Some Biochemical Consequences of a Consistent Framework for the Origin of Life

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Abstract

Enquiries in several fields have arisen from theories of the origin of life based on various axioms. This thesis develops a new theory fitting the assembled evidence. It takes as axiomatic:
1] Photophosphorylation involving purines and a natural laser based on water ice.
3] A basic nucleohistone structure.

Rigorous application of the principles of evolution and thermodynamics defines a primitive subset of modern life. Protein synthesis is absent from this life form, which provides a model for understanding endocrinology, pharmacology, bioenergetics and tissue differentiation.

The model is developed to show its consistency with known data in these fields, and extended to give a perspective on the mode of action of morphinan drugs and the dietary requirements for prevention of heart disease and cancer. The work is illustrated using a graphics system designed to promote the use of home computers in the study of chemistry, fostering a caring approach to the subject conspicuously lacking in contemporary industry, and an understanding deficient in government agencies.

The new model suggests that phosphate is assimilated as pyrophosphate with arginine as carrier, incorporating the atomic constituents of dAMP to a cell. Pathways regulating this process control cell division in eukaryotes; an essential role for silver is identified. Evolution of the associated polypeptides predates protein synthesis. The histone, spindle and centriole proteins involved in cell division derive from amino acid co-polymers.

Energy coupling, directed catalysis and metabolic regulation emerge as features of life without enzymes. The foundations of symbiosis, as in nitrogen fixation, the dietary importance of trace elements as illustrated for zinc, silver and selenium and the concept of control through substrate transport rather than enzyme catalysis are invaluable tools for the understanding and manipulation of modern biology.

Contents

1 Abstract
2 Legends
3 α1 Preface
5 α2 History
9 α3 Method
12 α4 A model for the origin of life
DISCUSSION

14 β1 Origin of life
15 β2 Ordered Cubic Ice
17 β3 Primordial photosynthesis
19 β4 tDNA Structure
20 β5 tDNA Function
22 β6 Thermodynamics
23 β7 Polypeptides & catalysis
25 β8 Nucleohistone structure
27 β9 Histone Function
EVIDENCE
28 γ1 Motility
29 γ2 Sensitivity
30 γ3 Excretion
30 γ4 Respiration
31 γ5 Growth
32 γ6 Rigidity
34 γ7 Assimilation

35 γ8 Reproduction
37 γ9 Osmoregulation
CONCLUSIONS
39 δ1 Differentiation
41 δ2 Trace elements
42 δ3 Conclusion
44 References
58 δ4 Appendix - Software
66 Figures

Legends
Figure 1. Known and proposed structures of ice compared. — Ferroelectric transition in ice
It and ATP-Mn\textsuperscript{++} complex showing relation of purine ring to phosphodiester bond during
phosphorylation, see Figure 18.

Figure 2. Transfer RNA structure related to the unit membrane. — Width of tRNAs
determines the triplet code, and their ‘hinged’ αα-binding arms introduce the bound αα
for transfer to the ribosome. Vitamin A, silver porphyrin and hexadrenaline-sodium
complex are shown to the same scale, see Figure 18.

Figure 3. Mechanism of tDNA. — The stages enabling, activating and driving directed
transport of an uncharged substrate by a charged carrier, and of exchange of charged
substrates by uncharged carriers.

Figure 4. Structures related to active transport & ion exchange. — Choline controls
membrane potential.\text{SO}_3\textsuperscript{−}, \text{SeO}_3\textsuperscript{−} & adrenaline rings exchange Ca\textsuperscript{++} / Mg\textsuperscript{++} | Mn\textsuperscript{++} & Na\textsuperscript{+} / K\textsuperscript{+}
control P\textsubscript{i} \sim P\textsubscript{i} energy release, osmolarity & viscosity \rightarrow BMR.

Figure 5. Codeine/morphine in K\textsuperscript{+}.adrenaline\textsubscript{6}, NaCl & O\textsubscript{2} transport. — Explaining
valinomycin action, drug addiction, kidney failure and bipolar disorder, see Figure 19.

Figure 6. Efficient NAD-NADP proton transport and N\textsubscript{2} fixation. — Ordered H-bonds eschew
Mitchell’s chemiosmosis and Haber’s thermodynamics.

Figure 7. Bone, tooth & plant SiO\textsubscript{2} skeletons use apatite\textsubscript{2},SiF\textsubscript{6}\textsuperscript{−}. — Adrenaline |
noradrenaline, serotonin | melatonin analogues reinstate Ag in biology.

Figure 8. Zn and Arg carry glucose, gulonate from vit C and P\textsubscript{P}. — Zn\textsuperscript{++}, Ag\textsuperscript{+}, creatine &
arginine carry β\textsubscript{D}glucose, 2keto-\textsubscript{L}gulonate, inositol & P\textsubscript{P}, explaining action of anti-cancer
drugs canaverine, imidazole, dacarbazine & chloroplatinate.

Figure 9. Se & vit E help 3-phospho-mevalonolactone pump water. — α-tocopherol releases
SeO\textsubscript{3}\textsuperscript{−} from vasopressin, carrying Mn\textsuperscript{++}, cofactor synthesising cholesterol from mevalonate,
controlling H\textsubscript{2}O transport, see Figure 19.

Figure 10. Nine Orthogonal Systems. — Parallels amongst endocrine control pathways &
interaction with cell division.

Figure 11. Silver controls phosphate transport as pyrophosphate. Vit A transfers energy from
Ag-porphyrin, esterifying P\textsubscript{i} to P\textsubscript{P}, carried by arginine.

Figure 12. Nucleohistone structure enables efficient replication — Anti-parallel β-pleated
proteins with alternate neutral & basic ααs hold DNA flat. Pro forms asymmetric bends,
creating coils of 21x 9-base pair units. 9 coils form ‘minions’, explaining chromatin packing
& directional transcription. See Figure 20.
Figure 13. Protein synthesis on DNA and memory storage on DNA. Transfer RNAs feed ααs to ribosomes for protein synthesis, proton-ordered arrays of H-bonds connecting Lys | Arg ω-amines to DNA phosphates enable memory storage.

Figure 14. Nine centriole pins send energy to chromosomes along conjugated H-bonds in the nine α-helices of a keratin spindle. — Each of three α-helices in spindle fibres affords three pathways of alternate double- & H-bonds, transmitting energy (accelerating chromosome protons along the cytoskeleton al features retained from early life. See Figure 20.

Figure 15. Differentiation & eukaryotes evolve from prokaryotes. — Prokaryotic chromosomes insert incorporated transport pumps to their membranes, eukaryotic exons and intons are nouns and verbs in transport genetics.

Figure 16. Oxidative phosphorylation. — Oxidative phosphorylation reinterpreted, using 4μ infrared quanta as intermediates.

Figure 17. Solids produced by neighbour binding. — Cell-cell binding determines tissue topology, five cell-cell connections are acceptable, a sixth allows tumours and cancers to form. The ‘five hook’ theorem, 3D equivalent of the 4-colour mapping theorem, if proven, would support this contention.

Figure 18. Ice It phase transition and width of adjacent tRNAs. — Red-green stereos created with Watanabe flat-bed plotter.

Figure 19. Hex-adrenline & Vitamin E interacting with vasopressin. — Red-green stereos created with Watanabe flat-bed plotter.

Figure 20. α-helices in keratin & β-sheet binding uncoiled DNA. — Red-green stereos created with Watanabe flat-bed plotter.

Figure 21. Periodic table showing availability of biological elements.

α1 Preface

Basic things have to be simple. Such are the chemistry of life and mechanisms which control it. Its structures rest largely on the tetrahedral bonding of carbon, nitrogen, oxygen and phosphorus. Such bonding occurs in diamond, but is not readily appreciated from every perspective:

Departures from the perfect symmetry of the tetrahedral components of this structure, occurring in silica and in water, yield a plethora of compromise structures - the clays and the ices: Diagram 1

Competing for variety, ice wins through the residual entropy in its hydrogen bonds and the possibility of loss of this entropy at low temperatures - of achieving order amongst disorder and the selective photophosphorylation of ADP to ATP in the primordial soup: Diagram 2
Ordered ice Ic is a natural laser formed by recrystallisation of ice in liquid N$_2$ - the conditions of ‘nuclear winter’. The ferroelectric crystals undergo an order-disorder transition at ~60 K [72 K], converting heat to monochromatic infra-red of wavelength 4μm - the free energy of the reaction ADP + P → ATP. The same process reversed drives active transport - an ion pump comprising a unit membrane pore lined with H bonds derived either from protein or α-helices or nucleic acid base pairs: Diagram 3

At rest, membrane potential is compensated by redistribution of ions on the membrane surface, and by polarisation of H-bonds within it. Excitation of the H-bonds by 4μ quanta, arising primordially from the ice transition, now from ATPase, electron transfer chains or adenyl cyclase, depolarises the pore, driving anion through the membrane against the potential gradient. Allosteric activation of adenyl cyclase, arising from substrate recognition, results in specific active transport. The new perspective on the origin of life points to a nucleic acid-based pump. The structure of tRNA fits the requirements: Diagram 5

A family of transport DNA’s, tDNAs, structurally analogous to the tRNAs involved in protein synthesis, resides in the cytoplasmic membrane. These genes replicate along with the chromosomes, they are not gene products. tDNAs are selected by ‘differentiation DNA’, dDNA (analogue of mRNA), arising from introns by reverse transcription. Selecting tDNAs determines cell diet just as selecting tRNAs determines protein composition. Contemporary Work on or-helical membrane proteins involved in vision, electric eels and neurotransmitter binding does not contradict this proposal. Such gene products do not allow equipartition of transport activity to daughter cells, nor explain tissue differentiation. The simplest complex ions pumped by tDNA are probably

\begin{align*}
\text{tRNA lines pore} \\
\text{size sets triplet} \\
\text{code, tDNAs are} \\
\text{genes, not} \\
\text{gene products}
\end{align*}
β-D-glucose, Zn$^{++}$ and O$_2$, H$_2$O, I$^+$: Diagram 6

Zn$^{++}$ is delivered by insulin, removed by glucagon. Its role in controlling glucose metabolism accounts for diabetes mellitus. Pharmaceuticals involved in its treatment bear the ‘triangle of sweetness’ which binds Zn$^{++}$. The complex which I$^+$ (iodinium) forms with oxygen hydrate suggests basal metabolic rate, BMR, is simply a measure of oxygen consumption, regulated by the thyroid. Whilst Be$^{++}$ poisons the Zn$^{++}$ system, Li$^+$ is used to treat I$^+$ system disorder, m-d psychosis.

Another important complex is that of Na$^+$, K$^+$ with a hexamer of [nor]-adrenaline, substitutable by morphinans and encephalins, shown here alongside the known ionophore, valinomycin: Diagram 7

The new model for [neuro]-endocrinology suggests that that all transport of hydrophilic substrates, and of water itself, is active. Mevalonic acid and its lactone are the most promising candidates for carrying water: Diagram 8. Its reversible formation of a lactone, suits it for this role.

Selenite arises from oxidation of Se carried by the pituitary hormones, (vasopressin and oxytocin) by or α-tocopherol. Mevalonate is primarily a breakdown product of saturated fatty acids. Under normal conditions, it is polymerised to cholesterol which is transported away for excretion as bile etc: Diagram 10

Control of mevalonate is susceptible to dietary saturated fat, stress (through variation in cardiac output) and dietary salt, which invokes Mn (as MnCl$_4^{2-}$) for salt transport. The 50% Se deficiency of ‘Western’ diets, combined with these factors, precipitates a majority of premature deaths.

Whilst the endocrine role of trace elements explains their tissue specificity, Se deficiency alone does not account for the pandemic of cancer. Ag controls assimilation of phosphate for chromosome replication. Formation of pyrophosphate, PP$_i$, mediated by retinal
is the critical step: ‘Esterification energy’ is passed as a soliton if its redox potential, mediated by silver porphin permits: Diagram 11

The trans-membrane environment suits not only assimilation, but also some important metabolism. 60mV across 20Å, or 30MV/m, can drive N₂ fixation (with Mo as catalyst?): Diagram 12

My thesis proposes assimilation and control of assimilation evolved before metabolism and control of metabolism. Life without protein predated its present counterpart, and this perspective reveals rules for understanding the modern version. The triplet code, cell surface antigens, neurotransmitters and peptide hormones evolved from entities with useful roles in protein-free life, and are better understood in this light. Should the thesis which follows be understood, then I hope this understanding will be used to bring greater harmony to earth life and not to achieve short-term profit.

α2 History

The axioms on which science is based call on the imagination and incredulity of the student. The request ‘let us suppose…”, first met in school mathematics, invites suspension of belief in previously held opinions and doctrines. Within mathematics, it is clearly harmless. Extend this concept to the natural sciences and it sometimes conflicts with deeply held conviction. To those ignorant of the scientific method, it can appear heretical. Despite its dependence on science, contemporary society freely abuses scientists and their research in favour of technologists. The history of science is not readily traced beyond 2000 BC, though it would seem likely that technological achievements at that time reflected on a considerable tradition of scientific enquiry and endeavour. Numerous civilisations have attached importance to their ideas about the origin of life.

Hindu, Chinese, American, Egyptian, Babylonian, Greek, Jewish, Christian and Muslim traditions all include creation stories in their mythologies. Such accounts of the origin of life relate to the underlying purpose of the creation rather than to its mechanics. Pre-Judaism, they are holistic, taking for granted the mutual dependence of all life forms, the earth and cosmos as parts of a single creation. By positing many deities of unaccounted origin, the pre-Jewish religions facilitated moral teaching based on natural models. Familiarity with circadian, lunar and annual rhythms naturally led to early astrology and the association of deities with cosmology.

The Jewish, Christian and Muslim monotheist religions, whilst less anthropomorphic than their predecessors, encouraged a view of nature and cosmology distinct from human affairs. The exploitation of non-human resources enabled the leisured classes of the
Renaissance to lay the foundations of modern cosmology and science, based on mathematically convenient axioms.

Modern science requires considerable vocabulary, literacy and mathematics. Without these, even the most trivial proposition cannot be adequately developed or communicated. The evolution of writing, including an efficient mathematical notation, and the technologies of copying and communication were essential to scientific advance. The following dates suggest a framework on this basis:

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Newtonian ‘action-at-a-distance’ mechanics and thermodynamics, whilst paving the way for the industrial revolution, contribute little to the life sciences, see above.

As the cost of military conflict has risen since the Renaissance, education has become increasingly specialised. Social levelling has reduced the scope for personal development. Public affluence masks private squalor. So the very recent advances in biology which this table presents are largely fashioned in dogmatic physical science; whilst physics and chemistry was in a state of flux, all derivations need regular review. Nowhere is this more apparent than in relation to theories of the origin of life.

Since Darwin, if not previously, an attempt has been made to place each feature of the biosphere in its evolutionary context. This is easier in the case of symbiotic species than of subcellular organelles. The vogue for applying statistical methods - for playing dice with nature - reinforced, perhaps, by Heisenberg’s uncertainty principle and the apparent willingness to put a ‘destruct’ button in the hands of ageing politicians - has encouraged the invocation of improbable events to fill gaps in evolution. This results in a view that science is not necessary to explain these facts or can be gainsaid when considering them if inconvenient or misunderstood. Description of the origin of life, with the implicit possibility of experimental verification, is inconvenient to current theology and to ‘big bang’ cosmology. Whilst those close to these specialties are dissatisfied with the ir axioms, and are prepared for a revolutionary change, most biologists are content to ignore these options.

Theories of the origin of life of the type currently debated date to the first clear distinction between and identification of living versus non-living matter, to which Pasteur contributed significantly. He countered assumptions of continuous creation, exemplified by the supposition that hibernating species were spontaneously regenerated from their winter hiding places, that putrefaction was innate to rotting material and not subject to invasive living organisms.
This distinctive continuity of the life process, whilst reinforcing the notion of a ‘life force’, also focuses attention on the first mover in the process, the god(s) of traditional stories of creation. Darwin’s contribution in establishing the relatedness of all terrestrial life, to one or at least to very few starting points, was seminal. This approach pointed to the pre-existence of a primitive condition in which relatively few species with relatively primitive characteristics could adequately explain the modern biosphere.

Appreciation of the time course of evolution has arisen largely from the fossil record, from observations of rates of sedimentation etc and more recently from radioactive dating techniques. All such considerations revolve around fairly sophisticated life-forms - exemplified by the dependence of the fossil record in large part on the preservation of skeletal structures likely to have arisen quite late in biochemical evolution. Indeed, Darwin’s work could be considered in the absence of any appreciation of biochemistry.

The idea of a ‘life force’ or other special property predicating life is not now respectable science, but has largely been replaced by the central dogma of molecular biology regarding DNA and protein synthesis. This turn of events starts as recently as the work of Mendel, which indicated that discrete characteristics could be transferred from generation to generation. The much later finding of order in macromolecules, particularly proteins, was firmly established by the work of Bragg in X-ray diffraction. The relatively recent discovery of the genetic code for protein synthesis by Watson and Crick has tended to eclipse the wider debate.

Observing the relative scarcity of complex organic molecules in the modern environment away from living cells clearly begs the question as to the condition in the absence of organisms, which, by whatever mechanism, will tend to sweep the seas clear of organic substrates on the one hand, but which would appear to be in themselves the only source of such molecules. Oparin and others have analyzed the likely composition of a primordial soup by realistic experiments on the consequences of artificial lightning etc applied to reasonable early atmosphere mixtures. Uncertainty as to the redox potential, atomic composition, etc of such an early atmosphere has been the subject of much debate.

The drift of such work has been essentially to arrive at a consensus as to the thermodynamic equilibrium likely to prevail on a planet subject to current ideas of cosmology. The arguments tend to start from the idea of a finite age for the solar system, and so of the earth’s surface, of a particular sequence of climatic changes consequent on the supposed cooling of a new earth, and then an organic chemical milieu which at some juncture favoured the spontaneous evolution of macromolecules competent to constitute available life form.

It is important to realize the centrality of cosmology to theories about the constitution of the biological soup. Proponents of the ‘big bang’ model of the universe appear to suggest that the life process on earth has continued with only relatively mild climatic variations for around half the supposed time since some cataclysmic event involving colossal temperatures and densities of matter dispersed sun and stars at random. The central theory of Hubble of universal expansion rests ultimately on the speculations of Isaac Newton as to the nature of light.

The willingness of specialists in one discipline to take the speculations from another as established fact is rooted in the economic necessity of educating scientists primarily to fulfil technological and professional roles in society. This is reflected in the various scientific
advances which emerged during the world wars. So the implications of recent work on continental drift, indicating a misfit between the tectonic plates and the Earth’s present radius, has not been taken into account by students of speciation and extinction insofar as it affects considerations of day/month length, ocean depth, atmospheric pressure and climate.

