate classes, reptiles, birds and mammals. This is of significance, as I shall show later, in indicating that the regulation of the inorganic composition of the blood plasma exercised by the adult kidney must have been exercised also by the kidney of the protovertebrate.

In order to understand what this regulation involves we must for a moment consider what the inorganic composition of the blood plasma is. The salts of the blood plasma in amount range between 0.78 and 0.88 per cent. of the weight of the plasma, and they consist of the chlorides, phosphates, carbonates and sulphates of sodium, potassium, calcium and magnesium. The salts of sodium are by far the most abundant, after which come those of potassium, calcium and magnesium in the order mentioned. The salts of sodium, chiefly the chloride, amount to more than 90 per cent. of the total inorganic solids of the plasma.

The composition in detail has been determined by Bunge for the horse, ox and pig, and by Abderhalden for the ox, horse, pig, sheep, dog, cat.

The composition of human plasma has not been redetermined since 1850 when Carl Schmidt published the results of a number of analyses which are quoted now in all the text-books. They were obtained by the methods in use seventy to eighty years ago, which gave less exact determinations than those now followed in making such analyses, and, consequently, the percentages, notably those of potassium, calcium, magnesium and chlorine, which Schmidt's determinations yield, are open to question.

The inorganic composition of the plasma in birds, reptiles and amphibia has not been ascertained, but the total percentage of the ash has been ascertained to range between 0.8 and 0.9 in birds and reptiles, while in the frog it has been estimated to be as low as 0.46, but this may possibly be due to the difficulty of getting enough of the plasma of the frog free from admixture with water or lymph. The fact that in birds and reptiles the percentage of the salts is as high as in mammals is an indication that the details of the composition are not widely different from those of the plasma of the mammals above mentioned.

The analyses of the blood plasma in fishes which we have today are only those of the cod, pollock and dogfish, which I made eight years ago, and they are of special interest in connection with the analyses of the blood plasma of mammals.

If one examines Bunge's and Abderhalden's tables, giving the results of their analyses, one is impressed only with the fact that the details obtrude themselves to the exclusion of all else, that in fact one does not see the woods for the trees, and, in consequence, the significance of the results are obscured.

If, however, one selects the cationic elements and arranges them in values proportional to the most abundant one, sodium, which may be made equal to 100, order is obtained from the maze of details in these analyses, and one finds surprising resemblances in the values obtained from plasmas of all the mammals. Further, the proportions obtained from the analyses of the plasma of the fishes referred to fall into line with those from mammals in such a way as to suggest that we have thus revealed a cardinal feature in the inorganic composition of the blood plasma of vertebrates.

This feature is indicated in the following table of ratios in which Na = 100.

	Na.	K.	Ca.	Mg.
Dogfish (*Acanthias vulgaris*)	100	4.61	2.71	2.46
Cod (*Gadus callarias*) . .	100	9.506	3.93	1.41
Pollock (*Pollachius virens*) .	100	4.33	3.10	1.46
Dog	100	6.86	2.52	0.81
Mammal (average) . . .	100	6.69	2.58	0.80
Man (C. Schmidt) . . .	100	9.22	3.37	1.76
Man (A. B. M.)	100	6.11	2.71	0.85

The ratios for man are derived from Schmidt's analyses carried out, as already stated, with methods which were less exact than those which are employed today, and, in consequence, they are accepted with reserve, more especially as in my own determinations on the blood plasma of man the values for potassium, calcium and magnesium are much lower than those given by Schmidt and in general accord with those of Abderhalden and Bunge for mammals.

The ratio of potassium in the blood plasma of the cod, as determined in my own analyses, is high, but this may possibly be due to hemolysis, the preparation of serum which I used having a reddish tinge and therefore probably contained the potassium of the hemolyzed corpuscles, which thus would give a higher ratio for this element than would be given by pure plasma or serum. The fact that so near a relative of the cod, as is the pollock, gives less than half the ratio of the cod and approaches very closely that of the dogfish supports the view that the ratio in the cod is less than that given above.

