The role of calcium in evolution is best understood from a perspective based on its intrinsic value as a divalent cation able to bind and precipitate inorganic and organic anions rapidly. This binding can be useful or inhibitory. Now treatment of binding or precipitation has two different interests in biological cells. The first is thermodynamic, that is the stress is on systems biology and the second is structure, that is molecular biology. In evolution both have equal weight being connected through exchange. This paper outlines first the systems biology of the evolution of calcium functions from prokaryotes to animals with brains. The calcium ion was the only good available candidate in the environment for the functions it performs. The second section of the paper describes the evolution of the proteins which allow the messenger function. We have discussed elsewhere the structure/function relationships of the proteins. Overall the evolving and increasing involvement of calcium as possibly the major control messenger of events outside cells to action inside them is an inevitable feature of the nature of ecological, that is environmental/organism, evolution.

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Keywords: Evolution; Calcium ion property; Calcium protein; Calcium cell concentration; Extracellular fluid; Calcium messenger

1. Introduction

As a full version of this paper will appear shortly [1], I give here the evolution of calcium function from a somewhat different angle using the material of that article. In essence I wish to put the view that the ecosystem we have inherited, that is the combination of living organisms and our environment has evolved in a series of inevitable steps due to the essential chemistry of life and the changing limitations on availability of chemicals from the environment which life itself imposed [2]. In this development, over a period of some four billion years, elements changed more rapidly in the environment due to waste from organisms and the living system slowly adapted to these very changes. This feedback loop (Fig. 1) is slow in that while environmental reactions of gases such as oxygen with iron and sulfur in the sea are fast the chemistry of cells is conservative and will only respond slowly to external chemistry change, at first because it is a threat. In this article I shall show the ever-increasing role that calcium has played in this ecological cycle after its initial rejection to “waste” bringing organisms and the environment into close interaction much though the condition of the calcium ion in the environment hardly changed. It acts in fact as part of an overall recognition signal of threat or advantage in the environment later in evolution. This study may provide an example of how the analysis of single elements and their compounds, extracted from cells, can be misleading unless seen in the context of the whole activity of cellular chemistry and its evolution together with that of the environment [2].

2. The essence of calcium chemistry

Calcium gives a seemingly simple divalent cation in water, Ca^{2+}, but note that it has a variable degree of hydration of 6–8 water molecules which exchange very rapidly so that Ca^{2+} is a faster binding agent than any other available divalent ion from the environment. It reacts 10^{3} times faster than Mg^{2+}. This is one factor which leads to the different abilities of the two ions to assist environment/organism interaction. Calcium also forms insoluble salts readily with both inorganic anions and organic anions, e.g. carbonates and phosphates, to give precipitates which limits its solubility to around 10^{-3} M—a figure which has remained a constant feature of the sea during all evolution.
Ca\(^{2+}\) in the presence of Mg\(^{2+}\) at 104 times higher concentration. bind Ca\(^{2+}\) much more strongly than Mg\(^{2+}\) since Ca\(^{2+}\) has longer dentate agent. However a multidentate chelate may prefer to reduction of CO and CO\(_2\) and if necessary of N\(_2\). We shall assume This chemistry from the being of life to today is brought about by and metabolism of proteins, nucleosides, saccharides and fats. 3. The essence of cytoplasmic cell chemistry