This lack of an interdisciplinary approach to the question of the primordial soup has led to a number of blind alleys. Whilst most biologists would accept *The Selfish Gene*’s message, and seek an early source for DNA, many investigators have been concerned to establish the pre-existence of amino acids, polypeptides and oligopeptides and their precursors - even to suggesting the origin of such in a clay matrix could be followed by *Genetic Takeover*. So central to the life process do such bystanders view protein synthesis, that they take its primacy for granted.

Following from that perspective, Hoyle and others have proposed that, given that such a complex system cannot have so arisen during the supposed age of the solar system, it must have arisen outside the solar system, and whatever process is involved, it must be continuously active. It is implicit in this sort of argument that macromolecular species which were unlikely to arise at thermodynamic equilibrium in the primordial soup were nonetheless stable in that soup when arriving from ‘outer space’ and able to thrive implicitly against the prevailing thermodynamics - and multiply there.

There exist at present, then, a number of more-or-less widely held views as to the nature of the origin of life, coordinated with a number of attitudes to the nature and importance of the question being addressed. The models are partial, not complete axiomatic theories, and fail outside the progenitor’s speciality. Current areas of doubt are illustrated by the search for nearby stars with earth-like planets, the aforementioned debate as to the bulk of the earth doubling based on tectonic plate data, the plethora of explanations for the extinction of the dinosaurs, appreciation of the susceptibility of terrestrial life to a ‘nuclear winter’, involving climatic changes quite trivial in cosmological terms. There exists a small but vocal lobby of individuals who take the Bible to be literally true. Others are prepared to use statistical analysis to support the spread of viral epidemics by intervention from outer space rather than from travelling salesmen.

The laws of thermodynamics, based firmly on statistical analysis, do not appear to be breached by any system yet investigated. The vast majority of ordinary phenomena depend on mass action and are subject to these laws. To be observable, any chemical process need occur a vast number of times at the atomic/molecular level and the products must be substantially in equilibrium with the environment. Even the most sophisticated techniques of flash photolysis used to study reaction pathways lay no claim to observe the history of individual atoms.

### α3 Method

In seeking to establish a consistent model of the life process - to apply reductionist science to the plethora of specialties once embraced by ‘natural history’ - I have met several problems. Prime amongst these has been the lack of peers, purpose or precedent. Of 280 approaches to possible peers, 74 were rejected, 99 were unenthusiastic and 107 went unanswered. Without preceding models for comparison, the power of Occam’s razor is unavailable. The criticism that my new paradigm constitutes purely speculative suggestions which are not based on established data, or the existing body of biological theory [Editor, J.
Theor. Biol. 1974] reflects a general view that biology is immune from reductionist logic due to the complexity of its data and the huge body of ad hoc theory surrounding it. As to purpose, antipathy towards pure science - to an amateur wishing to understand without seeking to exploit the natural world - is an obstacle to progress when ‘spin-offs’, such the possibility of preventing chronic illness, emerge.

My purpose was to answer the question ‘why ATP’. This large, complex molecule is ubiquitous. Present in nucleic acids as a letter in the genetic alphabet, as high energy intermediate throughout metabolism and as a structural component of tRNA. Against a general assumption that the simpler constituents of proteins must be primitive to nucleic acids, this anomaly fascinated me. My precedent was the work of Michael Faraday on electromagnetism - and a conviction that electromagnetic quanta must be incorporated in biomechanics. The mighty strength of locust tendons, the tidy separation of chromosomes, the similarity in size of sarcomeres from ant and elephant muscle – all inspire reduction of biology to physics and doubt as to the prevailing axioms of biology.

The vast resources poured into biomedical research by my prospective peers yield, at least, a body of literature, brought together in Chemical Abstracts. This has furnished the evidence necessary to test hypotheses. Whilst my searches for information have been catholic, they have also been methodical. It is with methods of accumulation and correlation of interdisciplinary data that I am concerned here.

There is no ‘established’ theory for the origin of life. Earlier accounts have concentrated on particular aspects of the topic. My model draws on the same information - on primordial soup composition, climatic variation, available time-span, etc, and owes earlier investigators a debt of gratitude for researching these factors. It differs in eschewing the element of chance inherent in the models which prompted that research. ORIGIN is not a good keyword.

The concept of evolution may be regarded as a logical tool. It requires that all natural historical progress had certain pre-requisites and afforded sufficient benefits to reward its costs. It applies to chemical species and biochemical pathways as much as to taxonomic species and their ecology. Just as the taxonomic tree need be complete, so must the history of biochemical control. At every stage, biochemistry must reflect thermodynamic equilibrium and respect continuity. Just as the fossil record maps the evolution of species, so the variety of pathways manifest across contemporary species maps the evolution of biochemistry. This is not sufficiently widely recognized for EVOLUTION to be a keyword.

If biochemistry evolved almost to its present state without benefit of protein, the prevailing dogma regarding enzyme catalysis does not make for a literature classification useful to my enquiries. HOMEOSTASIS is conventionally understood in terms of reaction catalysis rather than substrate transport, and is consequently not a useful keyword.

Contemporary [neuro-]endocrinology refers to hormones as converting ‘messages’ to the cell nucleus via membrane protein ‘receptors’, second messengers etc. implicitly, control is achieved via protein activation or synthesis. The perspective I seek to investigate, of control of cell metabolism through control of active transport, concomitant with hormone binding, independent of protein, makes the existing classification of HORMONE and ENDOCRINOLOGY unhelpful.

The nucleohistone structure I describe forms the basis or a powerful theory of memory storage involving DNA-histone H-bonds. From that theory comes the suggestion that
exist 9 orthogonal (mutually independent) control pathways in eukaryotic systems, loosely equivalent to 9 parallel processors in a digital computer. That work is not discussed in this thesis, but has proven a most useful basis for classification. The most useful classification is the Chemical Abstracts Substance Index for an individual ELEMENT, sub-head ‘BIOLOGICAL STUDIES’

Digital computers have three potential roles in this investigation. Reference material can be retained and searched, feedback control systems modelled and text and illustrative materials created with their help.

[1] I have accessed ~20M words in New Scientist, and ~10^5 titles in Chemical Abstracts with further inputs of information from Royal Institution lectures, media broadcasts, personal correspondence and a monthly MENSA ‘open house’, and initially created a file of 3 x 5” cards. This became too large to search, so I copied it to my word processing system, SPA. The software is described in the Appendix. It enables the sorting/selecting on content, which is adequate for browsing the selected data I hold. The assembly of data intended to be content addressable requires avoidance of ambiguous codes and unnecessary synonyms, and care with spelling.

To be used for the original Chemical Abstracts search, considerable ‘artificial intelligence’ would be needed. I have not used computer searches due to their expense and the difficulty of identifying suitable keywords. This choice, obvious with the benefit of hindsight, is difficult when a field is only partly understood; it involves ‘lateral’ rather than ‘vertical’ thinking, a role for which programs are not yet available.

[2] Computers may be used to model the dynamics of biochemical pathways. Small populations of molecules can invalidate statistical mechanical models – a ‘concentration’ of an enzyme or cofactor may amount to just a few molecules per cell or per organelle – and factors such as ionic mobility, local pH and rates of diffusion across membranes are often not known with sufficient certainty to create useful models. Representing individual molecules may be necessary to achieve realistic results, and so a rather powerful computer would be needed. The following account illustrates the problem to be faced:

Imagine scaling by a factor of 3 million. A cell of side 10 μ with a membrane 20 Å thick becomes a lecture hall of side 30 m lined with plasterboard 6 mm thick. Water molecules become the size of mustard seed (1 mm diameter), protein molecules (100 Å diameter) become ping-pong balls. Chromosomes become 10 m long, 2 m diameter coils of 6” diameter ventilation duct. Cell surface antigens become handles on the doors of the hall, active transport pores the size of keyholes. The illusion is shattered when trying to imagine 4 tons of sugar entering via such a keyhole in a minute, or a ping-pong ball filling a 100 kg vat in the same time. A concentration of only 5 ppb of a species of molecular weight 100 daltons occurs at one per cubic metre throughout the hall, molecules present at 3mM are found in any ping-pong ball volume. So many uncertain inputs cannot be expected to yield definitive, meaningful outputs testable by present techniques.

This does not disable the reductionist approach, or prove the use of computers to be inappropriate, but identifies current equipment as inadequate to molecular modelling on this scale. I have used computer models only for illustrative purposes.

[3] I have used computers to create diagrams and text. I prefer ball-and-stick to space-filling molecular models. The latter serve only in the special case of Van der Waals interactions. Starting from measurements on plastic models, generally based on X-ray
diffraction data, my *GRA* software package enables [stereo] projections of 7 molecules to be moved, scaled, and rotated interactively so as to optimize an illustration, which can be printed (as in my Preface) or plotted (as in my Illustrations). The combination of stereo representation and ease of manipulation which the computer affords in this application makes it invaluable. *GRA* also enables animation, if compatible hardware is available, or for generating illustrative video tapes. The same data can be used to check the validity of chemical structures and develop analogues, especially as pharmaceuticals.

The *SPA/GRA* specification seeks to optimize the use of cheap hardware, of which a researcher can have exclusive use. Computer graphics is a tool which benefits from much practice, expensive on high quality graphics terminals. I hope that the effort I expended to write 8-bit assembly code, comparable in speed with the same specification written in FORTRAN on more powerful machines, will benefit a wide audience.

Even with unlimited funding, current techniques in biochemistry are not adequate to test the present model directly. For example, it is impossible to identify 2000 tDNA molecules with 80 base pairs each against a background of nuclear DNA with 3 x10^9 base pairs and a large population of tRNA.

Just as the atomic theory of matter was successful long before X-ray diffraction verified its basis, so this biochemistry is justified by results without proving every part. Ice Ic, tDNA, substrate-carrier complexes and my nucleohistone structure are axiomatic. Though potentially falsifiable, they need not be verified before their implications are considered.

A theoretical scientist, like an artist, is creative. It behoves either to excel in technique – in reductionist science or in brushwork, but also, when introducing a new paradigm or art form, to demonstrate the need for change - to sell the product. To be viable, an idea must be communicable. Author and audience must have a common syllabus of symbol and dictionary, shared knowledge of data and theory. This is especially difficult in an interdisciplinary area. Since the control systems with which I am primarily concerned evidence themselves only through their effects, it is desirable that their structures be familiar in another context.

To test my models, I have extrapolated from them in many directions to establish consistency. I have also sought to present the new paradigm in the context of its predecessors. New axioms are justified through yielding more and better predictions. Occurrence of prediction with existing observations satisfies the theorist; only if it satisfies a laboratory manager will sceptics eventually be converted.

A new paradigm is easier to accept if pre-existing scientific laws can be derived from it. If axioms dictate new laws, then much reanalysis is needed. Since the opportunity to juggle with protein genetics, much speculation has surrounded this extension to the tool kit of plant and animal breeders. Over the past millennium, only the alchemists have so signally failed to meet their expectations. The search for magic proteins serves at least to arouse interest in the questions - nitrogen fixation, prevention of CHD and cancer, the structure of memory storage - to which the present thesis offers solutions.
α4 A model for the origin of life

The present thesis depends on three assumptions:
[A] Ice It selects ATP.

Life is characterised by the creation of order from disorder. The initiation of this process is the first requirement for life. Its precursor is the order-disorder transition in proton-ordered ice, ice It, crystallised in liquid N₂ (Figures 1 & 18). The transition yields coherent radiation, which selectively photophosphorylates purine nucleotides, resulting in a ‘primordial soup’ replete with DNA.

[B] tDNA selects substrates.

The growth which characterises life derives from the potential of DNA structures both to replicate and to function as an active transport ‘pump’, tDNA (Figures 2 & 18), concentrating specific substrates into primitive cells. Without localisation of substrates, replication of DNA would be no more likely than de novo synthesis. The active transport process distinguishes life from crystal growth; its primitive roots are reflected in modern life.

[C] Histone structure dictates genetic language. The organization which characterises life is imprinted with features of the amino acid [co]-polymers constituting early nucleohistones (Figures 12 & 20) and cytoskeletal proteins (Figures 14 & 20). Modern DNA coding, and control of cell division, differentiation and protein synthesis reflect these structures. Like the alphabet of a written language, the roles of the bioactive trace elements, the amino acids and their genetic codes are deeply embedded in biological systems, and must be adhered to for successful interaction. The proposed structures of ice It, tDNA and histones relate to their functions, mediated in each case by H-bonds:

[A] Ice It acquires its ordered H-bonds through crystallisation from super-cooled water vapour. The energy differential between the symmetric tetrahedral conformation of these bonds above 60 K and the asymmetric arrangement reflecting oxygen bond angles below 60 K determines the energy currency:

\[ 7 \text{ kcal/mole} = 30 \text{ kJ/einstein} = 4\mu \text{ infra-red} = 0.3\text{eV} = P_1 \sim P_1 \text{ bond energy} \]

and the size - 2μ-long sarcomeres in muscle, 2μ-circumference chromosomes and a 2μ free path for radiation within the mitochondrial cristae handling it.

[B] In tD NA, H-bonds provide a ratchet mechanism (Figure 3) for active transport of charged carrier-substrate complexes across unit membranes. At rest, the proton associated with an H-bond spanning a polarized membrane resides closer to the -ve surface, obstructing entry of a +ve complex. Excitation of the H-bond with ~ 4μ infrared moves it to a more central position, causing uptake of the complex. The same mechanism applies to recently characterized membrane proteins incorporating multiple trans-membrane α-helices.

[C] H-bonds in the histone structure form its β-sheet and also bind the P₁ of DNA to the ω-amines of Lys or Arg. These bonds protect DNA against corruption, and must be deliberately breached for transcription or replication to occur. They serve to store memory (Figure 13) and play a crucial role in base-pairing. In other cytoskeletal proteins, H-bonds serve as pathways for electrical conduction (Figure 14), basis for intra- and inter-cellular communication.

The structural role of H-bonds in the DNA double helix, in the protein or α-helix, and in the protein β-sheet is well established. This thesis suggests that they are functionally involved in active transport, chromosome separation, cytoplasmic streaming, the contraction of striated muscle and other mecano-chemical coupling, as well as in memory storage. H-
bonds are sensitive to temperature, pH, and electric fields, amongst other factors. In consequence, any biological enquiry which ignores the status of H-bonds needs review.

Chemical coupling, as in oxidative phosphorylation and photosynthesis often involves ‘free’ quanta of 4 μ infrared radiation. Interactions between components of electron transport chains can split a short wavelength quantum to one of longer wavelength and another of wavelength 4 μ (Figure 16). Light of such wavelengths is susceptible of absorption by water unless this is ordered. The ordering of water molecules in striated muscle is well established.

A consistent model for the origin of life need rest on a set of reasonable assumptions susceptible of empirical validation and not predicated on departure from thermodynamic equilibrium or other special conditions. The proposed structures of ice Ic, tDNA and histones relate closely to the known structures of ice Ic, tRNA and gramicidin S respectively. The novelty of my thesis resides in the relation of structure to function, and the idea that structure and function evolve in parallel. Functionless structures can no more survive than structureless function. Genetic takeover of function is as improbable as genetic takeover of structure. Every substrate along a biochemical pathway must once have been a valued product. Every operation in a sequence must once have been effectively controlled.

DISCUSSION

β1 Origin of life

To seek order amidst the chaos of universal thermodynamic equilibrium is futile. ‘Big bang’ advocates invoke a different physics, applying briefly, to cater for this. Equilibrium and uniformity are unusual in the steady state. In theory, almost any dis-equilibrium can be harnessed to the origin of life, distinguished only by the imprint on the product.

According to ‘big bang’ cosmology, the route to order from chaos invokes a ‘special’ event. Conditions on Earth passed irreversibly through various phases, enabling life to originate only during a finite time span when the universe was ~10^10 years old. According to this view, life is a chance phenomenon, a nuclear holocaust merely bringing forward its cataclysmic termination. The presumed uniqueness of the created universe invites the invocation of further ‘special’ events in evolution. Natural philosophy is weakened - science is reduced to rhetoric.

‘Steady state’ cosmology requires that life’s preconditions aren’t special, that the material conditions for its origin exist at any time. A planetary surface passes repeatedly through conditions for the origin of life, no cataclysm prevents it. Life is an inevitable component of the universe, if destroyed it’ll recur. The conditions for life can be sought in the aftermath of an imagined holocaust as logically as in looking backward. It is with this recurrent kind of life that I am concerned. Logical extension of the present thesis leads to a steady state cosmology.

Much attention has been paid to the centrality of carbon chemistry in modern life, and the energetic of carbohydrate metabolism in particular. It has been suggested that a thick primordial soup energised by lightning could be so far from thermodynamic equilibrium as to fuel early life via a chance catalyst of glycolysis. This argument is inconsistent - any amount of lightning can only speed arrival at thermodynamic equilibrium. Enzymes can only
enable exergonic reactions - energy coupling cannot be invoked without a detailed mechanism. What can be taken from studies with discharge tubes, is the likely existence in any primordial ocean of low concentrations of the molecular subunits of life, subject to continuous slow synthesis and degradation. The ocean surface serves to concentrate detergent molecules, forming coccervate membrane bubbles.

Temperature inequalities over time and space, arising from a variety of causes, seem the most likely phenomena to fuel early life. If the present configuration of Earth and Sun prevailed, then daily and seasonal temperature fluctuations occur. Alternatively, the nuclear chain reactions whereby progressively heavier nuclides form eventually go critical and precipitate natural nuclear fission explosions, as in Southern Africa.

Temperature differentials can give rise to phase changes - whether local solidification, crystallisation or distillation - tending to yield purer working substance. The most likely working substances are those involving the commonest nuclides. The earth’s crust contains more than 1% of O, Si, Al, Fe, Ca, Na, K & Mg, over 1% of H, Ti, Ar, Cl & P, and only .03% of C, Mn, F, S, Ba, Pb & N.

Setting aside the alkalis, alkaline earths and halides, normally present only in ionic form, and the relatively rarer elements, we have O, Si, Al, Fe, H, Ti, Ar, P. The only stable compounds to consider are oxides of Si, Al, Fe, H & P. (TiO₂ is too insoluble, Ar inert).

In every case, we find polymorphic oxides characterised by tetrahedral subunits - the aluminosilicate clays, zeolites etc, the multiple iron oxides, the range of oxo-acids of phosphorus and the wealth of crystalline forms of ice. Again eliminating ionic species, we are left with clay and ice. Clay suffers from too ready substitution of Si by Al to make for perfect order. Furthermore, it doesn’t melt, vaporize or undergoes any first-order phase transition.