Apart from these exceptions, if they are to be ranked as such and not due to errors in analysis or to abnormal composition, the striking feature is the very extraordinary parallelism between the ratios in mammals and those in fishes. This parallelism appears enhanced when one considers that the concentrations of inorganic salts in both classes of vertebrates differ. The concentration in the serum of the mammal, as already stated, ranges from 0.78 to 0.88 per cent. in the sera of the cod and pollock, from 1.282 to 1.293, respectively, while in the dogfish it is 1.774, or practically, double what it is in the serum of a mammal.

The parallelism in the ratios of the individual elements in the highest as well as in the lowest vertebrates is a cardinal fact, something more fundamental than the total concentration of the salts in the plasma. Its occurrence in two such widely separated classes of vertebrates suggests that it is an endowment received from the common ancestor of both, the protovertebrate, which must have existed in the early Cambrian or pre-Cambrian times.

What is the explanation of these ratios between the sodium, potassium, calcium, and magnesium?

The answer to this question I obtained some fourteen years ago when determining the inorganic composition of certain medusæ and comparing it with the composition of the ocean water of their habitat. *Aurelia flavidula*, the common jelly fish of our coasts in July and August, when it is liquefied, which happens when it is allowed to stand in a dry dish, furnishes a liquid in which, besides organic constituents, is contained a concentration of inorganic salts like that of the ocean water from which the animal was taken. From the analyses of its salts, compared with those of ocean water, ratios between the sodium, potassium, calcium and magnesium (with Na = 100) were obtained which revealed a very striking parallel.

	Na.	K.	Ca.	Mg
Ocean water (Dittmar) . .	100	3.63	3.91	12.10
Aurelia flavidula (Macallum)	100	5.18	4.13	11.43

The parallelism between the two series of ratios is very close and the conclusion follows that the fluid in the tissues of *Aurelia* is but very slightly modified ocean water and of the same concentration as the latter.

It was, however, when the ratios for sea water were compared with the ratios of the blood plasma of a mammal, for example, the dog, that one obtained a clue to the origin of the ratios in the blood plasma of vertebrates. We see in the latter:

	Na.	K.	Ca.	Mg.
Ocean water (Dittmar) . . .	100	3.61	3.91	12.10
Dog (Abderhalden)	100	6.86	2.52	0.81
Limulus polyphemus (Macallum) .	100	5.62	4.06	11.20
Homarus americanus (Macallum)	100	3.73	4.85	1.72

that the ratios are parallel to those of ocean water, except in regard to magnesium. Were the ratio of the latter reduced to 1, or thereabouts, the parallelism between the two series would be so striking as to render unnecessary further discussion of the question of the origin of the ratios in the blood plasma.

That these ratios are of oceanic origin can admit of no doubt when we compare them with those of the horseshoe crab and lobster.

The horseshoe crab, *Limulus polyphemus*, which has had its habitat in the ocean since its origin in the early portion of the Palæozoic age, has a plasma in which the parallelism between it and ocean water is uncontrovertible. This is no doubt due to the fact that the osmotic pressure of the ocean has been acting on its plasma through the many millions of years which have elapsed since the Cambrian age, and, though unquestionably the ocean has been undergoing, in all that time, changes, not only in concentration but also in the ratios of its salts, the blood plasma of the horseshoe crab has kept pace with it and today the concentration of its salts equals that of the ocean water in which it lives, and the ratios in its plasma are practically those of ocean water. We thus see that ocean water does in this one case determine the inorganic composition of the blood plasma.

In the plasma of the lobster, *Homarus americanus*, which has been associated with the ocean only since the Cretaceous period, though the concentration of the inorganic salts is as high as the ocean water of its habitat, the ratio of the magnesium only is different from that of the ocean.

In both the lobster and the horseshoe crab the concentration of the inorganic salts of the plasma appears to vary with the concentration of the ocean water of their habitat, and in brackish water it falls to that of the latter. The concentration of the salts of the plasma in these forms follows the concentration of the medium, whereas in the Selachians, which include the sharks and the dogfish and which have had their habitat in the ocean ever since the early part of the Palæozoic age, the concentration of the plasma salts exceeds half that of ocean water to a slight extent, although the osmotic pressure of the ocean has been exerting its effect on the Selachian plasma for at least several scores of millions of years.