When life became land-based the control of internal calcium had a different character. The calcium ion also forms a wide range of complexes in water with similar affinity constants to that of Mg\(^{2+}\) so long as the ligand is a simple mono- or bidentate agent. However a multidentate chelate may prefer to bind Ca\(^{2+}\) much more strongly than Mg\(^{2+}\) since Ca\(^{2+}\) has longer bonds than Mg\(^{2+}\). On folding around the two metal ions there can be steric hindrance around Mg\(^{2+}\) not present in the Ca\(^{2+}\) complex, e.g. compare EDTA with EGTA complexes of Mg\(^{2+}\) and Ca\(^{2+}\) and see Fig. 2. EGTA is effectively a reagent for complexes in water with similar affinity constants to that of Mg\(^{2+}\) so long as the ligand is a simple mono- or bidentate agent. However a multidentate chelate may prefer to bind Ca\(^{2+}\) much more strongly than Mg\(^{2+}\) since Ca\(^{2+}\) has longer bonds than Mg\(^{2+}\). On folding around the two metal ions there can be steric hindrance around Mg\(^{2+}\) not present in the Ca\(^{2+}\) complex, e.g. compare EDTA with EGTA complexes of Mg\(^{2+}\) and Ca\(^{2+}\) and see Fig. 2. EGTA is effectively a reagent for Ca\(^{2+}\) in the presence of Mg\(^{2+}\) at 10\(^4\) times higher concentration. Many calcium chelating proteins have this same selectivity in the cytoplasm of cells, in vesicles and even outside cells due to the same factors. The insolubility of calcium salts and the selectivity of interaction between Ca\(^{2+}\) and complicated organic molecules are the two other factors which have given Ca\(^{2+}\) such an important role in the total ecosystem but initially the unfavourable nature of the binding to very basic internal metabolites required Ca\(^{2+}\) to be rejected from the cytoplasm.

3. The essence of cytoplasmic cell chemistry

All cells have a central chemistry associated with the synthesis and metabolism of proteins, nucleosides, saccharides and fats. This chemistry from the being of life to today is brought about by reduction of CO and CO\(_2\) and if necessary of N\(_2\). We shall assume the other essential elements of Fig. 3 were in the appropriate oxidation states for functional use in primitive conditions. Clearly reduction required release of oxidising equivalents at first just of sulfur but then of O\(_2\) from H\(_2\)S and H\(_2\)O respectively. (Note that Ca\(^{2+}\) ions with manganese are involved in the O\(_2\)-release step in photosystem II and we offer an explanation of this strange fact in [1].) The switch to O\(_2\)-release forced evolution in that the redox potential of the environment, which was initially reducing at a potential around −0.2 V established by the presence of Fe\(^{2+}\) and H\(_2\)S in the sea, was forced to rise. (Note that −0.2 V is close to the average in-cell cytoplasmic potential of all cells.) The potential rose to today’s value of +0.8 V but very slowly due to the Fe\(^{2+}\)/H\(_2\)S buffer and small supply of O\(_2\), causing a slow systematic change in the content of the sea, especially at first but more quickly later, see Figs. 1 and 4. About 2.0 billion years ago Fe\(^{2+}\)/H\(_2\)S buffering was exhausted and it is at this time that life, which in prokaryote form had itself been modified somewhat to protect itself and then had been changed to utilise the increasing environmental content of oxidised materials, underwent profound change. The only really effective way of increasing simultaneously reductive (cytoplasmic) chemistry and oxidative cell chemistry in cells was by carrying out the oxidative chemistry mainly in new compartments that is outside the reductive system of the cytoplasm as seen in eukaryotes. (This use of compartments is the only way to carry out reductive and oxidative chemical acts simultaneously in chemical laboratories.) It is at this time that calcium ions are known to have begun to play a central role in organisms i.e. in the eukaryotes. Notice that in essence organisms switched increasingly from chemistry in one compartment to chemistry in many compartments, starting some one and a half billion years ago, that is successively from prokaryotes to form single cell eukaryotes and then to multi-cellular eukaryotes (including formation of organs) to animals with brains, as the oxygen increases. Each change increases chemical differentiation in separated spaces. We need to see that this is also the sequence of increase in utilised chemical diversity externally and the value of calcium ions in securing the viability of cells, which are longer-lived and more liable to damage. Why
were calcium ions so vitally important in this prokaryote/eukaryote evolution and then continued to expand their roles to today?

4. The roles of calcium ions

The sea was not an ideal environment in which cellular life could start due to the dominant presence of Na\(^+\), Cl\(^-\), Mg\(^{2+}\) and Ca\(^{2+}\). Any cell, which has to accumulate organic molecules, by its very nature will have inadvertent additions of Na\(^+\), Cl\(^-\), Mg\(^{2+}\) and Ca\(^{2+}\) unless it can limit the concentrations of these ions. It was necessary to remove:

1. the burden in cells of the consequent high osmotic pressure due to high Na\(^+\) and Cl\(^-\), and
2. the problem of precipitation in cells of the organic molecules, largely anions, by Ca\(^{2+}\) to maintain solubility.