The tetrahedron which H₂O forms is irregular and has a strong dipole moment: at high temperatures, it ionizes readily to H₂O⁺ and OH⁻. The H-bonds connecting water molecules in ice are deformed by pressures of a few kbar (an ice skate carries 100 kg on 1 cm² at atmospheric pressure). The H-bonds are only ordered over a short range at higher temperatures, leaving residual entropy in the structure

There are numerous phases of water ice, depending on temperature, pressure, history and mode of crystallisation. Those occurring only at high pressures may be ignored (though serving as models for the behaviour of low pressure forms). At atmospheric pressure, the familiar hexagonal structure crystallises below 273 K. Below 140 K, a cubic structure forms - analogous to the hexagonal wurtzite/zinc blende dimorphism of ZnS. Below ~110 K, water vapour condenses to form vitreous ice. A ferroelectric transition, (possibly involving long-range ordering) occurs at ~100 K. A first order order-disorder transition at 77 K occurs at 10 atmospheres pressure.

β2 Ordered Cubic Ice

Figure 1 shows the established structures of hexagonal ice (ice Ih), cubic ice (ice Ic), and ordered ice (ice II). Both Ic and Ih have disordered H-bonds - due to their vibration, the molecules present to one another as effectively regular tetrahedra. The structure of ice II, formed at around 2000 atmospheres, accommodates the true shape of the water molecules, and has ordered H-bonds. It has a static dielectric constant, ε₀ = 4.2 (c.f. ordinary ice ε₀ =
100) reflecting the close twinning of molecular dipoles. The high dielectric constant of ice Ih reflects the freedom of individual H-bonds to re-orient when an electric field is applied.

The entropy (disorder) inherent in ‘ordinary’ ice, arises from the weakness of the electrical forces tending to align molecules added to the crystal surface against their thermal rotations. Whereas the molecules satisfy their affinities with immediate neighbours, the disposition of their next nearest neighbours is ~ random. In the same way, iron does not form a magnet when solidified from the melt. Below ice’s ferroelectric transition temperature (~72 K), equivalent to iron’s ferromagnetic transition temperature, long range ordering takes over. This generally extends only to domains which, by twinning, negate the overall electrification or magnetisation of the crystal. At yet lower temperatures, the individual H₂O molecules cease vibrating. Their true shape is not a regular tetrahedron, and the tetragonal structure (icelt) is favoured.

The ordering phase transitions - hexagonal to cubic, residually entropic to ferroelectric, cubic to tetragonal - do not occur simply on cooling the disordered phase. Disordered H-bonds stay disordered even in liquid helium; ferroelectric ice has not been described (although the high-pressure twinned version of anti-ferroelectric ice is well characterised). The low pressure equivalent of the first order transition has not been reported. Cubic ice is only achieved by crystallisation at the appropriate temperature; attempts at creating tetragonal (ferroelectric) ice yield only vitreous material. Only in tetragonal ice can the low pressure order-disorder transition be anticipated.

The effects of conditions other than temperature on the crystallisation of ice are familiar. Snowflakes, hailstones, ice on a pond or on a windowpane reveal differences in habit; the effect of applying an electric field (e.g. 100 V/cm) is dramatic. Cubic and vitreous ices are usually formed by condensing ‘hot’ water vapour onto a cool surface. The speed with which a molecule lands on the surface, and the size of cluster it is a constituent, determine the degree to which it re-orientates relative to the crystal. Once attached to the surface, its orientation is literally frozen. If vitreous ice sublimed to another surface at the same temperature, there is every reason to believe that tetragonal ice would result. Re-crystallisation of vitreous ice in liquid N₂ enables this process.

Siberian winters average ~ 230 K. The biosphere sustains and is sustained by molecular oxygen which would otherwise be absent from the atmosphere. The combustion of the Earth’s biomass would result in a very different climate. Recent modelling of a ‘Nuclear winter’ suggests that extreme climates could easily arise. Current techniques limit the predictive value of these models. N₂ doesn’t liquefy (77 K) on Earth today, but the Moon lacks an atmosphere, falling to 116 K in the shade. Saturn’s moon Titan features N₂ gas. The icy crevasses of Jupiter’s moon Europa are ~170 K; and Neptune’s moon Triton has pools of liquid N₂. The comets must also periodically reach that temperature. Solar output varies by ~ 0.1% through its 11-year cycle, 0.5% variation accounts for recent ice ages.

Plate tectonic theory suggests that the Earth was recently half its present volume with oceans twice as deep, all continents connected and, shortly before that, the Moon was nearer to Earth – all factors making pools of liquid N₂ on the Earth plausible. N₂ boiling from ubiquitous ice surfaces carries super-cooled water vapour which crystallizes (rather than forming a glass) to ice it. Crystallisation might also arise on comets, but their brief proximity to Earth would make such a circumstance special.
The phase transition between ordered ice Ic and ice Ih is reversible, involving no exchange of protons between water molecules. Since no one molecule can adopt the tetragonal angles in isolation, a whole ferroelectric domain must undergo the transition simultaneously. The polarity of the molecules is such that ice it has much less electrical energy than ice Ic; the excess energy must be released. The energy released in the transition is approximately that of infrared light of wavelength $4\mu = 7 \text{ kcal/mole} = 30 \text{ kJ/mole}$\textsuperscript{B20}. The order-disorder transition is shown in Figure 1; its occurrence can confidently be predicted from the known ferroelectric and first order transitions and laws of physical chemistry.

The light quanta emitted during the collapse of a ferroelectric domain will be coherent, like the quanta in a laser beam. Such radiation drives photosynthetic reactions which isolated quanta would not; quanta following one another in wake of absorbed quanta discourage re-emission and promote chemical reactions. The free energy approximately equals that of the phosphodiester bonds central to bioenergetics, as in the reaction:

$$\text{dADP} + P_i + \sim\sim\sim \rightarrow \text{dATP}.$$  

The substrate, dADP, need be present at a water surface (water absorbs at $4\mu$; water serves to dissolve the reactants) located in range of the light beam.

The concurrence of liquid N\textsubscript{2} with liquid water in different regions is consistent with extrapolation of the previous observations on climate. Following multiple reflection (e.g. by ice clouds), the radiation can access substrates in warm ocean waters. Overall, ice Ih In liquid N\textsubscript{2} subject to random temperature changes generates synchronous $\sim 4 \mu$ infrared, photo-phosphorylating dADP.

\section*{B3 Primordial photosynthesis}

The purine moiety is well suited to its role in primordial photosynthesis. As shown in Figure 1, in combination with Mg\textsuperscript{++} or Mn\textsuperscript{++}, the light-absorbing ring structure is intimately connected to the phosphate groups. Since $4\mu$ infrared is strongly absorbed by water, evidence for the reaction arises only in sarcomeres, chloroplasts and mitochondria, where the water is locally ordered\textsuperscript{B21} and so transparent. Any species in the primordial soup absorbing $4\mu$ infrared will be energized, but few such events result in synthetic reactions. dADP resonates with the ice Ih transition. Darwin’s concept of natural selection applies equally to molecules and species, forming a necessary and sufficient basis for early life. From a diversity of possible outcomes, that occurs which most rapidly consumes limited resources.

The argument applies to any natural sources of coherent light, such as the population inversion of CO\textsubscript{2} in the Martian atmosphere\textsuperscript{B22}. The nature of the resulting life-form is predicated on the chemical environment of the selected photochemical reaction.

The primordial soup must have contained a little dADP. (Total hydrolysis of ATP yields:

$$P_3O_10C_{10}N_5H_{16} + 14H_2O \sim\sim\sim \rightarrow 3H_3PO_4 + 10CH_2O + 5H_2NOH$$

ATP water phosphate formaldehyde hydroxylamine

Insofar as ammonia coexisted with hydroxylamine, dATP has a redox potential closer to that of the primordial environment.) Dynamic equilibrium maintains its concentration. Over millions of years, dATP accumulated so that:

$$[\text{dATP}] = fn([\text{dADP}] , [\text{Ice Ih}] , |dT/dt|)$$

Trans-phosphorylation yielded other tri-phospho-nucleotides, and polymerisation (e.g. where evaporation locally concentrates the solution) will yield DNA\textsuperscript{B23}. Hence the effective [dATP]
will be greater. DNA was a natural component of the pre-biotic environment at concentrations exceeding that at thermodynamic equilibrium without ice it.

Biological energy inter-conversions, occurring in muscle contraction, photosynthesis and oxidative phosphorylation, are highly efficient, sometimes reversible. They have more in common with an electric motor than a heat engine. Biological structures are generally of uniform size and their chemical pathways are restricted to a limited range of themes, with a heavy dependence on nucleotides. Huxley’s model for muscle contraction and Mitchell’s model for oxidative phosphorylation depend on random, irreversible chemical interactions - chance collisions of cross-bridges with receptor sites, and of protons with pumps. Present understanding of photosynthesis has not been rewarded with emulation of the process. The models are independent of organelle size; the observed constancy of size implies function - accommodation of electromagnetic radiation of particular wavelengths. The sarcomeres of ants and elephants, the mean free paths for light in mitochondria and the circumference of chromosomes at cell division are all ~ 2μ - 1/2 the wavelength of the 30 kJ/einstein quanta associated with Pᵢ..Pᵢ bonds.

Like other high energy compounds, the minute concentrations of dATP at thermodynamic equilibrium in the conventional primordial soup are accompanied by their breakdown products - no useful work can be extracted by the provision of a catalyst. According to the present thesis, the action of ice It on the soup induced net purine synthesis, producing such high DNA concentrations that particular short DNA sequences would arise at random. This clear soup with noodles contrasts with a rich broth containing many high energy substrates. The energy and information encapsulated in 4μ infrared and in DNA noodles is a renewable resource, rendered obsolete only by life-driven climatic changes. By converting temperature fluctuations of pools of liquid N₂ into coherent infrared, ice It achieves order from chaos.

Any DNA sequence serving its own interest can be reckoned a living entity. The tRNA involved in protein synthesis, is the smallest contemporary nucleic acid moiety. Postponing consideration of tRNA function, I suggest an isomorphic species, transport DNA (tDNA, ignoring the usage of this abbreviation to signify the nuclear template for tRNA), which actively transports substrates across unit membranes.

Transport DNAs shares the Pᵢ-hydrophobe-Pᵢ structure of the unit membrane, and so is stable embedded in it, as shown in Figure 2. Such residence of tDNA in the unit membrane is consistent with the binding of polysomes to the endoplasmic reticulum during protein synthesis, and the attachment of bacterial chromosomes to the bacterial membrane. The incorporation of a tDNA arising by chance amongst the primordial DNA into a bubble of unit membrane (a coacervate) constitutes the origin of life. Coacervates accumulated specific substrates as described below, and so became the favoured location for replication of the effective pump. I consider it self-evident that coacervates carrying such tDNAs, perhaps accumulating dATP, could evolve to yield modern life.

Starting from the perspective of the fossil record, work on origins has focussed on constitution rather than function. Function is as important as structure in determining the course of development. Appreciation of the roles of chemicals, especially the trace elements, in biochemistry can lead to understanding of the nature and hierarchy of modern control pathways.
Modern prokaryotic life can be seen to have evolved from coacervates furnished with tDNA pumps, driven by radiation from ice. The transition to eukaryotic life - differentiation, endocrinology and dependence on protein synthesis, requires certain amino acid copolymers, especially the nucleohistones, considered later. By utilizing 4μ radiation as power supply, the earliest life-forms evaded the problems of energy coupling. Whilst the origin of life is predicated on random chemical synthesis, it focuses on concentrating substrate, not on catalysis, for survival. We witness a succession of concentrations - first the distillation and crystallisation of water, then the photo-phosphorylation and polymerisation of dATP to tDNA, the simultaneous coagulation of detergent molecules to make coacervates, and finally the active transport of (say) dATP favouring replication of the tDNA.

**β4 tDNA Structure**

The unit membrane consists of an impermeable phospholipid bilayer ~2μ thick constituting ~0.1% of cell volume. (Whilst modern cell membranes comprise a sandwich of protein and lipid, abiotic coacervates comprise only accumulated detergent molecules. Protein is unlikely to influence permeability. The chemical composition of the unit membrane is not critical to the present discussion.) Compare a cell 10μ in diameter with a polythene bag, (~10,000 times thicker), holding 1 litre of water. If the bag takes a year to leak its contents, a cell as leaky would empty in $10 \times 10^{-6}/12 \times 10^{-2}$ years = 40 minutes. If a cell membrane were made of thin plastic, it would survive for only ¼ sec.

The membrane potential is achieved by net uptake of

$$4 \pi \varepsilon_0 \varepsilon RV/Q_e = 17,000 \text{ ions}$$

where:

- $a =$ dielectric constant (water), 80
- $R =$ radius of cell, 5μ
- $V =$ membrane potential, 60 mV
- $Q_e =$ electronic charge

This corresponds to an intracellular concentration of

$$17,000/(6 \times 10^{23} \times 5 \times 10^{-13}) = .05 \mu M$$

The work needed to move ions across the membrane against the 60 mV potential is:

$$60 \times 10^{-3} \times 1.6 \times 10^{-19} \times .6 \times 10^{23} \text{ J/mol} = 6 \text{ kkJ/mol}$$

An electric field of 60mV across 20Å = 30 MV/m drives ions of mass 100 daltons through the membrane in:

$$\frac{2 \times 2 \times 10^{-9} \times 100 \times 1.7 \times 10^{-27}}{1.6 \times 10^{-19} \times 30 \times 10^{6}} = 10^{-11} \text{ sec}$$

The impermeability of the unit membrane negates the active transport of substrates. A short tube with hydrophilic ends and hydrophobic walls is stable in the membrane. (Insofar as tRNA likewise binds to membranes, this explains the binding of polysomes to endoplasmic reticulum, affords consistent energetics for amino acid acquisition and a pathway through the membrane for protein export. This doesn’t exclude protein synthesis on ‘soluble’ ribosomes. In bacteria, the places on the single chromosome visiting the membrane correspond to integral active transport sites.) If the tube walls contain H-bonds, then it serves as a substrate pump. Both a band of double-stranded DNA and a bundle of α-helices meet these requirements. *Ex hypothesis*, transport DNAs, tDNAs, isomorphic with and primitive
to tRNAs, mediate active transport. Some 2000 tDNAs of 64 types per cell (the full complement of $4^3$ associated with the triplet code) are invoked.

Membrane transport pumps constructed of protein are well documented. This does not preclude the coexistence of nucleic acid pumps. Protein pumps evolved in parallel to serve a special function; they have been isolated primarily from specialised tissues such as the electric organ of Torpedo and rhodopsin of the eye. There are close parallels of design between protein pumps and tDNA - protein pumps comprise some 5 or 7 or α-helices penetrating the membrane, presenting a similar arrangement of H-bonds and a pore of comparable dimensions to that found in tDNA. The ‘cost’ of constructing protein pumps is high. A typical tDNA has ~70 base-pairs, ~40 make up the pore and ~30 constitute the codon loop and amino acid binding arm. For protein pumps, 39 base-pairs encode the ~13 amino acids of each α-helix so five α-helices need at least 200 base-pairs. Since no amino acid is as acidic as the phosphate of phospholipids, protein pumps also need elaborate gateways, consistent only with a high-protein environment.

Protein pumps, being gene products, enable the creation of numerous pumps under metabolic control. Multiple pumps also arise through polyploidy, as in Drosophila salivary glands and liver. Some pathogens carry code for pump construction, e.g. dysentery and scrapie. Protein pumps aren’t equi-partitioned at cell division so they can’t substitute entirely for tDNAs, they’re genes independent of protein synthesis regulation. The eukaryotic cell’s complement of ~2000 tDNAs embraces 64 substrates.

Figures 2 & 18 show a modern tRNA molecule. Drawn approximately to scale, the tetramer or hexamer of adrenaline (vide infra) which carries Na$^+$ and K$^+$ across the unit membrane, and the fat-soluble vitamin A and a porphyrin together constitute the chief ingredients for active transport. The diagram also illustrates the way juxtaposed tRNAs enforce the genetic triplet code.

The unit membrane is made of phospholipids tail to tail (p to d); proteins other than adenyl cyclase are omitted. The functional part of the tDNA pump is a cylinder lined with DNA base pairs, their phosphates represented by d’s or p’s, their H-bonds by H:. The polarisation of H-bonds, N•••H-O or N-H•••O, is represented:

$$\begin{align*}
\text{H} & \quad \text{or} \\
\cdot & \quad \cdot \\
\text{H} & 
\end{align*}$$

The chain length of biomembrane lipids renders membrane thickness (phosphate to phosphate) closely similar to that of tDNA’s tube. This and hydrophilic/phobic interactions ensure the stability and orientation of the tDNA.

The stereo illustration shows some of the features of tRNA which support its proposed role as active transport site:

1. The orientation of H-bonds around the ‘hole’ at the bend of the ‘L’ shape of the molecule.
2. The fit of RNA-phosphate against phospholipid-phosphate, and of hydrophobic areas against the interior of the membrane when the pump resides there.
3. The way adjacent pumps bind to a common messenger (Introduce ‘differentiation DNA’, dDNA, analogue to mRNA, likely identical with the reverse transcriptase product of ‘oncogenes’) fall naturally 3 base-pairs apart.

A tDNA pumping dATP and/or a catalyst/substrate tending to promote DNA production yield a coacervate-tDNA favouring its own reproduction. Modern life could
evolve from such a system. The potential for replication involving base-pairing and for tandem mutation to enable accumulation of several substrates are intrinsic to DNA chemistry.

**β5 tDNA function**

Figure 2 shows the location of the trans-membrane H-bonds, Figure 3 the pump mechanism, depending on membrane potential, carrier, adenyl cyclase, ATP and a Ca$^{++}$/Mg$^{++}$ ratio favourable to enzyme function.

Establishment of the membrane potential polarises the tDNA H-bonds, and induces a compensatory distribution of ions on the membrane surfaces. Introducing energy to the H-bonds - equivalent to heating them - causes depolarisation without disturbing the surrounding heavier ions. The net effect is to produce a temporary electric field in the ‘up-hill’ direction, which carries the complex through the membrane. As the heat is dissipated, polarisation is re-established enabling ‘down-hill’ flow of spent carrier.

The time complex formation, activation and dissociation takes varies with species. A turnover number of $10^8$ - or 10nsec per cycle$^9$ - serves as a useful basis for discussion. Most time is spent waiting for matching molecules to arrive. Many factors affect molecular affinities, in modern life, specific enzymes catalyze some reactions.

Excepting substrates like choline, whose prime role is changing cell charge, an active transport operation need be electrically neutral. The two cases indicated in Figure 3, uncharged substrate with charged carrier and charged substrate with uncharged carrier, illustrate how this arises in practice. Zn$^{++}$, the carrier glucose, makes a return trip devoid of substrate. For charged substrates such as Na$^+$, adrenaline carries alternative substrate, K$^+$ on the return trip. Implicitly, the stabilities of the complexes involved favour these transitions thermodynamically.