In the marine Teleostean fishes, which, like the cod, have been denizens of the ocean for a time, perhaps, not half as long, the concentration in the plasma is but little more than a third of the concentration of the salts in the ocean.

In the marine invertebrates of today the circulatory fluid is but a more or less modified form of sea water. In some the circulatory channels freely communicate with the exterior with the result that the circulatory fluid is pure sea water, but, even when the circulation is closed as it is in the horseshoe crab, the blood plasma is sea water with proteins and other organic constituents.

There is then a profound difference between the blood plasma of vertebrates and that of invertebrates. That of the latter varies more or less readily with an immediate change in the medium of the habitat, while that of the former is affected, and then but appreciably, only after millions of years.

Are we then to conclude that the plasma of vertebrates was primarily of origin different from that of the plasma of invertebrates?

If we scan the tables of ratios for the sodium, potassium, calcium and magnesium in the plasmas of the different forms of vertebrates and invertebrates, we see in the parallelism already referred to an unmistakable indication that the blood plasma of vertebrates was also originally sea water, not indeed the sea water of the present age, but of a far past when the concentration of its salts was less than one-third of what it is now and when also the potassium was relatively more and the magnesium relatively less abundant than in the ocean of today.

The sea is the original home of all life on our globe, and it was in the sea that the differentiation between animal and vegetable life as well as the evolution of the great divisions of the animal kingdom were effected. Indeed, the great events in the evolution of animal forms have been rendered possible by changes which have taken place in the composition of the ocean. Among the fundamental results of these changes was the development of a closed circulatory system of vertebrates, the fluid contained in which became henceforth independent of the composition of the contemporary ocean, and, as we have seen, of the ocean of subsequent periods even after many millions of years, as in the case of the Selachians (sharks), marine Teleosts (cod, herring) and the Cetacea (whales).

The sea ever since the first condensation of water on the original cooled rock crust of our globe has been changing in composition by the leaching out of its bed the salts it contained and by receiving salts in the river discharge, also leached from the land areas of the globe. The quantity of salts annually discharged from the land areas is enormous and it is estimated by Joly at about one hundred and fifty-seven millions of tons (157,270,000), which, if divided into the amount of salts which he calculates as contained in the ocean today, namely, 14,151,000,000,000,000 tons, would give the age of the ocean as approximately ninety million years. The concentration has therefore been slowly changing and it must have been in the far past much less than it is now.

The relative proportions of the various salts must have changed also. All the salts discharged in the ocean by the rivers have not been retained, for, were they retained, the potassium and the calcium salts would be very greatly more abundant than they are now. Indeed the calcium salts in the ocean would have long ago reached a degree of high supersaturation quite impossible to conceive of, since the lime salts in the calcareous rocks of the earth's crust, deposited from sea water in the past ages, would thus be in solution in the sea. The potassium was, once, relatively to the sodium, more abundant than the present ratio indicates, and it has been and is being constantly extracted from the ocean in the formation of such minerals as *glauconite* apparently at a rate which keeps its concentration over long ages fairly constant. The magnesium salts also have been concentrating slowly, for the elimination of magnesium as carbonate in the formation of dolomitic limestone has been proceeding at a rate less than that of the constant addition through the river water. This would postulate that magnesium is not only absolutely but also relatively more abundant in the ocean of today than it was in that of the far past.

The only constituents that are not extracted from the ocean are the sodium salts. These have always therefore been on the increase from a time in the early pre-Cambrian when they were perhaps but slightly in excess of those of potassium. Their increase will proceed in the ages to come and finally produce such a degree of concentration and, consequently such a specific density that will, as in the water of the Dead Sea, permit the human body to float because of its lower specific gravity.

The differences in the series of ratios exhibited by the sodium, potassium, calcium and magnesium in the blood plasma of vertebrates on the one hand and in the sea water of today, on the other, parallel as these two series so strikingly are, can be explained as due to the blood plasma reproducing, approximately, the ratios obtaining in the ocean of the time when the original ancestral form of vertebrates, the protovertebrates, or eovertebrates, arose. The total concentration of the salts in the blood plasma can also be explained as due to a reproduction of the concentration of the sea water of the same age, that is, when it had less than 1 per cent. of salts.