Before cellular life could be started, survival of cell precursors demanded therefore rejection of Na\(^+\), Cl\(^-\) and Ca\(^{2+}\) from protocells while Mg\(^{2+}\) and K\(^+\) could be kept internally at reasonable levels to manage the excess negative-charge (K\(^+\)) and metabolism of the organic anions and their catalysis (Mg\(^{2+}\)). Here we shall concentrate on the established calcium gradient of about 10\(^{-4}\) M between the sea, 10\(^{-3}\) to 10\(^{-2}\) M, and the cytoplasmic concentration of <10\(^{-6}\) M to 10\(^{-7}\) M. Before doing so we return to the value of the external Ca\(^{2+}\) ion to prokaryotes. In passing note that in fresh water calcium uptake is essential in multi-cellular organisms to maintain extracellular fluids but the cell membrane gradient is unaffected and carefully monitored.

5. The interaction of Ca\(^{2+}\) and prokaryote cells

In effect the evolution of Ca\(^{2+}\) ion function illustrates the general nature of evolution that is of a system to a poison. As stated the cytoplasmic chemistry of prokaryotes, and much the same goes for eukaryotes, is not compatible with high free Ca\(^{2+}\) concentration. (The same applies to Cl\(^-\) and Na\(^+\) and possibly Mn\(^{2+}\).) Hence Ca\(^{2+}\) ions had to be rejected before a reproductive system could be established which implies that rejection, now by pumps made from synthesised proteins, had a very early history. Possibly a system arose first in which energised proton gradients across protocell membranes were used to reject Ca\(^{2+}\). All life as we know it today has protein pump equipment coded at DNA and protein synthesis is limited by feed-back mechanisms, but note that such feed-back controls do not need a code—see Ref. [2]. A simple vesicle with organic contents can be stabilised in the sea by energised rejection of Na\(^+\), Cl\(^-\) and Ca\(^{2+}\). The Ca\(^{2+}\) pump synthesis control mechanism in prokaryotes at the DNA level is not known to the author.

The outside of the cell could utilise Ca\(^{2+}\) ions in two ways; as a binding agent to stabilise cell surfaces and as a catalyst in breakdown of large molecules so as to provide food for the cell. Both are still well recognised today in that Ca\(^{2+}\) outside cells is a stabilising agent of connective tissue and a cofactor in nucleases, proteases, saccharases and so on in digestion in animals. Especially interesting are the interactions between carbohydrates and proteins, for example in the C-lectins.
In passing we note that once the initial cytoplasmic system of controlled activity, based on the synthesis of the basic biopolymers through energy and material capture, evolved it remained the essence of all life. In the system the cytoplasmic messages to maintain activity were carried by substrates, Fe$^{2+}$, Mg$^{2+}$ and phosphates and so it must remain. Everything is then added on but any added on message system must not interfere with these primitive information carriers.

Now we must note that the release of oxygen from water by later prokaryotes at a CaMn$_4$ centre caused a rise in environmental availability of some elements such as copper and zinc and a fall in others such as iron and sulfide while Na, K, Mg, Ca, P and Cl ions remained unaffected. Prokaryotes could either escape this general pollution caused by O$_2$ finding niches free from this poison and its products or attempt to counteract them. We see various protective metabolic devices including wasting NADH to destroy O$_2$, SO$_2$ and H$_2$O$_2$ in the cytoplasm with Fe or Mn enzymes. However there is also a need to reduce the increasing Fe$^{3+}$ and SO$_4^{2-}$ to get essential Fe$^{2+}$ and RSH. Now such reductions are also sources of energy as is the reduction (possibly later) of N/O compounds and O$_2$ itself. This coupling occurs across the outer membrane with the oxidising agents acting externally. There are then a succession of sulfate and Fe$^{3+}$ “anaerobes” (really micro-aerobes since they live in zones of increased redox potential due to O$_2$ metabolism of the environment), denitrifying bacteria and strict aerobes. As stated this use of oxidative metabolism is not easily made compatible with the reductive Fe/S catalysed chemistry of the cytoplasm. We observe that the two are in fact largely separated in that much of the oxidative chemistry is carried out in the periplasm—a separate compartment. Note O$_2$ is produced here. We also observe that it is only here that one new element in the environment, copper, is functional in redox reactions and we note Fe/S proteins are absent but heme iron proteins working generally at higher potential are present. (We must not over generalise as a few oxidative enzymes, e.g. cytochrome P-450, can be found in the cytoplasm but they have extremely protected localised active sites.) Of course it is required that the DNA has adapted to this two-compartment system and it would be of great interest to follow steps including the introduction of essential new control mechanisms. As far as I can discover the required communication between periplasm and cytoplasm has little or no Ca$^{2+}$ dependence in these prokaryotes. DNA sequences do indicate that the EF-hand motif so prevalent in later organisms may have existed as a single-hand of low binding constant and is a possible precursor of the two-hand unit in eukaryotes of high binding constant, see below.