There is no direct evidence for the occurrence of 4μ infrared radiation in modern life. Water absorbs at this wavelength$^{10}$, so this is unsurprising. Absorption by water will interfere with energy coupling unless its molecules are highly ordered - they are known to be so in the sarcomeres of striated muscle, and adjacent to the proteins involved in the cytoskeleton responsible for cell division. Sarcomeres are ~ 2μ long and chromosomes at cell division have circumference ~ 2μ, consistent with the participation of standing waves of 4μ radiation in their movements.

Energy coupling in oxidative phosphorylation and photosynthesis uses 4μ quanta as intermediates. The cytochrome pairs of the ‘electron transport chain’ enable splitting of 4μ quanta from visible light. These quanta are contained by the mitochondrial cristae, and form the same phosphodiester bonds on the Green’s particles as described above for the primordial condition. Photosynthesis can be understood in the same terms. In each case, the containment of 4μ quanta by biomembranes is implicit.

The nucleic acid pump is self-replicating (it is single stranded, the complementary strand may be functional) it has an affinity with the membrane, always pumps against an electric gradient. It’s driven by 4μ infrared or adenyl cyclase. The H-bond ratchet mechanism is simpler than any invoking rotation, diffusion or a chemical pathway. Transport DNA provides a recognition site for substrate and carrier, and the arrangement of H-bonds around the ‘hole’ is such that, in a polarised membrane with compensating bound charges, energy in the form of 4μ radiation released by adenyl cyclase depolarises the H-bonds,
producing a local electric field engendering active transport of a charged complex. The carrier makes a passive return trip with an alternate substrate can occur when the bonds re-polarise. Local concentration of dATP adjacent to a tDNA enhances its chances of replication and favours gene proliferation. In eukaryotes, tDNAs replicate along with the chromosomes at cell division.

The proposed eukaryotic complement of ~2000 tDNA molecules are genes, not gene products, constituting \( \frac{1}{20,000} \) of cell DNA. tDNA mediates active transport of metabolites under the control of differentiation DNA dDNA (possibly synonymous with oncogenes and introns), hormones or carriers they transport, an energy supply (either direct from the cytochrome chain or from adenyl cyclase), membrane potential and substrate availability.

tRNAs also line membrane pores, but being gene products, cells possess variable numbers of copies. Figure 2 shows the way in which the hinged amino acid binding arm can deliver its load via the hole in the pump. Guanyl cyclase and GTP fuel tRNAs.

### β6 Thermodynamics

Whilst the life process creates order from chaos, it does not breach the laws of thermodynamics. Many accounts of active transport seem to disregard the second law of thermodynamics. Maxwell’s Demon appears in many guises, specious proposals must be eliminated. Substrate recognition is denied by any reference to ‘opening a channel’ or ‘diffusion’, implying no interaction between the transport mechanism and its substrate. Where a ‘binding site’ is invoked, a scheme for release from this site is needed. In the tDNA, recognition is between carrier and substrate and the laws of thermodynamics are obeyed. Recognition and consequent binding outside the cell result in active transport; decay of the complex within the cell releases the carrier for return.

To be controlled, transport must be active. The 30 mV/m membrane potential compresses the unit membrane by \( \sim 5\% \), creating a formidable barrier to diffusion. No concrete evidence for ‘facilitated diffusion’ has been advanced, numerous counter-examples exist. Active transport is evidenced when the process is saturable, substrate specific or subject to specific cofactors. To be controlled, transport must be endergonic, it need overcome a force. Only Maxwell’s Demon could detect a concentration gradient; the force must be electric to act on charged complexes.

If the direction of transport depended on the pump’s orientation in the membrane then, since only one end has a binding site, some orientation mechanism is required. Binding of tDNA to dDNA (c.f. tRNA to mRNA, vide infra) keeps tDNAs pointing the right way. Importantly for the evolution of the system, the H-bond interactions are determined by membrane potential independent of orientation. Free-standing active transport systems lacking an orientation mechanism are suspect.

All tDNAs are presumably driven by the action of adenyl cyclase:

\[
\text{ATP} \rightarrow \text{cAMP} + \text{PP}_i + \text{Mg}^{++} \rightarrow
\]

(More energy is consumed by: \( \text{ATP} \rightarrow \text{cAMP} + 2\text{P}_i \) than by: \( \text{ATP} \rightarrow \text{ADP} + \text{P}_i \), but it affords more control via cAMP and PP concentrations). In mitochondria, chloroplasts and prokaryotes, 4μ quanta derive from the cytochrome chain. Protein synthesis depends on guanyl cyclase and GTP rather than adenyl cyclase and ATP; esterification of glycosides on
UTP, fat metabolism on CTP. This division of labour enables control via energy supply. The cost of binding amino acids to tRNA is another example of the cost of specificity.

The concept of second messengers to the nucleus, for which cAMP and Ca$^{++}$ are popular candidates, implies nuclear involvement in hormone action unnecessary to the present model (suggesting cAMP is a by-product of fuelling the pump and Ca$^{++}$ is released from adenyl cyclase in favour of Mg$^{++}$ when the enzyme is activated). It implies nuclear involvement of tissue differentiation not required by this model. If adenyl cyclase activation only produced cAMP or released Ca$^{++}$ as second messenger, biochemistry would be more complex than here described.

I eschew the terms ‘ionophore’, (applying to substrate-carrier complexes such as crown ethers capable of diffusing through hydrophobic membranes) and ‘clathrate’ (implying encapsulation of substrate in a bulk carrier – e.g. drugs carried on plastic beads). I take ‘complex’ to imply a weak but specific substrate-carrier interaction. The complexes discussed may only be stable within tDNA, a hydrophobic vacuum. Reference to a ‘receptor’ implies transient recognition, a Maxwell’s Demon. ‘Activation’ implies binding followed by allosteric activation of processes including release of the activator. The variety of base sequences possible around the tDNA rim, enhanced by possible inclusion of methylated and otherwise modified bases, enables a variety of catalytic sites on which a carrier-substrate complex may be assembled before allosterically activating adenyl cyclase.

The idea that a hormone can act as a ‘signal’ or ‘first messenger’ assumes a constant state of thermodynamic dis-equilibrium in the ‘target’ cell. Unless the hormone provides a source of metabolic energy, it must undergo an exergonic interaction with its ‘target’ recognition site, then initiate a further exergonic reaction through allosteric interaction with adenyl cyclase etc. Enzymes can only catalyze exergonic reactions. Control can only involve provision of alternative exergonic routes. The signalling idea invokes a layer of complexity absent from my model. It also fails to acknowledge the primacy of life without enzymes, in which tDNAs had overall metabolic control.

The tDNA pump mechanism is irreversible, depending on a heating process, disallowing Mitchell’s chemiosmotic coupling of proton transport to oxidative phosphorylation. Adenyl cyclase is feedback-inhibited, unabsorbed infrared infrared builds up within the cell, inhibiting the enzyme. The ‘twitching’ of active mitochondria C$^{4}$ suggests infrared interacts with the cytoskeleton. tDNA activity is an anabolic process, substrate concentration within an envelope suffices to sustain early life.

None of these assumptions requires a unique and improbable time, place or material. They constitute a consistent model for the repeatable, inevitable, origin of life. The cell envelope isolates genes and substrates and conserves quanta involved in energy coupling. These conditions are not met for life evolving on clays or in outer space.

β7 Polypeptides and Catalysis

Emil Fischer’s lock and key dictum applies to both tDNA and proteins, though 4 bases supply less variety than 20 amino acids. The importance of convening substrates and adjusting the physical reaction environment is often overlooked. tDNAs orientated by membrane potential enable the active concentration of reactants and affords the prerequisites for nitrogen fixation. NADH reduces di-nitrogen using the energy of a proton accelerated by the membrane potential, rather than heating the N$_{2}$ to:
60 mV x 1.6 x 10^{-19} \text{coulomb} x 6 x 10^{23}/\text{mole} = 690 \text{ K} = 420^\circ \text{ C}

(\text{the Haber process operates at } 500^\circ \text{C and 300 atmospheres pressure). If this reaction occurred on an isolated protein, genetic engineers could transfer it between species. The reaction is prerequisite to biochemical evolution, dependent on N-containing amino acids and nucleosides: Diagram 13}

\begin{align*}
\text{Juxtaposed tDNAs (possibly arising through tandem mutations) can assemble amino acids and catalyse the formation of amide linkages to form [co-]polymers. Due to their homogeneity, the products will contain high proportions of the } \alpha\text{-helix or } \beta\text{-sheet structures found in all types of structural protein fibres, histones and rods. I propose their primordial functions were to provide electrical conductors, flat surfaces and supports. The } \alpha\text{-helix affords an electrical conduction path:} \\
H-N-CH-C=O \cdots H-N-CH-C=O \cdots \\
\downarrow \\
H+ N-CH=C-O \cdots H^+N-CH=C-0 \cdots
\end{align*}

\text{In fibrinogen, Figures 14 and 20, 3 } \alpha\text{-helical strands twine around one another, constituting 9 parallel conducting paths. The arrangement of rods in the centriole or basal body, see Figure 14, is associated with cell division and the control of cilia and flagella. Centrioles invariably have 9 peripheral and 2 central rods. Triple } \alpha\text{-helices can simultaneously carry quanta released by ATPase on the peripheral rods of a centriole to the chromosome’s centromere.}

\text{Figures 12 and 20 illustrate the interaction of an anti-parallel } \beta\text{-sheet of a copolymer } [\text{Ala-Lys}]_N \text{ with double stranded DNA. By suppressing DNA coiling, this arrangement enables dDNAs resident in the membrane to bind several tDNAs, } \text{vide infra}. \text{ The same applies to tRNAs bound to mRNA. The involvement of such histones in protein synthesis is energetically favourable, membrane-bound tRNAs need bind only once to mRNA. The structure is held together by 4 sets of H-bonds: Diagram 14} \\
\text{Each of 9 fibrinogen-type conductors carries a quantum from the centriole, breaking 9 H-bonds on the nucleohistone, enabling copying of genetic code.}

\text{For modern cell division, H-bonds between DNA phosphate and the } \omega\text{-amine of lysine make the super-coiled chromosome into a solenoid conductor, Figure 13. The chromosomes become electromagnets. The electromagnetic field between identical chromosomes alternates at a characteristic frequency, causing their mutual repulsion, coupling energy (initially from external } 4\mu \text{ radiation) to chromosome separation: Diagram 15}

\[\text{Double 'south' poles at the centromere mutually repel 4 times more strongly than the distal 'north' poles}\]
Huxley’s model for actinomyosin interactions in muscle contraction$^{D3}$ invokes conformation changes local to phosphorylase sites causing hinging, binding and releasing of the cross-bridges and feedback inhibition of the driving reaction. The mutant variants of this process haven’t been reported, the model fails to explain the constant size of sarcomeres despite genetic variability. The interaction between 4μ quanta ($\sim\sim\sim\rightarrow$) released in the reaction:

$$\text{ATP} \rightarrow \text{ADP} + \text{P}_i + \sim\sim\sim\rightarrow$$

Mg$^{++}$

$\alpha$-helical H-bonds account for muscle contraction as readily as for active transport. For this model, almost any amino acid sequence will serve. The ‘resting state’ of the material contains ordered H-bonds conforming to the overall crystalline structure common to actin, myosin and microtubules, with heavy ions neutralizing polarities. As in the active transport model, H-bonds are depolarized by absorption of $\sim\sim\sim\rightarrow$, leading to a conformation change similar to that postulated for ice It. The population inversion, not gradual contraction, accounts for the sub-sonar ‘clicks’ accompanying skeletal muscle contraction$^{D4}$.

Proteins involved in protein synthesis must have evolved from a primitive version of the process. The evolutionary pathway from the [co-]polymers forming fibrinogen and histones to a process dependent on ribosomes for catalysis is straightforward. In modern life, all proteins except the ‘hook’ proteins involved in cell-cell binding, vide infra, are probably encoded on mRNA. The electrical conduction of energy and information around the cytoskeleton affords more efficient metabolic control than random diffusion of substrate and ‘messenger’ molecules. The cytoskeleton might be re-named the ‘cytoharness’, serving to communicate rather than support.

The model embraces all contractility in biology, striated muscle isn’t a special case. Previous accounts of the spindle at cell division breach Newton’s Action and reaction are equal and opposite when the centrioles, floating in the cytosol, ‘draw’ chromosomes towards themselves rather than moving together. Chromosomes containing double helices could not behave in this way. Treating $\sim\sim\sim\rightarrow$ quanta as substrates enables feedback inhibition of chromosome separation and other mechano-chemical coupling. Dr Colin McClare questioned the existing dogma$^{D5}$.

I propose differentiation, protein synthesis and immunology characterising eukaryotic organisms arose from a single primitive process. Histones stabilise membrane tDNAs bound to differentiation DNA, dDNA, Figure 15, binding adenylyl cyclase. tDNAs participate in active transport only when selected by a dDNA, probably encoded as an ‘intron’ or ‘oncogene’. Similarly, tRNAs selected by mRNAs bind guanyl cyclase for protein synthesis. Some indeterminate factor distinguishes the cell membrane and endoplasmic reticulum for binding tDNAs or tRNAs respectively. tRNAs mediate amide bond formation. Under special circumstances, dDNA-bound tDNAs behave like mRNA-bound tRNAs, producing oligopeptides instead of actively transporting substrates. This behaviour leads to cell differentiation by restricting substrate uptake and providing tissue-specific surface proteins. Concatenation of tDNAs to produce a surface protein is the basis of the immune process.

Early life without protein underpins modern biochemistry. A creator forearmed with protein synthesis might eschew trace elements and vitamins in favour of equivalent peptides. Evidence for tDNAs in modern life forms is circumstantial. The model affords insights, especially in endocrinology and pharmacy, many of its predictions relating to the role of
trace elements in endocrinology, nucleohistone structure and control of cell division have been realized since its inception.

β8 Nucleohistone structure

The structure of nucleosome core particles has been partly established by X-ray diffraction studies\(^6\), they contain short sections of double-helical DNA separated by kinks, conforming to a denatured ‘minion’ coil: Diagram 16

The 21 9-base-pairs hairpins are substituted by 9 units: H1 binds 45 base-pairs and two copies of H2A, H2B, H3 and H4 each bind 18 base-pairs. H-bond breakage during extraction displaces H1, leaving 144 base-pairs forming two 72 base-pairs coils around a histone octamer: Diagram 17

This is consistent with histone amino acid compositions:

<table>
<thead>
<tr>
<th>HISTONE</th>
<th>TOTAL</th>
<th>BASIC(^1)</th>
<th>NEUTRAL(^2)</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>218</td>
<td>95</td>
<td>91</td>
<td>32</td>
</tr>
<tr>
<td>H2A</td>
<td>130</td>
<td>41</td>
<td>59</td>
<td>30</td>
</tr>
<tr>
<td>H2B</td>
<td>126</td>
<td>56</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>H3</td>
<td>136</td>
<td>50</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>H4</td>
<td>103</td>
<td>38</td>
<td>47</td>
<td>18</td>
</tr>
<tr>
<td>Σ</td>
<td>100</td>
<td>39</td>
<td>40</td>
<td>21</td>
</tr>
</tbody>
</table>

\(^1\)Arg, Lys, Ser, Thr, Tyr\(^8\)
\(^2\)Ala, Gly, Ileu, Leu, Val

As for histone amino acid compositions reported elsewhere, around 40% basic and 40% neutral residues are present in sufficient numbers to form two or more β-pleated sheet hairpins. The published sequences do not form simple 9-unit hairpins - nor is that necessary to my thesis. The sequences do have the potential to form equivalent structures with shared properties. The structure of Gramicidin S\(^9\):

\[
\begin{align*}
\text{L-Pro} - \text{L-Val} - \text{L-Orn} - \text{L-Leu} - \text{D-Phe} \\
\text{D-Phe} - \text{L-Leu} - \text{L-Orn} - \text{L-Val} - \text{L-Pro}
\end{align*}
\]

c.f.

\[
\begin{align*}
\text{L-Pro} - \text{L-Ala} - \text{L-Lys} - \text{L-Ala} - \text{L-Lys} \\
\text{L-Ala} - \text{L-Lys} - \text{L-Ala} - \text{L-Lys} - \text{L-Pro}
\end{align*}
\]

matches the ‘minion’ β-sheet structure, its toxicity lying in the D-phenylalanine displacing a base. \textit{In vitro} studies have shown [Ala-Lys]$_N$ sandwiching DNA\(^10\).

Polymers of chiral subunits are inevitably coiled unless, as for the β-sheet, twinning occurs. Being cyclic, Gramicidin S retains its structure on crystallisation; where twinning is
broken or absent, nucleic acids will irreversibly form B-helices and protein α-helices. In the case of histone proteins, the tendency to form β-sheets is strong. Reviewing diffraction studies would illuminate chromosome structure. The structure could be tested by predicting its X-ray diffraction properties. Modern histones appear to bind 18 or more base pairs rather than 9. Histones tend to form dimers, a dimer of a 9 base-pair histones binds DNA with hairpins opposed, obstructing copying in either direction. An 18 base-pair histone can have its constituent hairpins aligned correctly, its size enables copying without complete dissociation. For control purposes, replacement of the 18-base-pairs unit by a dimer of 9-base-pairs units obstructs copying. If such histones are to be base-specific, the base sequence must be palindromic. Substituting Gly, Ileu, Leu and Val for Ala in the basic structure can yield a sequence-specific histone. Supposing Gly-Ileu (G-I) and Leu-Val (L-V) specify A=T G=C respectively, then whilst ‘standard’ histone:

/A| A| A| A| A| A| A| A| A| A
/\| A| A| A| A| A| A| A| A| A

holds any base sequence flat, the control histone:

/G| G| G| I| I| I| L| L| L| L|
\ I| I| I| G| G| G| V| V| V| V|

might be specific for the base sequence:

/A| A| T| T| T| G| G| G| G| G
/\| T| T| T| A| A| C| C| C| C

DNA-binding proteins are known where a dimer binds 18 or 36 base-pairs, corresponding to 2 or 4 units. Initially, extraction of nucleohistones for X-ray diffraction study yields strings of 9 beads corresponding to the minion’s 9 coils: Diagram 18.

There is no evidence for punctuation of genetic information. If the 45 DNA base-pairs connecting nucleosomes were significantly more or less strongly bound to protein than the other 144, then proteins with multiples of 63 residues would be favoured. The kinks and coils in nucleosome core particles are not evidenced in copying, nor do core particle dimensions match those of the chromosomes. They are too thick to explain the observed chromosome packing density. Taking a β-sheet repeat of 6Å [7.4 Å], a chromosome with circumference 2μ carries 20,000/55 = 364 minions per coil. Minions are around:

189 x 6 / π + 40 = 400 Å wide, giving a density of
364/400 x 1,701 =1,550 base-pairs /Å, packing
3,000 M base pairs into 194 μ.