How far back in geological time this period was it is difficult to determine exactly. It must have been earlier than the earliest or most ancient fossil remains of vertebrates indicate, that is, in the earlier Cambrian or even pre-Cambrian, for the protovertebrate must have long preceded the vertebrates to which, through evolution, it gave origin. How long the intervening period has been is also difficult of determination. Estimates made on various bases give different results and the only satisfaction that one obtains from them is the recognition of their extreme limits, the maximal and minimal. Prof. Strutt in determining the content in helium of a mineral derived from Cambrian rocks of Renfrew County, Ontario, Canada, calculates that it was over seven hundred million years old. If, on the other hand, one follows Joly's method, based on the amount of salts in annual river discharge into the ocean, and the amount now in the ocean, and also accepting as approximately correct the percentage of salts in the ocean when the protovertebrate arose as less than 1 per cent., and therefore less than one-third of the concentration in the ocean of today, it follows that more than sixty millions of years must have elapsed since the protovertebrate appeared and disappeared on the geological horizon.

Whether we accept the higher or the lower estimate, or even a lower one still, the enormously long period during which the blood plasma has been simulating Palæo-oceanic conditions in the concentration of its salts and in the ratios of the sodium, potassium, calcium and magnesium it contains, emphasizes the importance in one respect of the organ which has maintained through the long ages of vertebrate history this concentration and these ratios, practically unchanged.

This organ is the kidney. There is in invertebrates no structure with a similar function or with a function even distintly approaching that of the vertebrate kidney. It is this organ that has made a fundamental difference between the vertebrate and the invertebrate, not only in the struggle for existence but also in the capacity to evolve higher forms of animal life. The animal form that must accommodate its internal medium to that of its habitat has an enormous handicap when it changes its environment, from ocean to fresh water or to land, as compared with one whose internal medium, under all circumstances, is constant in composition. With such a handicap vertebrate life and all that it involves would have been impossible.

This function of the kidney is fundamental and is more ancient than that of excreting the waste products of the tissues of the body. In the dogfish, as in Salachians generally, whose history has been associated with the ocean since their origin in the Silurian period and in whose blood plasma the concentration of salts has in consequence been increased to only about half that of the sea, the difference between the osmotic pressure of the ocean water and that given by the salts of the blood plasma is equalized by urea which amounts to more than 2 per cent., and by ammonium salts, which amounts to more than $\frac{N}{10}$ reckoned as NH_3. This retention of urea and ammonium salts undoubtedly developed as a result of the tendency of the blood to balance the slowly increasing osmotic pressure of the sea water. The very fact that the kidneys in these forms exhibit inertness in the elimination of urea while they are extremely active in the elimination of salts is extremely significant. What they do most rigorously is the regulation of the inorganic composition of the blood, therefore the more firmly fixed physiological habit must be the more ancient one and, consequently, their earliest function was not the elimination of waste metabolic products but the regulation of the inorganic composition of the blood plasma. The function of excreting waste products developed later and in Selachians never acquired the fixity that characterizes the other function.

In the long ages the kidney has thus performed a function which for constancy and unvarying regularity is unrivalled in the world of life. This constancy, this unvarying regularity contrasts strikingly with the variation in function which the other organs have undergone and indicates how basic the kidney is in the vertebrate system and why it takes precedence in the body as a vertebrate organ *par excellence*.

How it happened that the kidney in the protovertebrate acquired this fixity of function we do not know. Geologists concede a very long time to the pre-Cambrian, a duration which, according to different estimates, ranged from one-third to nine-tenths of the whole geological period. In this long cycle of time many things could have happened and conditions must have obtained which impressed on the primitive kidney of the protovertebrate an abiding character, not to disappear even though the original organ underwent a marked transformation in structure before it developed into the renal organ of the vertebrate of today.

The question now arises, whether this Palæo-oceanic character is ever disturbed in disease of the kidney and, if it is, what are the results.