Another striking separation of different chemotypes of bacteria which had taken place was that of photosynthetic from non-photosynthetic bacteria. This led of course to the distinction between plant and animal life forms. However for two billion years Ca$^{2+}$ ions had little new functional significance except in photosynthesis with oxygen release. It may well be that awareness of the environment which developed in eukaryotes is hardly necessary for prokaryotes as their major activity is reproduction and they can change species quite quickly by genetic mutation.

### 6. Single cell eukaryotes

In Introduction, we pointed out that internally compartmentalised cells, eukaryotes (Fig. 5) appeared as oxygen increased and once the reducing capacity of the sea had been decreased. These new cells were larger with a flexible shape, but relatively fixed internally by filaments, and had a longer lifetime. They then needed protection, an ability to recognise favourable and unfavourable factors of the environment as well as to be able to coordinate the internal activity of the cell compartments. These cell compartments now included mitochondria and chloroplasts, which are organelles, apparently derived from pre-existing bacteria. They all needed a new messenger system. Table 1 shows that calcium-binding proteins of high binding strength are present in all these eukaryotes and even in the organelles but in small numbers. These proteins may be distantly related to the external Ca$^{2+}$-binding proteins of prokaryotes, but they become the sensors of messages. The calcium ion is the messenger not only about the environment but also in coordinating action between internal compartments even switching on the activities of the organelles. There had to be managed shape and control of mechanical filaments as well as of metabolism to be able to engulf large particles and to adapt physically. Furthermore the calcium ion could be used to actively trigger protective protein release.

As we have described in Fig. 4 the rise of oxygen brought with it a changed environmental chemistry. In turn by using compartments the eukaryotes could develop new chemistry in them using these new components of the environment. We observe sulfation and glycosylation for example in the ER. Now the ER is also a zone of control over protein-folding of proteins for export and export itself. Both became managed, calcium, chaperones for folding, again demanding a new set of proteins but now of low binding strength as Ca$^{2+}$ is imported into the ER, Table 1. Vesicles are also the place of synthesis of calcium mineral units for export to give shells. In this way mineral layers...
of eukaryotes such as foraminiferae are quite differently formed from the shells of prokaryotes, even corals.

In most of this internal development the messenger system of the cytoplasm was not affected remaining largely dependent on transcription factors based on organic substrates of a variety of kinds and on Fe$^{2+}$, Mg$^{2+}$ and phosphate. The Ca$^{2+}$ messages from outside acted on the phosphate compounds of transcription only indirectly as the Ca$^{2+}$-proteins did not interact with targets of the other ions. Of course Ca$^{2+}$ ions after entry had to be rapidly rejected by pumps to vesicles, organelles or vesicles. A surprising feature is that all these activities appear at once. However we must remember that organised systems (uncoded) arise and are persistent only as an overall unit. Vast numbers of less persistent systems may well have existed, see Fig. 6, but disappeared.