The minion shares the pairing, spacing and overlap of bases, and the separation of phosphate residues with the B-helix. Unlike the helix, it affords homogeneous support for genetic information and the open end of the hairpin provides a directional reading frame for copying. Each of $10^{14}$ body cells contains $3 \times 10^9$ DNA base pairs condensed to coiled coils an aggregate 210 μ long. Each chromosome has ~40,000 minions, each coil 21 histone hairpins with 9 base pairs. DNA in beads is present in B-helices ~9 base-pairs long separated by kinks arising from bends in the original histones.
Minions can replicate without uncoiling and re-coiling. As shown in Figure 13, a stable non-helical structure enables permanent binding of tRNAs to mRNA or tDNAs to dDNA. The DNA-protein H-bonds are ordered like those in ice. It, Figure 13. Copying yields daughter minions with different histones (e.g. containing Arg in place of Lys).

**β9 Histone function**

Adjacent tRNAs or tDNAs in a unit membrane lie 3 base-pairs apart. Their anti-codon triplets pair with another nucleic acid if a histone counters the tendency to B-helix formation. Infrared quanta can breach H-bonds between tRNAs and mRNA, tDNAs and dDNA, β-sheet or base-pair bonds. They facilitate unbinding like a lock rather than a clasp, securing genetic information.

Coupling to adenylic or guanylic cyclase is prerequisite to active transport or protein synthesis. DNA- or RNA-histone H-bond chains serve to conduct the energy released by these power units to their targets. In this way, one cyclase enzyme drives several pumps. Since histones form part of its active site, unless a pump is selected, the cyclase is inactive.

tRNAs encode proteins, depending on the orientation of the binding histone, tDNAs can either serve as substrate pumps or synthesise proteins: Diagram 19

Minions require less gyrase action than nucleosomes: Diagram 20

Minion replication introduces the possibility of creating daughter chromosomes at meiosis with distinctive histones (e.g. all-Arg or all-Lys). Thus histones enable triplet coding and chromosome replication: Diagram 21

The hairpin-like structure of the β-sheet ensures copying occurs in the right direction, palindromic sequences binding histone dimers serve as controls. When DNA is coiled in a B-helix, palindromic sequences are less symmetrical. The human complement of $3 \times 10^9$ base-pairs comprises $\sim 170 \text{ M}$ 18 base-pair sequences. There are $4^{18}, \sim 70,000 \text{ M}$ possible 18 base-pair sequences; any of which can be a unique control code. Control codes 9 base-pairs long would select from only $4^9 \sim 1 \text{ M}$, and not be unique. The structure is a multiple of 3 base-pairs in length, ensuring a reading frame. Uniform binding enables punctuation-free code.

Apart from binding palindromic control proteins, histones enable electrical control of gene copying via the cytoskeleton. 3 α-helices in keratin bundles deliver 9 quanta of energy. The simultaneous breach of 9 H-bonds and removal of a histone unit conveys a hormone ‘signal’ to nuclear or messenger nucleic acid.

At cell division, a succession of quanta passing along the spindle yield a net flux of charge along the chromosomes, rendering them mutually repellent magnetic solenoids.
Apart from the potential of base-pairing to maintain genetic integrity, histone binding enhances DNA repair and control genetic messages. In eukaryotes, tDNAs are selected by dDNAs derived from reverse-transcribed introns. When cells line an enclosed cyst at blastulation or gastrulation, the deficiency of substrates causes the histone to reverse, binding guanyl cyclase rather than adenyl cyclase (as shown above) and pump amino acids rather than substrates. The result is a differentiated cell with a restricted molecular ‘diet’, bearing a characteristic oligopeptide on its surface.

As on mammalian erythrocytes, a saccharide sequence is formed, determining ABO blood groups. This is another interpretation of the genetic code subject to histone control, additional to active transport and protein synthesis. Vitamin A is essential for cell division: Diagram 21, see Reproduction.

Depending on their orientation and whether binding adenyl or guanyl cyclise, histones enable diversification, substrate uptake, polypeptide or polysaccharide production. Evolution evidences the essential continuity of their functionality. The genetic code for substrates and their carriers is consequently universal from the earliest to the most sophisticated modern life forms. The following accounts of these carriers and substrates omit reference to protein synthesis, though some clearly involve enzyme catalysis.

γ1 Motility

H-bonds participate in all forms of biological motility. The mechanism found for active transport by tDNA, based on slow polarization followed by rapid depolarization through absorption of 4μ infrared by H-bonds is paralleled in striated muscle, chromosome separation and the action of cilia and flagella, confirmed by the uniform dimensions of the compartments where they occur. The energy source for these processes being:

\[
\text{ATP} \rightarrow \text{ADP} + \text{P}_i + \sim \rightarrow \text{Mg}^{++}
\]

The reaction is feed-back inhibited by excess 4μ quanta, ‘switched’ by an ATPase substituting Ca^{++} for Mg^{++}. Exchange of Ca^{++} and M^{++} is mediated by SO_3^-

The distinction between Mg^{++} and Mn^{++}, due to their differential affinity for SO_3^- and SeO_3^- respectively, was mentioned in α1. The special affinity of SeO_3^- for Mn^{++} has caused problems in electrolytic refining Mn E1. Ca^{++}.SO_3^{--}.Ca^{++} and Mg^{++}.SO_3^{--}.Mg^{++} complexes are doubly charged, giving them higher energy thresholds for active transport than singly charged species. Consequently, the exchange is more sensitive to membrane potential than most other transport processes. Choline uptake alters membrane potential, activating motility: ATPase promotes Ca^{++} ↔ Mg^{++} exchange
Cholinesterase releases choline
ATPase releases \( \rightarrow \) triggering motion
Choline uptake enhances membrane potential
Cholinesterase action:
\[
H_2O + CH_3CO.O.CH_2CH_2.N^+(CH_3)_3 \rightarrow CH_3CO.OH + HO. CH_2CH_2.N^+(CH_3)_3
\]
releases the choline cation from its hydrophilic ester. The situation is paralleled for heroine, diacetyl morhine and melatonin, N-acetyl methoxy tryptamine. Sulphur metabolism is intimately related to 1-C metabolism e.g. in methionine, enabling feedback mechanisms controlling SO_3^- and choline concentrations. SO_2’s sharp smell and NH_3 precipitating involuntary muscular spasm suggest the bioactivity of SO_3^- and NH_4^+ ions.

Changing the membrane potential increases the resting polarization of tDNA H-bonds. Depolarization yields a sufficient field to enable exchange of doubly charged ions. Independent control of single charged ion pumps depending on pH and redox potentials is unaffected. Both motility and active transport are driven by breakdown of P_i \sim P_i bonds, an orthogonally controlled process. ATPases with divalent cations as cofactor involve complexes as in Figure 1. 

Adenyl cyclase drives the reaction: Diagram 22
\[
ATP \rightarrow cAMP + PP_i + \rightarrow
\]
losing the capacity for divalent cation binding. ATP breakdown driving active transport is independent (orthogonal) to that producing other motion. 

Figure 4 illustrates acetylcholine and the cation-sulphite complexes. Pharmacy has concentrated on cholinesterase inhibition - sulphur and 1-C metabolism are too central for modification. The suggestion that Ca^{++} or cAMP act as ‘second messengers’ is thermodynamically unsound; its empirical basis is rooted in the behaviour of the Ca^{++}/Mg^{++} exchange tDNA pump. Magnesium deficiency in mammals is rare, but for plants it’s a major problem, Mg^{++} is a component of chlorophyll. This gives a vacant orthogonal control slot in plant metabolism connected with photosynthesis - perhaps uptake of CO_2, a component of 1-C metabolism.

\[\gamma^2\text{ Sensitivity}\]
Active exchange of Na^+ and K^+ ions across nerve membranes is well established, it’s involved in nerve transmission and information transfer invoking no metabolic changes. The potential for valinomycin\textsuperscript{E2}, Figure 5, and ring ethers\textsuperscript{E3} to carry these ions obscures the ability of catecholamine tetramers and hexamers to perform this function. Figure 2 illustrates K^+-adrenaline\textsubscript{6} entering a tDNA pore. Figure 3 shows how extra methyl groups on noradrenaline\textsubscript{6} make it bigger than adrenaline\textsubscript{6}; Figure 7 shows the analogous case of methoxytryptamine\textsubscript{6} and serotonin\textsubscript{6}.

Many pharmaceutically active catecholamine analogues can form hexamers, c.f. morphine and codeine, Figures 5 and 19. These ring structures interact reversibly; encephalins, natural opiates match them, unlike valinomycin. Cation exchange enhances sensitization to pain and other stimuli. Physiological opiate addiction arises from obstructing tDNAs. Pumps invoked to compensate render the subject oversensitive to pain after drug
withdrawal, leading to addiction. Na\(^+\) / K\(^+\) exchange controls cell-sap viscosity. Na\(^+\) ions are similar in size to water molecules, retaining clouds of molecules, e.g. Na\(^+\).28H\(_2\)O. Larger K\(^+\) ions form K\(^+\).4H\(_2\)O.

Exchanging Na\(^+\) for K\(^+\) changes cell sap viscosity, when K\(^+\) replaces Na\(^+\), all molecular movements, whether chemical pathways or muscle contraction, are accelerated, the ‘fight or flight’ reaction. Exchanging hexamers for tetramers, not the nerve fibre’s chemistry, explains the ratio 3:2 between Na\(^+\) and K\(^+\) exchanged in nerve transmission. Presuming morphine interacts with a binding site, not with catecholamines, has delayed treatment for addiction. Morphine’s unsaturated ring interacts with tDNA. Codeine’s methyl group reduces its affinity for Na\(^+\). Na\(^+\) slows metabolism, K\(^+\) restores efficiently.

\(\gamma_3\) Excretion

Anion excretion matches cation uptake, especially exchanging Cl\(^-\) with HCO\(_3\)\(^-\), the ‘chloride shift’. Cl\(^-\) complexes with Mn\(^{++}\), forming MnCl\(_4\)\(^-\) and MnCl\(_6\)\(^{4-}\), Figure 5, enabling NaCl excretion. Aldosterone facilitates MnCl\(_4\)\(^-\) assembly, c.f. 1,25-dihydroxycholecalciferol, derived from Vitamin D\(_3\) enabling SiF\(_6\)\(^-\) assembly: Diagram 23.

Steroid ligands are indicated, not mechanism. Vitamin D\(_3\) energetics match those of SiF\(_6\)\(^-\) synthesis. Angiotensin, renin, and aldosterone help creation of MnCl\(_4\)\(^-\) and its delivery to NaCl transport sites forming the carrier complex:

\[
\text{MnCl}_4\text{Cl}_2 + 2\text{NaCl} \leftrightarrow \text{MnCl}_6\text{Cl}_4^{2-}2\text{Na}^+
\]

Likewise, parathyroid hormone and vitamin D\(_3\) create and deliver SiF\(_6\)\(^-\) for apatite transport, see Rigidity. The processes have co-evolved, sharing steroid involvement with Osmoregulation. Mn both activates ATPase for cholesterol synthesis and transports salt, confusing disorders of salt excretion and osmoregulation, suggesting blood pressure control involves osmosis. Aspirin and histamine treat the symptoms of failed salt excretion and blood pressure (via mevalonate polymerisation) without addressing their causes.

When life first left the seas, problems of salt and water metabolism and skeletal strength arose. Mevalonate is converted to cholesterol promoting steroid production, some steroids are catalysts. Aldosterone and vitamin D metabolism rely on enzymes, protein hormones angiotensin, renin and PTH evolved after protein synthesis. ‘Steroid’ derives from the Greek word for solid, stereos, c.f. gallstone.

Messengers controlling pathways need inactivating and recycling to avoid chain reactions, failure creates gall and kidney stones and seafloor Mn nodules. Trace element carriers have inherent advantages. Active transport pump carriers must be recyclable. SO\(_3\)\(^-\) and SeO\(_3\)\(^-\) oxidise to SO\(_4\)\(^2-\) and SeO\(_4\)\(^2-\), catecholamine metabolites are excreted, MnCl\(_4\)\(^-\) and SiF\(_6\)\(^-\) can be hydrolysed.

Cl\(^-\) controls stomach acidity and enucleate erythrocytes perform the ‘chloride shift’, exchanging HCO\(_3\)\(^-\) for Cl\(^-\). Choline\(^+\), Na\(^+\), K\(^+\), Ca\(^{++}\), Mg\(^{++}\), F\(^-\) and Cl\(^-\) ions control
environmental conditions - membrane potential, levels, viscosity and acidity. The substrates they carry aren’t incorporated into cell fabric.

\( \gamma_4 \) Respiration

\( \alpha_1 \) and \( \beta_7 \) suggested nicotinamide’s role in nitrogen fixation. Figure 6 indicates the involvement of membranes in the process and the possibility that NADP’s extra phosphate fuels the pump. At A, Diagram 24, nicotinamide is shown fixing \( \text{N}_2 \) alongside two parallel reactions, cytochrome oxidase at B and transfer of reduction potential at C. The mode of action of cyanide shown at D explains the effectiveness of 100% \( \text{O}_2 \) as an antidote. Figure 16 indicates the stoichiometry of oxidative phosphorylation.

The symbiotic relationships associated with \( \text{N}_2 \) fixation (e.g. root nodules on legumes depend on their host plant for energy) and with oxidative phosphorylation (mitochondria are dependent on the host cell) reflect similarities between the tDNAs serving these functions. That for \( \text{N}_2 \) fixation may have co-evolved with \( \text{H}^+ \) transfer for accepting \( \text{O}_2 \), normally present as its hydrate, \( \text{O}_2 \cdot \text{H}_2\text{O} \), to which unit membranes are impermeable. Figure 5 shows it forming a complex with iodinium, \( \text{I}^+ \), active ingredient of thyroid hormones, displaced by the reaction:

\[
\text{T}_4 + \text{H}^+ \rightarrow \text{T}_3 + \text{I}^+
\]

On this basis, the ‘basal metabolic rate’ reflects oxygen consumption. Figure 5 also how \( \text{Li}^+ \) mimics \( \text{I}^+ \) for treating ‘bipolar disorder’; \( \text{Li}^+ \) and \( \text{I}^+ \) have a similar size and shape. The isotope \( ^6\text{Li}^+ \) performs differently to \( ^7\text{Li}^+ \), an isotope effect implying a low MW partner for the ion in its active role.

1 in 7 sibs inherit \( \text{Li}^+ \)-sensitive conditions (the data is equivocal). Insofar as this evidences 7 copies of the tDNA for \( \text{I}^+ \cdot \text{O}_2 \cdot \text{H}_2\text{O} \) early selection of a defective one explains the observed statistic. \( \text{I}^+ \) reduces to \( \text{I}^- \) for recycling to the thyroid, \( \text{Li}^+ \) does not degrade, resulting in a narrow therapeutic dose range. Hormones such as glucagon and somatostatin actively remove spent carriers.

\( \text{O}_2 \) transport by haemoglobin fails to account for oxygen entering tissue cells surrounded by membranes impermeable to hydrated oxygen. The high iodine content of littoral seaweeds reflects their need to tolerate fluctuating \( \text{O}_2 \) concentrations. The difficulty, in all branches of chemistry, of measuring oxygen concentrations, has delayed recognition of its biological control.

\( \gamma_5 \) Growth

Anabolic activity depends on amino acids, \( \text{aas} \), as protein components, be they structural proteins, enzymes or neurotransmitters/hormones. I assume \( \text{Cu}^{++} \) mediates the active transport of \( \text{aas} \) and their assimilation by tDNAs evolved before tRNAs and protein synthesis. In the simple scheme of neuro-endocrinology:
tDNAs in the endocrine gland (liver) are loaded with Cu carrier by growth hormone. The gland consequently accumulates αs, they are assembled to form somatomedin, delivering Cu to tissue tDNAs which enable their αa uptake, promoting anabolism or growth. Somatostatin removes Cu from these tDNAs. The hypothalamus and anterior pituitary are sensitive to Cu or αa levels, responding by releasing growth hormone: Diagram 25

To estimate the amplification factors associated with neuro-endocrinology, if one Cu ion primes a brain tDNA, causing uptake of (say) $10^8$ αa molecules, then $\sim 10^7$ neuro-peptides result, each primes uptake of a Cu ion by the liver for packaging in somatomedin, priming tissue αa tDNAs, each taking up $\sim 10^7$ αas. Thus, some $10^{14}$ tDNA cycles arise from a single signal - one transport event per body cell, an optimal signal-response ratio. A hierarchy of Cu-binding sites is implied. Metallothionein binds serum pool of Cu, somatomedin binds Cu, enabling appropriate tDNAs to release it; somatostatin undergoes a conformation change on binding to tDNA, enabling Cu-binding and a further conformation change frees it from the tDNA. The brain is sensitive to αas, regulated by liver and kidney metabolism, growth hormone is one of several neuro-peptides generated in response. Brain tDNAs select unusual αas, e.g. selenocysteine and hydroxyproline or ‘spent’ carriers, e.g. I, Zn$^{++}$ and SeMe$^{3+}$, signalling metabolic imbalance.

Ex hypothesis, tRNAs specific to 20 αas, evolved from tDNAs have associated kinase enzymes which attach αas. Figures 2 and 13 suggest a process enabling αa delivery to the tRNA pore, coordinating transport with peptide bonding. β9 suggested histone reversal and substituting guanyl for adenyl cyclase enables αa binding to tDNAs. Neuro-peptides are synthesised on plasma membrane tDNAs, not endoplasmic reticulum tRNAs.

The αa binding arm’s flexibility is temperature dependent. Inefficient metabolism generates heat, as in the oestrus cycle and fever, promoting enzyme synthesis for catalysis. Warm-blooded species’ temperature reflects the tDNA hinge’s ‘melting point’. The way RNA’s extra OH groups discriminate endoplasmic reticulum from cytoplasmic membrane deserves further study.

Figure 16 illustrates how the width of tRNAs enforces the triplet code. Nucleohistone structure is sensitive to RNA’s extra OH group, explaining the ‘wobble’ and degeneracy of the genetic code, embracing 20 αas, the dDNA/tDNA system caters for 64 substrates. The constancy of intron/homeobox genes may reflect tDNA combinations, not peptide sequences. dDNA sequence integrity in is more critical than for mRNAs. The assumption that tRNAs repeatedly bind and unbind to mRNA and ribosomes is thermodynamically inefficient. According to my model, membrane-bound tRNAs engage with mRNA and
histone throughout the life of the messenger. ‘Soluble’ ribosomes operating around an aggregate of tRNAs constitute membrane vesicles.