To this question there is not much to offer in the form of an answer. There have been very few investigations of the inorganic composition of the blood plasma in disease, and these only of a very limited scope, bearing almost wholly on the chlorine content, the amount of which was supposed to give an indication of the total concentration and of the sodium present. The conclusions based on such analyses are, of course, accepted only with reserve simply because of the tenuity of the data on which they are based. Plasma that are accessible are those of Schmidt.

Believing that the subject had possibilities in a clinical line, I undertook during the last five years investigations on the inorganic composition of normal human plasma, with a view to comparison of the same with the blood plasma in cases of Bright's disease, and, more especially, in cases of puerperal eclampsia. These investigations are not yet completed, owing to the time-devouring character of the work involved, but some of the results so far obtained are definite and interesting and they may be mentioned here.

It is to be premised, first of all, that the determinations in Schmidt's analyses, so far as sodium, potassium, calcium and magnesium are concerned, give too high values. Those for sodium range from 0.3173 to 0.3438 per cent. and for potassium from 0.0314 to 0.0332, while in my analyses the range of sodium is from 0.29 to 0.316 and of potassium from 0.019 to 0.0212. It may thus be seen that Schmidt's values are quite too high, and especially in the case of potassium, his average for the latter being 60 per cent. in excess of mine. The results obtained for the plasma in Bright's disease are quite incomplete, but those for puerperal eclampsia are far enough advanced to enable me to give some points of interest.

In 4 cases the ratios on the bases of Na = 100 were:

Cases	Na.	K.	Ca.	Mg.
1	100	17.66	4.02	3.42
2	100	26.70	3.27	2.37
3	100	10.60		
4	100	10.10	2.59	0.68
[5 (normal)	100	6.11	2.71	0.85]

The magnesium and calcium content is high in Cases 1 and 2 and normal in No. 4, but in all the potassium is in excess and in No. 2 extraordinarily so, as much as four times the normal, while in No. 1 it is nearly three times the normal.

There was a minute quantity of hemoglobin in the serum of all the four cases, as revealed by the spectroscope, and some of the potassium found in excess of the normal may have been derived from hemolyzed red corpuscles which are rich in potassium salts, but this would not explain the excess in No. 2, in which the amount of hemoglobin in the serum did not exceed that in Nos. 3 and 4. It is possible that hemolysis in the circulating blood may be responsible ultimately for this excess, but this does not explain the non-elimination of the potassium in excess above normal by the kidneys. Temporarily, at least, in eclampsia the cellular elements of the kidney concerned in maintaining the normal ratio of potassium in the blood plasma must suffer a partial or total eclipse of function.

I am inclined to infer from the results of my observations that the very first change from the normal to the definitely established primary condition in some of the forms of Bright's disease is a loss of the power to maintain the Palæo-oceanic ratios.

The structures in the kidney involved in maintaining these ratios are the proximal convoluted tubules, which, with the glomeruli, are derived from and therefore represent the original parts of the kidney of the earliest vertebrates and of the protovertebrates. The proximal convoluted tubules are also concerned in reducing the H-ion concentration of the blood, for they secrete acid, not acid salts, into the urine, a function which is also very ancient, a function performed in invertebrates by all the cells of the body situated near the body surface, and still performed intermittently and with a high degree of specialization by the gastric glands of vertebrates. In some invertebrates other tissues have specialized in this matter also, as for example, in the salivary glands of the carnivorous mollusc *Dolium galea*, the concentration of the sulphuric acid of the "saliva" of which exceeds 4 per cent.

It may be that the function of preventing the ever-tending-to-increase of the H-ion concentration of the blood plasma is as ancient as the Palæo-oceanic function, a view which their common localization in the proximal tubules supports.

Enough has been said here to emphasize the view that behind the functions of the renal organ is a history which links up the human body with the far past, with an age of the earth when its oceans contained only what would now be regarded as brackish water and the earliest type of vertebrate life was just beginning to appear as a marine form. From the facts advanced it will be gathered also that the blood plasma, so far as its inorganic salts are concerned, is but a reproduction of the remotely ancient ocean, and that it is an heirloom from the life in

"that immortal sea
Which brought us thither."

not indeed in the Wordsworthian sense, but in the literal one, for the sea is the original home of all life on the globe and gave our blood, and, accordingly, the tissues of our bodies, a character that long ages have not effaced and will not efface.