7. Multi-cellular eukaryotes

As oxygen levels rose higher we observe that the single cells and colonies of eukaryote cells became accompanied by organised differentiated cells in a single body. Now to maintain such differentiated organisation requires three quite novel features: a connective tissue, a self-controlled external fluid environment, and a new communication systems. To bring such advances about the chemical elements newly released into the environment in quantity, copper and zinc were used. In the connective tissue formation copper proteins aided cross-linking chemistry to stabilise the network, and calcium ions assisted. Zinc proteases became used to break this tissue so that cell growth can occur. These proteases are not unlike those used by earlier cells in extracellular digestion. It is between cells in fixed positions that the new messengers were deployed so that the whole developed, metamorphosed and then was maintained in adult form. The initial stages of growth, fertilisation of a single cell, were in part mediated by calcium ion entry, and immediately subsequent change could be controlled by cell–cell contact. However when the cells separated into organs held some distance apart in a connective tissue network and an extracellular fluid, quite novel communication messenger molecules, transmitters and hormones, were required. Copper ions could not act in this capacity as they had to be $>1$ mM in the extracellular fluid in order to maintain the outside to the inside of a cell existing message system. (N.B. Zn$^{2+}$ ions can be used after concentration in vesicles.) The transmitters are short-lived organic molecules released from cell, A, by an environmental event. The molecules are produced in vesicles and release is stimulated by Ca$^{2+}$ ions invasion caused by an external event. These organic molecules are largely the product of oxidative metabolism in the vesicles catalysed by copper enzymes e.g. adrenaline and amidated peptides. The messengers are recognised specifically by receptors on cell type, B, which on binding them on the outside allows Ca$^{2+}$ entry. The Ca$^{2+}$ then acts as a messenger much as for a single eukaryotic cell responding to an external event. The action is fast as is recovery and no connection to a code is required. Organised systems do not need a code which acts to give reproduction, that is apparatus production, and assists in management but a flow system itself can be very persistent [2].

The hormones act differently and although they are products of oxidation their enzymes are often heme enzymes in the cell cytoplasm. The enzymes, such as Cytochrome P-

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**Table 1**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Location and function</th>
</tr>
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<tbody>
<tr>
<td>Calmodulin$^a$</td>
<td>Cytoplasm, trigger of kinases, etc.</td>
</tr>
<tr>
<td>Calcineurin$^a$</td>
<td>Cytoplasm, trigger of phosphatases</td>
</tr>
<tr>
<td>Annexins</td>
<td>Internal associated with lipids, trigger</td>
</tr>
<tr>
<td>C-2 domains</td>
<td>Part of several membrane-link enzymes</td>
</tr>
<tr>
<td>S-100$^+$</td>
<td>Internal and External: buffer, messenger, trigger</td>
</tr>
<tr>
<td>EGF-domains</td>
<td>External growth factor but general protein assembly control e.g. fibrillin</td>
</tr>
<tr>
<td>GLA-domains</td>
<td>External, associated with bone</td>
</tr>
<tr>
<td>Cadherins</td>
<td>Cell–cell adhesion</td>
</tr>
<tr>
<td>Calsequestin</td>
<td>Calcium store in reticula</td>
</tr>
<tr>
<td>ATP-ases</td>
<td>Calcium pumps</td>
</tr>
</tbody>
</table>

$^a$ EF-hand proteins.
450, protect the oxygen reactions in pockets, and are maintained at fixed levels in one organism condition. These hormones travel to neighbour cells but the slow response is now most commonly from the nucleus mediated by zinc (finger) receptors. Changes in concentration bring about slow development and Ca²⁺ is not involved. Basically there are fast transmitter and slow hormone responses but intermediate examples are well known. As the number of organic messenger molecules increased so the variety of responses to them by Ca²⁺ ions increased (Fig. 7 and Table 2) and new calcium-associated proteins were synthesised.

8. Multi-cellular internal fluids

Clearly the organised cells in single organisms have to be surrounded by fluid and the more this fluid is held with a constant composition the better the coordination of action. In later organisms the observed concentrations of the elements in the fluids becomes fixed quite closely. The control of Ca²⁺ ions here is very strict in say man. Now at the same time these fluids develop new proteins such as carriers for elements as well as in connective tissues. Many of these proteins have oxidatively modified side-chains such as hydroxy-aspartate and carboxylated γ-carboxyglutamate. These are centres of Ca²⁺ binding. Other proteins are used in assisting internal mineralization, that is internal to extracellular fluids not cells. Most notable is bone a remarkable Ca²(OH)(PO₄) material which is piezo-electric. This means that it is a mineral which responds to stress and in fact is a “living” mineral being adjusted throughout life much as is a protein inside an organism and unlike a shell. The developed complexity of the calcium ion signalling is given in Fig. 8 showing the connection to filaments and minerals.