More Cu serves as enzyme cofactor. Protein synthesis requires ∼1 ppm and more for protein synthesis than for αα assimilation by tDNA. Direct evidence of Cu’s involvement in αα homeostasis and metabolic control is sparse, studying differentiated systems such as lactation and haematopoiesis might confirm it. Figure 15 shows how exons and protein synthesis on the endoplasmic reticulum using GTP→ cGMP relate to introns. dDNA, reverse transcription, tD NA and active transport on the cytoplasmic membrane use ATP → cAMP. Three ‘machine tools’, messenger, ribosomal and transfer RNA, all composed of nucleic acids, not proteins, translate DNA code to protein, reflecting the evolution from nucleic acid to protein. The difference between eu- and pro-karyotic ribosomes suggests protein synthesis evolved after tDNA-based oligo-peptide synthesis.

γ 6 Rigidity

The biosphere’s skeletal structures are constructed either of rigid polymers, as in crustacean exoskeletons, tree trunks and porcupine quills, or solids crystallised from aqueous solution, as in bones, teeth and diatom skeletons. The second category uses three materials: apatites, silica and carbonates, sharing parallel metabolism. Figure 7 shows apatite transport by fluorosilicate for bone and tooth formation in animals or fluorosilicate by apatite for the silica skeletons of plants. Diatoms and higher plants employ SiO₂ rather than apatite because sunlight is plentiful for creating SiF₆⁻ and phosphate scarce. There are close parallels with other systems:

<table>
<thead>
<tr>
<th>Gland</th>
<th>EXCRETION</th>
<th>RESPIRATION</th>
<th>RIGIDITY</th>
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<tbody>
<tr>
<td>Halide</td>
<td>Chlorine</td>
<td>Iodine</td>
<td>Fluorine</td>
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<tr>
<td>Hormone</td>
<td>Angiotensin</td>
<td>Thyroxine</td>
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<td>Steroid</td>
<td>Aldosterone</td>
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<td>Vit D¹³</td>
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<tr>
<td>Carrier</td>
<td>MnCl⁴⁺</td>
<td>I⁻</td>
<td>SiF₆⁻</td>
</tr>
<tr>
<td>Substrate</td>
<td>NaCl</td>
<td>O₂H₂O</td>
<td>Ca₄[PO₄]₃.CaOH</td>
</tr>
<tr>
<td>Purge</td>
<td>Gastrin</td>
<td></td>
<td>Calcitonin</td>
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The high reactivity of F⁻ entrains special endocrine features, parathyroid hormone, PTH is continuously secreted, not accumulated in the gland like other hormones. γ3 showed 1, 25-diOH-cholecalciferol from Vitamin D₃, requiring sunlight for its activation - such high energy quanta aren’t readily available from normal metabolic pathways. Excess F sequestered in bones and teeth confers useful strength to tooth enamel.

HF and HCl are fully ionised in solution, the insolubility of CaF₂ distinguishes F. Gastric HCl secretion, kidney HCO₃⁻ and lung CO₂ excretion control pH. The piezoelectric effect promotes bone maintenance, disabled by weightlessness during space travel. It’s pH-sensitive, osteoblasts use alkaline phosphatase and osteoclasts acid phosphatase. Ca, bone and phosphate metabolism are sensitive to the acidosis of kidney failure. The pH-sensitive reaction is:

\[ \text{SiO}_₃⁻ + 6\text{HF} \rightarrow \text{SiF}_₆⁻ + 3\text{H}_2\text{O} \]

Vit D₃

Metallo-enzyme carbonic anhydrase, catalysing:
H$_2$O + CO$_2$ ↔ H$_2$CO$_3$ ↔ H$^+$ + HCO$_3^-$

is Zn$^{++}$-dependent, explaining the aetiology of post-menopausal osteoporosis, Zn deficiency has also been implicated in Alzheimer’s disease$^{E15}$, osteoporosis and Alzheimer’s disease are commoner in women. The alumina-silicate deposits are characteristic of Alzheimer’s disease, reflecting F import. Al also accumulates where bones form. Excess F in brain cells disrupts the citric acid cycle and protein folding causing neuro-fibrillary tangles. At low pH, aluminium competes with silica for fluoridation:

Al$^{+++}$ + 6F$^-$ → AlF$_6$═

When exposed to acid air pollution, both AlF$_6$═ and SiF$_6$═ are created in the nasal cavity$^{E16}$, causing uptake of F$^-$ to the brain via the olfactory nerve, involving enzymes, aldosterone and 1,25-diOH-cholecalciferol, predicated on protein synthesis, it has inherited components. Acid air pollution leads to F$^-$ uptake in the nasal cavity and corrodes high-alumina cement. Alzheimer’s Disease’ symptoms resemble Al poisoning arising in renal dialysis, Al and Si are ubiquitous. F has high renal clearance, excessive intake is toxic, not normally crossing the blood-brain barrier. SO$_x$ and NO$_x$ are clearly to blame for the Alzheimer’s disease pandemic, it’s non-infectious and rarely fatal, an embarrassing mental condition only reliably diagnosed at autopsy.

Micronutrient supplementation, initially ascorbate for scurvy and iodine for goitre, stalled on fluoride for dental caries. Aluminium is deliberately added to the diet: USA water purification uses 270 kton/anum as a flocculant, 1-5g Al(OH)$_3$/day is prescribed as an antacid and food additives contribute 20 kton/anum, Al cooking utensils make a further contribution. F is supplements preventing dental caries and F$^-$ in tea are innocent, air pollution is the prime cause of Alzheimer’s Disease.

γ7 Assimilation

Zn$^{++}$ is commonly bound to citrate$^{E17}$:

\begin{align*}
\text{CH}_2\text{-COOH} \\
\text{HO-C-COOH} \\
\text{CH}_2\text{-COOH}
\end{align*}

at the root of carbohydrate metabolism, it’s the carrier for actively transporting glucose. Figure 8 shows the β$_D$glucose-Zn$^{++}$ complex. Zn$^{++}$ is a cofactor for many enzymes, especially in carbohydrate metabolism. That involved in active transport is immeasurably smaller than that bound to protein. Citrus fruits, regular source for Vitamin C, contain little Zn$^{E18}$. Diketo$_L$gulonate, metabolite of ascorbic acid, forms diketo$_L$gulonate-Zn$^{++}$, see Figure 8.

Vitamin C-responsive conditions generally require Zn, diketo$_L$gulonate delivers Zn to tissues inaccessible to insulin. Zn-deficiency in the skin and genitals is symptomatic of scurvy. Incorporation of the hydroxy-ααs$^{E19}$ OH-proline to collagen and aminocitric acid, β-carboxy aspartic acid and γ-carboxy glutamine to nucleoproteins for haematopoiesis and sperm uptake of glucose require Zn. Cu-coil contraception inhibits sperm, in diabetics$^{E20}$ IUDS are ineffective. Cu prevents Zn incorporating hydroxy-ααs to protein and several other aspects of metabolism.

There are several proposals for the mechanism of Zn and vitamin C suppressing rhinovirus infection. Cell penetration occurs via a tDNA, as established for pancreatic necrosis virus$^{E21}$, predicated on priming the pump with Zn. Vitamin C transports Zn to the nasal mucous membrane, inhibiting uptake of viral DNA. Tandem polymer transport by
tDNA transfers nascent proteins across the endoplasmic reticulum via tRNAs encoded at the N-terminal. S-S bond formation occurs either in the tRNA or on associated proteins. Differential tDNA activation in different tissues explains tissue-specific virus entry. γ instances another example, Se prevents viral infection of the large intestine in cattle.

The incorporation of Zn to insulin and similarity between glucagon and somatostatin afford support:

| Substrate: | αα glucose |
| Carrier: | copper zinc |
| ‘On’ hormone: | somatomedin insulin |
| ‘Off’ hormone: | somatostatin glucagon |
| Gland: | liver pancreatic β-cells |

Failure of Zn-insulin production prevents tissue glucose uptake and its resorption by the kidneys. Shock is one of many factors precipitating diabetes. The ‘fight or flight’ reaction disables insulin- dependent food absorption by the gut. Excessive β-cell depolarisation permanently disables insulin production. Acupuncture relieves some types of diabetes. Drugs causing e.g. Alloxan and treating diabetes, sulphonylurea Tolbutamide and biguanide Phenformin and its side effects, Diamox treats glaucoma and inhibits Zn-dependent carbonic anhydrase have structural features in common with barbiturates, caffeine and theobromine: Diagram 26

Barbiturates precipitate with Hg, evidencing complex formation with elements in group 2B, transferring Zn to the liver for breakdown and reducing glucose transport to the brain. Zn usage for hepatic alcohol dehydrogenase also explains inebriety and the potentiation of barbiturates by alcohol. Conjugation of bilirubin with glucuronic acid is another Zn-dependent liver activity. The usual treatment for neonatal jaundice is photochemical breakdown by exposure to blue light. Formerly a pewter spoon was used, silver for the blue-blooded.

Zn mediates the sensation of sweetness. Injecting Zn to the hypothalamus boosts a goat’s food consumption by 40%. Zn manages anorexia nervosa. An implanted Zn electrode and artificial pancreas might replace insulin injections. Appreciating Zn’s role in perceiving satiety and understanding the interactions between endocrine Zn-carriers and neurotransmitters would aid obesity management.

Beryllium can usurp Zn binding to insulin, glucagon, citrate, diketo-gulonate, glucose, barbiturates, caffeine, sulphonyl-ureas, carbonic anhydrase and many other enzymes. It’s the only alkaline earth forming zinc-blende and wurtzite type sulphides and originally named gluconium for its sweet taste. Cd and Hg compete with Zn. HgMe interacting with SeMe₂ is probably more significant than Hg Interfering with Zn. The ‘triangle of taste’ comprises Zn-binding ligands. Toxic elements over-ride Zn binding, it need be reversible to be effective and is difficult to measure in vitro. Figure 8 shows complexes probably stable

37
only within tDNA. Injection of Zn-insulin corrects diabetes and topical application of Calomine lotion promotes wound healing.

Zn deficiency is more likely to cause neonatal jaundice or scurvy than diabetes. Epidemiological evidence suggests pandemic Zn deficiency causes type 1 (early onset, insulin-dependent) diabetes. Eye pathologies associated with diabetes and Wilson’s disease arise from Zn or Cu accumulation, not sugar or ααs, ion-binding agents might treat them. tDNAZn-glucose answers thermodynamic objections to diffusion and ‘second messengers’. If βD-glucose diffused across the membrane to be trapped by phosphorylation within the cell, a flux of non-phosphorylated sugars would be observed; if the by-products of active transport, PPi, cAMP and Ca++, were ‘second messengers’, then cell responses to insulin negate the proposition.

Colostrum provided by breast feeding supplies neonates with Zn and other micronutrients to all but premature babies. Refined sugar and fat substituting for starchy foods in Western diet cause Zn-deficiency. Reducing total food intake, exercise and fresh fruit and vegetables would correct it. In Middle Eastern countries, these factors yield frank Zn deficiency, it’s probably pandemic in the Western population.

γ8 Reproduction

According to the precepts of this thesis, phosphate, P_1 controls cell division, apart from the apatite transport described in γ6. P_1’s dipole moment obstructs its transport by tDNA; arginine carries its dimer, pyrophosphate, PPi as PPi.Arg. PPi, see Figure 8. Phosphodiester bond formation: P_1 + P_1 → PPi. Imported PPi adds to that produced by adenyl cyclase:

\[ \text{ATP} \rightarrow \text{cAMP} + \text{PPi} \]

Figure 2 shows Ag-porphyrin and Vitamin A. ATP hydrolysis or oxidative phosphorylation energise Ag-porphyrin; vitamin A’s conjugated double bonds convey energy as solitons. Figure 11 presents the postulated order of events. α1 showed the distinction between oxidised, conducting retinal and reduced, non-conducting retinol. The system’s essential features are: Diagram 27

Inositol lacks the ‘triangle of sweetness’, it doesn’t interfere with carbohydrate metabolism, but provides an alternative esterification substrate. Plant seeds normally store phytate (inositol hexaphosphate). Animal tissues contain phosphoinositides; inositol phosphate is a ‘second messenger’. Blood phosphatase destroys PPi produced in error, preventing its transport. Figure 8 shows anti-cancer agents mimicking Arg. PPi produced by adenyl cyclasefeedback inhibits PPi uptake.

The N:P ratio of Arg2,PPi (16:2) matches that of DNA (15:2), supplying the atomic ingredients for DNA synthesis. Coupling the energetics of vitamin A-driven esterification to oxidative phosphorylation and photosynthesis independently of motility is equally primitive. Ag-porphyrin is a rare Ag compound with several stable oxidation states whether the Ag^+/Ag^+++ or Ag^0/Ag^++ couple is involved is indeterminate. The cell/nucleus volume and
associated membrane capacitance enable quanta of energy to reach the Ag-porphyrin ‘aerial’, blue asbestos fibrils export these wavelengths inappropriately. Arginine and argentaffin tissues get their names from their affinity with Ag. Ag porphyrins and hematoporphyrin derivatives (targeted for tumour irradiation) are characterised by the ‘shocking pink’ colour seen in spring leaf buds. The perceived colour is not necessarily produced by Ag-porphyrin.

Peripheral roles for Ag support this scheme, it carries creatine\(\text{\textsuperscript{-}\text{P}}\) across intracellular membranes via a complex similar to those in Figure 8, participating in regulating intracellular [ATP], carried by a hexamer of serotonin/methoxytryptamine, Figure 7, a structure closely analogous to that of [nor-]adrenaline, see γ2. The relationship between melatonin and methoxytryptamine parallels that of acetyl choline with choline. Pineal gland atrophy at puberty is significant, serum P\(\text{\textsubscript{i}}\) concentration decrease with age\(\text{E36}\), it may control the balance between oxidative (fat) and carbohydrate metabolism and determine ATP levels. The essentiality of Ag isn’t certain, its ingestion little researched and physiological requirement unknown. Ag does not feature in any enzyme. It’s strongly precipitated by Cl\(^-\), so cannot pass through the stomach but is absorbed by large intestine if encapsulated in ‘roughage’. The recently acknowledged requirement for roughage in nutrition may signify a need for Ag.

Enucleate mammalian erythrocytes lack subcellular organelles, phosphocreatine metabolism and oxidative phosphorylation instance Ag-independent metabolism, performing the ‘chloride shift’. The role of P\(\text{\textsubscript{i}}\) in fat/carbohydrate metabolism coordinates accumulated energy reserves with hibernation, gestation and fruit/seed/tuber production associated with reproduction. Pineal endocrinology is coordinated with with biological clocks, determining appropriate times for reproduction. Obesity is associated with pineal hormones acting as neurotransmitters. Ag regulates sleep because Cl\(^-\) precipitates it, reducing access to ATP and switching metabolism from fast, P\(\text{\textsubscript{i}}\) -dependent to slow P\(\text{\textsubscript{i}}\) -independent oxidative reactions. Br\(^-\) -induced anaesthesia resembles sleep, both the diurnal sleep and reproductive cycles are light-driven. Cl-compounds are toxic, anaesthetics disable creatine transport in Ag-based contractile tissues.

Vision involves protein pumps (barrels of α-helices) showing parallels with P\(\text{\textsubscript{i}}\) transport\(\text{E37}\). The structure of Vitamin B\(\text{\textsubscript{12}}\), see Diagram 28, has much in common with the tDNA/vitamin A combination.

The many circumstances, factors and agents known to induce Cancer, Anxiety, Neoplasia and Tumours – CANT – severally impinge on the active transport of P\(\text{\textsubscript{i}}\). Hypervitaminosis A, skin cancer from sun-bathing, high acid phosphatise levels in prostate cancer, in invertebrates, Arg functions as a phosphagen analogous to creatine\(\text{E38}\), of which it is precursor in man. Arg releases growth hormone and insulin\(\text{E39}\); it is an essential αα for man and has been described as a hormone. CANT correlates with obesity.

\[\text{Vitamin B}_{12}\]

\[\text{A molecular AC/DC transformer?}\]

\[\text{Ring of conjugated bonds}\]

\[\text{Ring of hydrogen bonds}\]
Lewis Carroll’s treacle well dwellers drew only treacle\(^{\text{E40}}\). The active transport of water in an aqueous environment poses similar problems. Early life forms were sea-dwelling and needed only to maintain constant volume. Land plants characteristically invest a high proportion of their metabolic energy in the construction of cell walls to resolve the problem. Terrestrial animal life needs to transport water. The principal components of the proposed system are:

Figures 9 and 19 show the release of selenite from vasopressin and the structure of phospho-mevalonate and phospho-mevalonolactone. The synthesis of cholesterol from Mev and the complexes of selenite with Mn\(^{\text{++}}\)/Ca\(^{\text{++}}\) are illustrated in \(\alpha.1\). [P]Mev is suited to the role of water transport: Diagram 29

1) By reversible lactone formation, Pharmaceutical analogues of Mev for cardiovascular disorders may act here. Mev is synthesised from saturated fat\(^{\text{E42}}\)
2) Its concentration is regulated by aggregation to cholesterol
3) Mediated by an endergonic sequence of reactions catalysed by Mn\(^{\text{++}}\)\(^{\text{E43}}\)
4) Control of dietary fat and cholesterol are advocated to reduce the level of cholesterol leading to atherosclerosis. Aspirin\(^{\text{E44}}\) may affect the level of Mn\(^{\text{++}}\), by controlling Ca\(^{\text{++}}\) levels
5) By direct supplementation\(^{\text{E45}}\) or by a low-salt diet, see \(\gamma.31\). Monitoring Mn levels might follow recovery from cardiac infarction\(^{\text{E46}}\), the involvement of Mn in both salt and water management may reflect the evolution of these pathways. SeO\(_3\)\(^{=}\) exchanges Mn\(^{\text{++}}\)/Ca\(^{\text{++}}\), see \(\gamma.11\). The control of blood pressure consequently rests on the control of SeO\(_3\)\(^{=}\) concentration, which controls Mn\(^{\text{++}}\) concentration which controls Mev concentration which determines the active transport of H\(_2\)O.
6) \(\gamma.8\) recounts an analogy with vitamin A’s role. Spent carrier is metabolised\(^{\text{E47}}\) to
7) To Me\(_2\)Se or Me\(_2\)Se\(^+\) which compete with MeHg\(^+\) for a brain binding site\(^{\text{E48}}\) probably on the pituitary.
8) The synergy of Se nd vitamin E was early established\(^{\text{E49}}\). Oxytocin and vasopressin provide binding sites for vitamin E, \(\alpha\)-tocopherol, enabling release of SO\(_3\)\(^{=}\) or SeO\(_3\)\(^{=}\) from the cystine -S-S- or selenocysteine -S-Se- bond, Figure 19. Fat soluble vitamin E carries oxidising potential through the membrane from intracellular glutathione

Gross deficiency of Se or vitamin is pandemic in society\(^{\text{E50}}\) and accounts for the high morbidity arising from disorders related to osmoregulation – coronary heart disease and
cancers of breast, bowel and prostate, the tissues differentiated, *vide infra* to specialize in active water transport.