9. Animals with nerves and a brain

Animals are scavengers of plant (and other animal) chemicals. They have no chance of an independent existence and must forage. While the essence of plant development within the community of plants is growth to capture more light that of animal development is improvement in scavenging. Clearly a static system is desirable for a plant with its root/ stem/leaf body while an ability to move and to move rapidly is of advantage to an animal scavenger both in capturing prey and avoiding predators. As the animal organisms took advantage of coordinate differentiated cell activity in larger
bodies the faster was the need for the coordination and total body movement necessary to provide survival strength. This requires very fast messengers, faster than the modes of action of calcium ions and of organic transmitters between organs, were possible. To accomplish this end the elements of fastest diffusion Na+, K+ and Cl− have been pressed into service for their movement is unimpeded by organic molecules since they have only trivial binding strengths, contrast Ca2+. Moreover by using physical electrostatic effects of the ions an effective wire can be built carrying electrolytic depolarisation pulses which have great speeds of transmission over many centimetres. These wires are the tubular nerve cells of higher animals. The disadvantage of such a simple physical message of Na+, K+ and Cl− is that it cannot be used to bring about chemical triggering of protein changes such as the conformational changes in muscle. The last step at a nerve junction or synapse following nerve transmission is then that depolarisation allows Ca2+ ion channel entry. The events which follow are common to eukaryote organisms without nerves and involve direct physical or chemical change such as the energised action of muscle or the release of organic transmitters. Observe that once again evolution utilises initially rejected ions, Na+ and Cl−, to later advantage.

To develop this messenger system further requires that the nerve messages are coordinated and it is this coordination centre which becomes the brain. This is a most interesting systems development, quite different from one based on a code. We have seen that the DNA is the main centre of single cell coordination from the most primitive cells up to multi-cellular organisms but some coordinate systematic flows were also present. However when cells became multi-cellular organisms there had to develop a faster response system to the environment depending on novel feed-back systems not at all related to synthesis as an activity, for example energy use in movement. This activity does not relate to a DNA trace, except that the machinery requires the synthesis of biopolymers, and the activity does not leave any trace after recovery. All the dominant characteristics of cellular organisms until there is a brain have the limitation of slow coded response and fast unrecorded response. The brain came to be different in that it created traces, memory storage, of events independent of the organisms DNA and synthesis. It used instead of a linear code of unique intensive storage of information a variable code of extensive storage of molecules and charges in a 3-dimensional cell network which we call a memory. This memory can be recalled rapidly in response to external events. The organism is then a product not just of reproduction but of experience. Moreover experience can be shared (taught) and transmitted (not via DNA) from animal to animal. (The whole of this development produced two independent control centres in one body or organism or even collection of organisms led up to the complicated nature of mankind which cannot be thoroughly treated as robotic depending on genes. The central role of Ca2+ ions remained at synapses and in storage release. This development of a brain aware of and responsive to the environment may be a last step in the purely biology/environment ecosystem evolution.)

### 10. The Evolution of Calcium-Binding Proteins

Here we have only the space to summarise the way we see this development of the calcium binding proteins in Table 1.

1. Early weak-binding constants (10^3 M^−1) at cell surfaces.
2. Early weak-binding proteins for Lewis acid catalysis.
3. Early pumps—strong internal binding constants (10^7 M^−1).
5. Arrival of Ca2+-entry channels and Ca2+ trigger proteins calmodulins, S-100, C-2 domains (strong binding).
6. Vesicular storage proteins (weak-binding).
7. External EGF-domains oxidised side-chains (weak binding also lectins see (1)).
8. Further development of Lewis acid digestive functions in vesicles (weak-binding).
9. Annexins, new trigger proteins with cooperative binding (strong) with phospholipids. The appearance of S-100 proteins.
10. Gla-domains—oxidised glutamate.

The sequence 1. to 4. is in prokaryotes and that of 5. to 10. is in eukaryotes.