Numerous specious accounts for this morbidity and appropriate interventions have arisen. The free radical model \(^{E51}\), invokes Se-dependent enzyme superoxide dismutase (SOD)\(^{E52}\) protecting against O radicals, vitamin E is described as an ‘anti-oxidant’, preventing cancer by neutralizing O•. The benefits of Se supplementation for preventing cancers are tissue-specific\(^{E5}\), inconsistent with this hypothesis. An element’s role as enzyme cofactor explains it’s essentiality, not function. Glutathione peroxidise, GP usually has Se as cofactor, the existence of Se-independent GP\(^{E54}\) indicates its secondary importance. Keshan’s Disease in China\(^{E55}\) reflects the high Se requirement of an inbred community. Like the variety of Se deficiency symptoms between species, this can not be extrapolated to Western CHD. The underlying chemistry is similar but not protein affinities. Studies of genetic variations in high/low density lipoproteins\(^{E56}\) show cholesterol’s role in their clearance, not why there’s so much to clear. Using the activities of GP or other enzymes to assess Se status\(^{E57}\) needs review to understand its role in osmoregulation.

Waste accumulation is often associated with osmoregulation; plants accumulate cell walls, the sea-floor is littered with Mn nodules\(^{E58}\), and cholesterol plaques are symptomatic of atherosclerosis, reflecting deficient recycling. An aerospace experiment demonstrated Se deficiency in Western diet\(^{E59}\): mice survived heart attacks better when their US diet was supplemented with Se. In animal husbandry\(^{E60}\), the occurrence and correction of Se deficiency is well established. With the notable exception of Astragalus, plant growth is independent of Se status. Treating pastures of marginal Se status with superphosphate (high in S), induces deficiency in grazing animals\(^{E61}\). People genetically predisposed to CHD may be addicted to tobacco smoking due to its Se content\(^{E62}\), explaining the correlation of smoking with CHD. Augmenting cigarette tobacco with Se\(^{E63}\) may increase this addiction, increasing morbidity. Tobacco Se also explains the effectiveness of smoking in preventing ulcerative colitis.

Prostaglandins may serve as water carriers where oxytocin and vasopressin cannot reach, just as Vitamin C augments Zn distribution by insulin. Prostaglandins can diffuse through unit membrane like Vitamin E. Prostaglandins and the plant alkaloids made from Mev responsible for Se toxicity, subject to Se levels, prostaglandins may interconvert between prostaglandins A & E: Diagram 30

Zn inhibits rhinovirus uptake, Se treats viral bowel infection in cattle\(^{E64}\). Carcinomas of breast and colon and most CHD are attributable to Se deficiency. The involvement of tDNA\(_{Mev}\) in water handling explains the tissue-specificity of Se in cancer prevention. Differential tDNA selection accounts for the incidence of cancer in oxytocin/vasopressin’s target tissues.

Lack of reliable human morbidity data\(^{E65}\), cultural and environmental variables obstruct analysis of the correlation of CHD incidence with the geographical distribution of surface rocks. Crude CHD, breast and bowel cancer death rates anti-correlate with surface rock, Se is associated with sedimentary rocks postdating amphibian evolution. The
correlation with water hardness is attributable to Se, not Ca. Poor irrigation management caused toxic Se levels in California. The correlation of Se related morbidity with Se deficiency in Europe suggests it is the main cause of Western morbidity.

Active transport of H$_2$O’s late evolution reflects its sophisticated control. Selenized posterior pituitary hormones are biactive, other evidence for this control is circumstantial. Membrane potential reinforces tightly ordered biological membranes’ impermeability to water. Osmotic models imply water diffuses across membranes.

A 10% osmolar differential requires the net transfer of 200 litres per organ/day. One such organ, the skin, doesn’t accumulate bathwater or perspire more than ~1 litre/day, nor does it leak when subject to 3rd degree burns.

δ1 Differentiation

Differentiation metabolic control in prokaryotes falls naturally into the orthogonal categories explored in $\gamma_1$-$\gamma_9$. They have independent substrates, hormones and pumps, but there are many mutual interactions. Figure 10 summarises those affecting reproduction. In eukaryotes, tissue differentiation enables sophisticated developments in each pathway. When cells differentiate functionally, they need associate with their sisters and limit growth. Loss of active transport activity must be concomitant with oligopeptide or oligosaccharide synthesis to achieve this. A possible mechanism is histone reversal and replacing adenyl by guanyl cyclase:

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<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<..<[..]
During haemopoiesis, bone marrow provides an isolated environment, inducing differentiation by starving cells. tDNAs connected together at random on a cell membrane, possibly the thymus creates dDNAs producing appropriate cell-cell binding protein. Detachment of the oligopeptide precipitates cell division, proliferation and protein synthesis. This regime explains the arcane science of immunology. Cells with random hooks lose their sting to a matching foreign body, inducing their replication, affording protection against similar invaders. If hook cells matching proliferating body tissues are outnumbered, cancers and tumours can develop. Auto-immunity arises by their attacking healthy tissues. Evolution has played many tricks from such simple beginnings.

Reverse transcription from nuclear DNA via ‘dRNA’ generates the proposed dDNAs, or dDNAs may be independent chromosomes. Unlike the DNA encoding mRNAs, their transcription is associated with cell division. Studying retroviruses should elucidate the biochemistry. The tDNA population is fixed, scarcer types limit dDNA implementation. The constancy of oncogene/ intron code between species has prompted the term homeobox. Protein code, 64 triplets encoding 20ααs, can withstand neutral mutations, especially the ‘wobble’ bases and positions where substituting a similar αα doesn’t affect enzyme function. In active transport code, all 64 triplets may have unique functions. E.g. Zn-glucose pathways could have separate tDNAs for:
1] Zn uptake by gut
2] Zn uptake by β-cells
3] Insulin-driven glucose uptake by body cells
4] Vitamin-C-driven glucose uptake by body cells, and
5] Zn uptake by hypothalamus.
Osmoregulation features distinct tDNAs for oxytocin/vasopressin-sensitive tissues. Alkali metal ion exchange uses adrenaline, noradrenaline, tDNAs etc. Other tDNAs involving B, Mo, Co, Ni, Fe and several vitamins relate to transport systems omitted from the thesis.

Genes are equipartitioned between daughter cells at cell division, gene products, membranes, cytoplasm and substrates are not. The number of protein molecules of any species apportioned to the daughters, it’s uncertain whether structural, enzymes, active transport pumps, hormone receptors or cell-cell recognition molecules. No purge of proteins occurs at cell division. The idea that tDNAs behave as genes, not gene products, has profound consequences. If all active transport moieties were proteins, not equipartitioned at cell division, daughter cells might inherit different collections of pumps, rendering them different from their sisters. Contrary to histologists’ experience, tissue cells with different numbers of hormone receptors and pumps would have divergent characteristics. The tDNA system is composed of genes, not gene products, achieving uniformity amongst tissue cells, pathology or chance would otherwise deny it.

Various unreported pathologies would arise if differentiation were a nuclear phenomenon. The existence of special histones and genes controlling transcription does not prove this is a universal principle. Unlike nuclear DNA, membrane-bound tDNAs are exposed to DNA-binding species responsible for CANT, Cancer, Anxiety, Neoplasia and Teratogenesis. The familiar manipulation of frog egg membranes supports the present model. Oligopeptides synthesised on strings of tDNAs can include non-standard ααs, e.g. selenocysteine and vasopressin. The cytoskeleton enables communication between nucleus
and cell membrane; release of tDNA/dDNA-bound histone is a standard response to such signals.

A vitamin-A-based system assembles the glycosphingolipids\(^{\text{F1}}\) determining A/B/C blood groups, see \(\gamma_8\). tDNAs code for both substrates and \(\alpha\)s, they also specify sugars. ATP drives active transport, GTP drives protein synthesis and glycoside formation is UTP dependent. The glycosphingo-lipids confer non-sticky hooks on erythrocytes. Gamete formation involves dedifferentiation. The procedure of egg formation\(^{\text{F2}}\), Diagram 31, evidences partition of dDNAs to polar bodies, leaving the egg cell undifferentiated, c.f. stem cells. Study of the poly-nuclear phase in Drosophila embryology would confirm this.

\(\delta 2\) Trace Elements

The importance of trace elements in active transport is independent of their role in enzyme catalysis. The biologically essential elements underlined in the periodic table in Figure 21, it shows their distribution in the earth’s crust and biosphere. The elements established as biologically essential are underlined. The ‘major’ elements, marked \##, include S and Cl, implicated in active transport carriers. Boron is essential only in plants; in some plants, Si assumes a major role. The biological concentrations of ‘minor’ elements reflect their function. Their involvement as enzyme cofactors accounts for their higher concentrations. Zn is involved in many enzymes, Se only in glutathione peroxidase and Ag not at all. The requirement for an element in its active transport role is small.

I have not studied the roles of V, Ni, Cr, Fe, Co, As, Mo or Sn. Fe, Co, Mo are confined to their well-established biochemical roles, endocrine glands may be loaded with regular trace elements by trace- trace elements. The assembly of trace element complexes may involve other trace elements as catalysts. If the set of 64 tDNA’s may include such options as an iodide pump for the thyroid, a fluoride pump for the parathyroid, an iron pump for the erythropoietic system and a zinc pump for the pancreas.

These tables explain the evolutionary selection of elements for participation in the biological economy. Those failing the test, such as Li\(^{++}\) and Be\(^{++}\), lack chemical flexibility when compared with the amphoteric I\(^{-}\) and the wealth of complexes Zn\(^{++}\) forms with which they compete. Group 3B elements: B, Al, Ga, In [?] are excluded; they’re in too similar to group 4B. Diagonally related B and Si feature more in plants than animals, and Al interferes with Si. Sc is scarce and the apparent lack of a role for Ti is surprising.

The chemical similarity of the rarer, heavier elements are excluded in favour of commoner, lighter species, so Ga, Ge, Br, Rb, Sr, In, Sb, Te and periods 6 and 7 are excluded. The commoner transition elements of the 5th period, Zr,Nb, Ag and Cd, deserve attention. Heavy ions such as MeHg\(^+\) as antidote for Me\(_2\)Se\(^+\) poisoning, may suggest pharmaceutical approaches, but their accumulation in body tissues doesn’t recommend them. Homologous species might be useful in drug design.
Zn deficiencies arise in neonates due to exclusion of access to colostrum, and in alcoholics. Introducing Zn-deficient citrus fruit, carbonated beverages, ascorbutic diets, sucrose and excluding fats in favour of carbohydrates disrupted Zn metabolism, explaining pandemic diabetes. Zn deficiency causes skin conditions, infertility and obesity and allows rhinovirus infection. Zn, Ag and Se have different active transport roles: Zn is cofactor for many enzymes, masking its endocrine function in relation to insulin, glucagon and vitamin C. Since Ag does not participate in enzyme catalysis and its affinity for halides makes it hard to measure and been overlooked. The synergy between Se and tocopherol is well established, but the free radical model has obscured other functions. The specificity of cancer prevention by Se supplementation to breast, bowel, cervix and prostate is hard to prove. Free radicals are not tissue specific.

Ag is more likely than Se to be accidentally added to the diet, formerly in pewter or silver-plated cutlery and vessels. Ag and Se assimilation requires intact cells, roughage to reach the large intestine; they’re lost in food processing. The use of Cl in water purification, pesticides and plastics is relevant. Ag supplementation might prevent many cancers, their more obvious causes are smoking, occupational exposure to chemicals, consumption of mouldy food, some viral infections and radiation hazards.

The importance of Zn, Ag and Se in human nutrition has been side-lined. They are deficient from ‘Western’ diet for three main reasons:
1] Adopting a sedentary lifestyle in a thermostatic environment reduces energy requirements and overall food consumption, reducing micronutrient intake.
2] Food processing for preservation or palatability reduces micronutrient availability. Se and Ag are susceptible to heat and preservatives respectively. They’re lost in peelings, stewing water and evaporate in hot fat.
3] Producing food on poor soils, using fertilisers, irrigation and heavy cropping, introduces food low in trace elements due to surface geology and interaction with agricultural chemicals.

Traditional diets contained sufficient micronutrients, a 20% reduction on each count yields a 50% overall deficit, it applies to Se and may apply to Ag. Zn deficiency is not pandemic, jogging and consuming organically grown ‘health foods’ from selected areas could restore the balance for the wealthy. Supplementing veterinary micronutrient supplementation is precedent for their medical use.

Statistics on human trace element deficiency are scarce and difficult to compile, it is unethical to restrict micronutrient intake deliberately. Comparable populations need share race, culture, economy, eating habits and climate. Regional national surveys, USA states or UK boroughs provide the best data, it needs adjusting to allow for regional, socioeconomic and climatic variations and cultural/culinary practices. Available morbidity data are inadequate.

δ3 Conclusion

Viewed retrospectively, evolution through survival of the fittest is obvious. Fitness depends on the slings and arrows of fortune. Darwinism is a theory of history, making predictions relating to undiscovered histories, not laboratory investigations. It cannot predict what will, should or ought to happen. Darwin’s theory is not false in the sense Karl Popper introduced. Its testable prediction is a consistent tree of life without unconnected branches or
roots. Endocrinology reflects life without proteins. Most metabolic pathways predate the evolution of protein synthesis and tissue differentiation, focusing on trace element metabolism with many consequences. Substrates controlling metabolism differ fundamentally from genetic control.

The axioms underlying this thesis constitute a new paradigm. Most descriptions of the biosphere describe designs, not evolutionary pathways. They lack a consistent evolutionary background. Their accounts of energy coupling are inefficient, not thermodynamically sound; those for metabolic control fail historically, those for differentiation utterly. It is easier to restrict than encourage, a philosophy of listing what not to eat to stay healthy and consuming pharmaceuticals when sick, has usurped micronutrient nutrition. Genetic engineering diverts attention from this underlying science by dogmatic adherence to 1-gene-1-enzyme dogma and reference to catalysts as active participants, overseers rather than metabolic assistants.

This thesis endeavours to show that, subject to appropriate research of its findings, supplementation of various trace elements would benefit Western diet, reducing the incidence of heart disease, cancer, diabetes and viral infection and that reducing air pollution would likewise reduce senile dementia. My proposals, if verified, for substrate-carrier complexes promise better pharmaceutical design by molecular modelling. Understanding the role of trace elements in endocrinology enables creation of artificial endocrine glands for treatment of metabolic imbalance. Rational evaluation of chemicals leads to efficient agriculture and pharmacy, testing drugs, fertilisers, additives, pesticides and cosmetics by automated assessment of trace-element binding before bulk synthesis or animal testing. Creating life in a test-tube and re-enacting each critical episode in its evolution is possible, presenting the prospect of creating a different, incompatible, ‘fitter’ life form with different alphabets of trace elements, substrates and tDNAs. This goes further than genetic engineering, resembling an enhanced breeding program. The dangers of designing tDNAs and dDNAs exceed those for mRNAs.

Designing microorganisms to harvest metals from the sea and clear pollutants from effluents is possible, as is enhancing symbiosis in nitrogen fixation and producing vitamins using gut microflora. Ecological diversity could be easily maintained by nutrient recycling. Conservative multi-cropping could replace the monocultures threatening the planet’s soil. Targeting differentiation DNAs could replace the search for magic bullets against viruses and cancer. Classifying morbidity by pathway, not process, combined with such software as is described in the Appendix, would facilitate diagnosis and educate the public sufficiently to understand dietary regimes. These warnings may seem to signal ‘back to nature’ unless science is more widely understood.

Open peer review would ease promotion of these ideas, not:
You discuss some questions about which I do not have much information, and some about which I have information. Many of the statements that you make are new to me. In general, it seems to me that many of these statements are probably wrong. In any case, the arguments that you present in your paper to support them are not sufficient to convince me or come anywhere near convincing me that they are right... Your various statements about infrared radiation seem to me to be arbitrary and without sound justification... Professor Linus Pauling, 11/9/74
... We do not accept purely speculative suggestions which are not based on established data, or the existing body of biological theory... Professor Lewis Wolpert, 28/10/74.

... I am afraid that I cannot agree with your ideas on the origin of life... Professor Sir George Porter, 19/7/77.

In reviewing Linus Pauling, John Rivers wrote\textsuperscript{F4}: The fact of the matter appears to be, as he suggests, that the biomedical professions don’t want his theories, but have no arguments to erect against them. Whether ultimately he’s right or wrong in his theories, the controversy looks perfect material for the philosophers of science as an example of the futility of trying to break out of a still viable paradigm.

Richard Dawkins remarks\textsuperscript{F5}:

It is amazing that you can still read calculations about the chances of building a working enzyme molecule used as though they constituted arguments against Darwin’s theory. The people who do this, often expert in their own field, astronomy or whatever it may be, seem sincerely to believe Darwinism explains living organisation in terms of chance – “single-step selection” – alone. This belief, that Darwinian evolution is "random", is not merely false. It is the exact opposite of the truth. Chance is a minor ingredient in the Darwinian recipe, but the most important ingredient is cumulative selection which is quintessentially non- random.

This thesis demonstrates the existing paradigm is inconsistent and presents a viable alternative, hoping for action on its consequences. Albert Einstein wrote\textsuperscript{F6}:

The most beautiful thing we can experience is the mysterious. It is the source all true art and science. He to whom this emotion is a stranger, who can no longer pause to wonder and stand rapt in awe, is as good as dead: his eyes are closed. The insight into the mystery of life, coupled though it be with fear, has also given rise to religion. To know that what is impenetrable to us really exists, manifesting itself as the highest wisdom and the most radiant beauty which our dull faculties can comprehend only in their most primitive forms - this knowledge, this feeling, is at the centre of true religiousness. In this sense, and in this sense only, I belong in the ranks of devoutly religious men.

References


A6 E.g. Alexander Fleming’s discovery of penicillin, reported 1929, not developed until 1940.


B2 My work on relativity and cosmology deriving from properties of the nucleohistone structure is excluded from this thesis, it does not bear on metabolic control.


B5 A natural accumulation of fissionable material resulted in an explosion yielding craters near Pretoria.


B8 CA104 #136999f Ice Ih-Ic transition. CA 105 #30492r Energy change between ice Ih and ice Ic ~50J/mol


B10 CA76 #1732y Ferroelectricity of ice Ih. Ferroelectrics (1970) 1(3), 169-75.

B11 CA 104 #43527k O Mishima et al, Apparently first-order transition between two amorphous phases of ice induced by pressure Nature 314 76. CA 104 #120358k D2O Ice Ih has phase transition at 76 K. 155J/mol if well annealed, lost 64% of residual entropy. Ordered ice Ih called ice XI.

B12 See B7.