Note. Undoubtedly each group of protein functions also evolved through gene duplication. The numbers of proteins in a given class increased rapidly especially in animals to meet the needs of the increased scavenging systems.

### 11. Summary of biological calcium ion evolved activities

Before we touch on the new chemistry of calcium in the hands of man it is useful to look at a summary of the development of messengers and controls as calcium has had a central role in this unavoidable one way increase in complexity and organisation (Fig. 8). It is the very ability of the genetic apparatus to construct cells then multi-compartment apparatus, messengers and their storage (chemical and physical) together with energised flow systems of ions which allowed a network of fast response not dependent on genes, except for basic construction. In turn this was to gain deeper and deeper involvement of the environment in the organisms. The calcium ion messenger introduces this involvement in its permitted...

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Primitive Organisms</th>
<th>Mg2+/ATP4− controls phosphorylations</th>
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<tbody>
<tr>
<td></td>
<td>Prokaryotes</td>
<td>Fe2+ controls redox equilibrium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Na+ K+/Cl− control osmotic pressure</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Single Cell Eukaryotes</td>
<td>Ca2+ controls activated states and relationship to environment Mn2+ controls development of plant-related organisms</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Multi-cellular</td>
<td>Zn2+ controls hormonal responses relating to growth of organisms and development Cu2+ and Zn2+ control connective tissue syntheses and degradations Extended use of Ca2+ in excited state signals. Generation of Na+ (K+) signalling and the evolution of the nervous system</td>
</tr>
</tbody>
</table>
movement into and out of cells since before this time in single cell bacteria the overwhelming drive is to multiply using a cytoplasm free of calcium and not to interact with environmental fluctuation. Bacteria meet environment change by fast mutation. The ions of Na+, K+, Cl− and in part Ca2+ allowed some environment contact through membrane potential sensors not invasion in these bacteria. Sophistication, after the unicellular eukaryote development of Ca2+ message systems, grew through the use of organic molecule signalling between cells in an organised body of organs. The simple inorganic ion messenger system itself could arise just because of the nature of the physical chemical needs of even the most primitive cells – Ca2+ had to be rejected – even uncoded protocells. Later, greater speed of response was demanded in nerves dependent on the rejection of Na+ and Cl− also essential in the most primitive cells or protocells. Thus an energised ionic system was created as well as an energised synthetic system of chemicals and both can become knitted into a unity of activity but with fast and slow responses at least partially independent (Table 3). The slow response could be linked to synthesis at the DNA but the fast response became linked to an independent control centre based for its structure on DNA but not for its subsequent activity. Its nature became in the brain an independent response system for it retained the impressions of environmental events, which could be recalled, activated by a second environmental event. Action independent of DNA based on impressions came into being besides DNA dominated activity and probably confused with it over long time periods. I give this explanation as something of this kind is required to explain the next phase in the development of the ecosystem of the organisms and the environment. It is the sequence of messenger development and storage of messages in an independent (from genes) system that led to mankind. These actions of mankind cannot be traced simply to gene functions.

12. Mankind

In so far as calcium functions are concerned man has developed value to an organism but completely outside the organism, that is in the environment, with no basis in information coded in DNA but retained in stored images in the brain and in recorded external stores. We could call this non-biological evolution for it is environmental change not organism change. This information is used in material constructions e.g. in cement, mortar and plasters. It is also used in repair of internal bones and teeth and in assisting plant growth. Man is attempting to make the environment much more interactive with organisms. In our book [2] we try to show that this final evolution of calcium functions is but one example of the way in which the changing environment, changed by organisms, back reacts on the organisms themselves for we are becoming town not forest animals. Finally this has produced organisms which, by understanding the environment begin a new process of changing it. This change will then back-react on all the different chemotypes but not in a simple obvious manner. We are not able to predict the consequences of global warming and we are not able to predict the effect of remodelling the chemical environment including the ways in which we use calcium. (Behaviour in towns is not based on genetics but on the ionic gradients including those of calcium introduced into the brain. We need to remember that persistent systems exist and can be produced time and time again through energised activity of materials (Fig. 9) and a code adds to this possibility giving reproduction.)

References