B15 NS 96 (1337) 783 report on American Geophysical Union, San Francisco Dec 1982. Icy crevasses on Europa (moon of Jupiter) reckoned possible for life-support. No atmosphere, surface temperature ~100 K.

B16 NS 100 (1380) 177 Triton, moon of Neptune, has liquid N\(_2\) on surface. NS 109 (1494) 24 Triton has equivalent of 10m of earth’s atmosphere and lakes of liquid N\(_2\).

B17 NS 112 (1538) 28 Fluctuation in solar output 0.1% over 11-year cycle. 0.5% would account for ice ages etc. Science 234 1114. NS 94 (1305) 413 quotes C Sagan & G Mullen considering a 30% variation in solar output.


B19 NS 95 (1316) 301 Variation of earth–moon distance. Geophys J Royal Astron Soc 70 6 261. D J Webb Derstenkorn Event’ when Moon was only a few Earth diameters away was 3.9Byr ago (c.f. solar system 4.6Byr ago).

B20 The work done in bringing a charge Q from infinity to distance R from a like charge is \(k/R\) where \(k = Q^2/4\pi \varepsilon_0\). For identical parallel dipoles of length d, displaced by Z axially, X laterally, there are 4 such interactions:

\[
2k/R - k/R_1 - k/R_2
\]

where \(R = \sqrt{(X^2 + Z^2)}\), \(R_1 = \sqrt{(X^2 + [Z + d]^2)}\), \(R_2 = \sqrt{(X^2 + [Z - d]^2)}\)

Using the Maclaurin expansion: \((1 + \alpha)^{-\frac{1}{2}} = 1 - \alpha/2 + \frac{3\alpha^2}{8} - \frac{15\alpha^3}{48} + \ldots\)

\[
2k/R + k(R^2 + 2zd + d^2)^{-\frac{1}{2}} + k(R^2 - 2zd + d^2)^{-\frac{1}{2}}, k/R(-d^2/R^2 + \frac{3}{4}(s^4 + 4d^2z^2)/R^4)
\]

\approx kd^2/R^3(3z^2/R^2 - 1)

If each water molecule in ice Ic or It is treated as a dipole, the energy of each dipole-dipole interaction is \(\approx k(3z/R^3 - r^3)\), where \(k = D^2N/4\pi \varepsilon_0\)

\[
D = \text{Dipole moment}, \text{ see B7, p109) = } 3.8 \times 10^{-18}\text{esu-cm} = 1.27 \times 10^{-29}\text{ Joul-m},
\]

\[
N = \text{Avogadro } N_0 = 6 \times 10^{23}, \varepsilon_0 = \text{Dielectric constant} = 8.85 \times 10^{-12}
\]

\[
K = (1.27 \times 10^{-29})^2 \times 6 \times 10^{23}
\]

\[
\frac{4\pi \times 8.85 \times 10^{-12}}
\]

The coordinates of molecules are:

<table>
<thead>
<tr>
<th>Cubic</th>
<th>Tetragonal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta x = \Delta y = (b+h) \sin(\theta_b/2) = 2.255\text{Å})</td>
<td>(b \sin(\theta_b/2) + h \sin(\theta_c/2) = 2.315\text{Å})</td>
</tr>
<tr>
<td>(\Delta z = (b+h) \cos(\theta_b/2) =1.495\text{Å})</td>
<td>(b \cos(\theta_b/2) + h \cos(\theta_c/2) = 1.597\text{Å})</td>
</tr>
</tbody>
</table>

where \(h = \text{H-bond length, 1.75Å, b = O-H bond length, 1.01Å, } \theta_b = \text{tetrahedral angle, 109.5°, } \theta_c = \text{H-O-H bond angle, 104.5°, } \theta_c = \text{charge cloud angle, 120°. 4 distinct decks of molecules:}\)

\[
x = 2n_x \Delta x, \quad y = 2n_y \Delta y, \quad z = 4n_z \Delta z
\]

\[
x = 2n_x \Delta x + \Delta x, \quad y = 2n_y \Delta y, \quad z = 4n_z \Delta z + \Delta z
\]

\[
x = 2n_x \Delta y, \quad y = 2n_y \Delta y + \Delta y, \quad z = 4n_z \Delta z + 2\Delta z
\]

\[
x = 2n_x \Delta x, \quad y = 2n_y \Delta y + \Delta y, \quad z = 4n_z \Delta z + 3\Delta z
\]

Energy change in the cubic tetragonal transition is:

\[
\delta E = K[R_c^{-\frac{1}{3}} (3Z_c/R_c - 1) - [R_t^{-\frac{1}{3}} (3Z_t/R_t - 1)]] \text{ where } Z = z^2, R = x^2 + y^2 + z^2
\]
For 100, 13,000 and 20,000 neighbours, $\Sigma \delta E = 21,882$, 22,278 and 22,279 kJ/mol. This estimation suggests the difficulty of achieving reliable results for more complex cases.

B21 W Saenger, Nature 279,343 *The ordering of water associated with biomolecules has been studied in several cases. E.g. in relation to dextrins.*

B22 NS 90 (1248) 85 *Laser on Mars* - 10.33μ CO₂-based laser in Martian atmosphere.

B23 Volcanic activity regularly concentrates aliquots of the ocean, enabling polymerisation of dATP to DNA and other reactions requiring concentration and heat. J Scott in NS 89 (1236) 153*DNA once so formed would be stabilised by hydrated electrons.*


B26 I F Danielli & H L Davson, A contribution to the theory of permeability of thin films, J Cell Comp Physiol 5,495-508 1935.

B27 See B3.


C2 NS 107 (1476) 20 *Acetyl choline receptors from electric eels shown similar to those in calves’ muscle cells.* Nature 313, 364 & Science 225, 1335. Protein acetyl choline receptors from electric fish. 5 protein subunits, $\alpha\beta\gamma\delta$, all rather similar. 26 variants made. 9nm across. NS 112 (1529) 22, Nature 323, 396 & 411. *Electric eel receptors cloned - review of other protein pumps.*


C4 NS 90 (1252) 352 *Polytenic genetics in Drosophila.*

C5 NS 110 (1510) 26 Liver cells are polyploid - to 8 copies in man, 64 in mice.

C6 NS 97 (1340) 90 *Protein pores in dysentery.* NS 115 (1574) 22 Dysentery bacterium has same toxic enzyme as ricin of castor oil.
C7 Prion S B Prusiner in Science Infectious agent, MW about 50,000, not fully characterised. NS 113 (1545) 32, M Bruce & A Dickinson, J Gen Virology 68 p79. Scrapie agent displays mutants; ‘prion’ hypothesis discredited.


C9 tDNA Turnover number of $10^8$, or 10 nsec per cycle. Estimates of turnover rate for active transport embrace a number of unknowns: the number of cells involved, the number of active pumps per cell, and the effect of concentration of substrate on activity. Assuming the 100kg body has $10^{14}$ cubic cells of side 10μ, and tissues have $10^{12}$ (tissues are assumed to weigh 1kg), and its epithelium, area $1m^2$, has $10^{10}$ cells, the turnover numbers for known transport rates in frequency units (molecules per pump per second) are:

Gut resorption of 20 litres/day of water, MW18, by $10^{10}$ cells each with 20 pumps:

$$\frac{6 \times 10^{23} \times 20 \times 10^3}{20 \times 10^{10} \times 18 \times 24 \times 3600} = 40 \times 10^9 \text{ Hz}$$

Kidney resorption of 350 mg/min glucose, MW 120, by $10^{10}$ cells each with 20 pumps:

$$\frac{6 \times 10^{23} \times 350 \times 10^3}{20 \times 10^{10} \times 120 \times 60} = 0.15 \times 10^9 \text{ Hz}$$

Lung uptake of oxygen (4%) from 22 litres (1 mole) of air per minute by $10^{10}$ cells each with 20 pumps:

$$\frac{6 \times 10^{23} \times 0.04}{20 \times 10^{10} \times 60} = 2 \times 10^9 \text{ Hz}$$

Comparable to transit time predicted by transport model, electrical energy, QV, of substrate-carrier complex with unit charge $Q = 1.6 \times 10^{-19}$coulomb, and membrane potential $V=60mV$, → kinetic energy $\frac{1}{2}mv^2$. Mass, $m \sim 100$ daltons, gives final velocity $v$:

$$v^2 = \frac{2 \times 1.6 \times 10^{-19} \times 60 \times 10^3}{100 \times 1.67 \times 10^{-27}}$$

Whence the time to cross the 2nm membrane is:

$$2 \times 2 \times 10^{-9} = 0.012 \times 10^{-9} \text{ sec (corresponding to } 80 \times 10^9\text{Hz}).$$

The above figures are mutually consistent. The higher rate for water transport reflects greater substrate conc, the lower rate for glucose greater inertia of substrate molecules. Best test comparing with expectations from models invoking diffusion and osmosis, suggesting water passes easily across the membrane, osmolarity determining the rates in either direction. An osmolarity difference of 10%, yields transfer corresponding to net transfer 10 x greater and 200 litres/organ/day, e.g. human skin doesn’t accumulate bath water or perspire more than 1 litre a day - nor even to be so leaky when subject to 3rd degree burns.

C10 See B7.
C11 CA 83 #159360c Two conformers of tRNA found. CA 84 #39845p Mn induces structural change in tRNAVal, greater in valyl-tRNAVal involving change in tertiary structure.

C12 J Jeans, Kinetic Theory of Gases, p271 CUP 1962, quotes from J C Maxwell, Theory of Heat, p328: One of the best established facts in thermodynamics is that it is impossible in a system enclosed in an envelope which permits neither change of volume nor passage of heat, and in which both the temperature and the pressure are everywhere the same, to produce any inequality of temperature or of pressure without the expenditure of work. This is the second law of thermodynamics and it is undoubtedly true so long as we can deal with bodies only in mass and have no power of perceiving or handling the separate molecules of which they are made up. But if we conceive a being whose faculties are so sharpened that he can follow every molecule in its course, such a being, whose attributes are as essentially finite as our own, would be able to do what is at present impossible to us. For we have seen that the molecules in a vessel full of air at a uniform temperature are moving with velocities by no means uniform though the mean velocity of any great number of them, arbitrarily selected, is almost exactly uniform. Now let us suppose that such a vessel is divided into two portions, A and B, by a division in which there is a small hole, such that a being, who can see the individual molecules, opens and closes this hole, so as to allow only the swifter molecules to pass from A to B, and only the slower ones to pass from B to A. He will thus, without expenditure of work, raise the temperature of B and lower that of A, in contradiction to the second law of thermodynamics. See also: SA Nov 1987, p88 Demons, engines and the second law C H Bennett.

C13 Affirmed in conversation with worker in that field.


D1 L Pauling, R B Corey & H R Branson, α-Helix PNAS 37, 205. L Pauling & R B Corey, β-sheets PNAS 37,729.

D3 See B24

D4 G Oster, NS 95 (1313)102 20-30Hz sound from muscle.


D6 R W Burlinghame et al, Crystallographic Structure of the Octameric Histone Core of the Nucleosome at a Resolution of 3.3Å, Science 228, 546. T J Richmond et al, Structure of the Nucleosome Core Particle at 7Å resolution, Nature 311, 532. Polemic between Burlinghame
et al & Richmond et al, *Crystallographic Structure of the Octamer Histone Core of the Nucleosome*, Science 229, 1109.


D8 Biochemistry 1982 21(12) 3028 Evidence for involvement of Tyr in DNA-histone interactions.


D10 F Azorin et al, J Mol Biol 1985 185 (2) 371-87. Peptides including poly (Ala-Lys) bound to DNA. Different types of complexes found in which a monolayer or double layer of β-pleated sheets is intercalated between layers of DNA molecules.


D13 NS 70 (999) 291 J Corden et al found strings of 9 beads in the adenovirus. NS 83 (1162) 8 Beads of Life M Robinson, ‘superbeads’ of 8 beads with one bead between. CA 96 #30164f strings of 8, 14-16, and 21-24 nucleosomes.


E1 CA 69 #82808f Corrosion of Mn related to cathode process during electrolysis. N A Shvab, D P Zosimovich, Ukr Khim Zh 1968 34(6) p569 ... SO₃⁻ and SeO₃⁻ reduce the rate of solution of α-Mn and their effect on the current yield is due to a balance between a decrease due to α-Mn formation and an increase due to a reduced rate of corrosion.


E3 H Colquhoun, F Stoddart and D Williams NS 110 (1506) 44 Review crown ethers. NS 116 (1583) 31 Nobel Prize to Pendersen and Cram for early work on them.
E4 R B Heslop and P L Robinson, Inorg. Chem. 3rd ed, Elsevier, p687-8: The +4 state for Mn is not common - it exists in some hexachloro and hexafluoro complexes...


E7 K Fushitani et al, J Biol Chem 1986 261(18) 8414 Oxygenation of earthworm haemoglobin affected by Li⁺ more than K⁺ or Na⁺ - ionic size, not ionic strength important.


E9 Research of the inheritance of psychotic disorders NS 113 (1551) 23. Since MD psychosis manifests is heritable, with a variety of periodicities, the syndrome embraces several disorders. A defective tDNA may be involved in some cases (as distinct from defective enzymes), enabling the study of tDNA genetics. A family with a tDNA defect would display MD psychosis in a proportion of sibs related to the number of normal tDNA_{O2,1+s}. Such a study needs phenotypic expression and correct diagnosis.

E10 Aminoaciduria is characteristic of Wilson’s disease, just as glucosuria of diabetes mellitus (see Assimilation). Cu^{2+} known to form strong ligands with aas. Penicillamine, chelates Cu^{2+} and treats Wilson’s disease.

E11 Classifying the 20aas:

\[\begin{matrix}
A= & A1a & F=Phe & @ & K=Lys & N & P=Pro & o & T=Thr & O \\
C= & Cys & S & G=Gly & o & L=Leu & o & Q=Gln & o & V=Val & o \\
D= & Asp & o & H=His & N & M=Met & S & R=Arg & N & X=Trp & @ \\
E= & Glu & o & I=Ile & o & N=Asn & o & S=Ser & O & Y=Tyr & @ \\
\end{matrix}\]

where: @ = aromatic, N = nitrogen ligand, O = oxygen ligand, S = contin sulphur, o=other

Active parts of hormones:

Somatostatin: \(AGCKNFFXKTFTS\)

Glucagon: \(HSQGFHTSDYKLYLSSRAQDFVQXLMNT\)

ACTH: \(SYSMEHRXCKPKVGGKRGPV_K\)VP\_\_\_AEDESAEAFLEF\)

γ -rat atrial natriuretic peptide:

\(NPVYSAVSTDLMDKFKNLDDLDDKMPVEDEVMPQALSEQTDEAGAAALSSLSELVPXTGEVNPQRDGGGALGRGPXDPSDRLALLKS\_KRALLAGPRSLRRSCFFGRIDRI\)

GAQSGLGCNSFRY

all have groups of intercalating/chelating residues enabling sequestration of divalent anions from tDNAs:

Somatostatin: (Cu^{2+})

\(AGCKNFFXK\)

\(ooSNo@@@N\)

CSTFT

SOO@O

Glucagon: (Zn^{2+})

\(HSQGFHTS\)

\(NOooO@@O\)

\(>\)

54
In each case calls for detailed investigation. It’s reasonable to suggest these hormones conform to tDNA-binding, \( M^{++} \)-binding, tDNA-release, transport to liver and degradation releasing \( M^{++} \) for recycling. Unbalanced \( \alpha \alpha \) ratios cause headaches. Peptides are > specific than spirin and ethylene diamine tetra-acetate as metal chelating agents as pharmaceuticals.

E12 L A Grivell *Mitochondrial DNA*, SA Mar 1983 p60. F H C Crick’s original wobble proposal enables 32 tRNAs to match 64 mRNA triplets. In mitochondrial protein synthesis, some tRNAs match 4 mRNA triplets. There is relatively less ‘intron’ code in mitochondrial and prokaryotic DNA.

E13 \( 1,25\)-di\( \Delta \)cholecalciferol derived from Vitamin D\( \text{3} \), see Excretion. Irradiation of 7-\( \Delta \)cholesterol yields ergocalciferol = Vitamin D\( \text{3} \), with a \( C_8H_{17} \) side-chain. Calciferol = vitamin D\( \text{2} \) has a \( C_9H_{17} \) side-chain. An IU for human nutrition is 0.05 \( \mu \)g vitamin D\( \text{2} \) or 0.025\( \mu \)g vitamin D\( \text{3} \). Fish employ another sterol. There is species variation in the effectiveness of Vitamin D\( \text{2} \)/Vitamin D\( \text{3} \).

E14 Gastrin, calcitonin and secretin remove spent halides from active transport sites, see E11. Using the same convention, we have:

**Calcitonin (F)**

\[
\text{CGNLSTCMGLGTYTQDFQKFHTFPQTAIGVGAP}
\]

\[\text{SoSoOSSooO@OooooO@NO@NO@OooOoooooo}\]

**Gastrin (Cl)**

\[
\text{EGPXMEEEAY5GXMDF}
\]

\[\text{ooO@SoOooooo@ o@So@ (Sulphonate on Try)}\]

**Secretin (HCO\( _3^- \))**

\[
\text{HSDGTFTSDLSRLDASLQRLLLQGLV}
\]

\[\text{NOooO@OOooONoN oOoNooNoooooo}\]


E19 NS 89(1243) 602 Aminocitrate in ribo-nucleo-proteins, RNP FEBS Letts 123, 141. Zn deficiency may lead to a reduction in protein synthesis because Zn is needed for RNP synthesis to incorporate amino-citrate. NS 92 (1278) 371 β-carboxy aspartic acid in RNA-binding proteins - cf α-amino citric acid and γ-carboxy glutamine. CA 105 #114032d Zn deficiency decreases rat liver histones.

E20 Contraceptives go on trial for diabetics NS 91 (1267) 463.


E22 R F Doolittle Fibrinogen and Fibrin SA Dec 1981 p92. Structure contains 3 α-helices super-coiled and connected by S-S bonds. Zn could be involved in linking the chains.

E23 CA 76 #136936m Zn-insulin structure. NS 73 (1039) 386 T L Blundell et al Diabetes l972 (21), supp 2, p492, insulin structure etc.

E24 NS 89 (1236) 143 Nature 288, 383

E25 CA 79 #101266c Alcohol augments hypoglycaemic effect of insulin, possibly by inhibiting gluconeogenesis in liver resulting from alcohol oxidation. CA 83 #161815y High Zn (about twice normal) in semen of alcoholics. CA 83 #174713p & CA 83 #189804t Zn in horse-liver alcohol dehydrogenase. NS 112 (1538) 26 Benzodiazepine derivative affects alcohol metabolism. CA 104 #16390d Zn deficiency occasionally associated with alcoholism. CA 105 #2059m Zn protects rats against alcohol toxicity. CA 105 #189806t Zn deficiency in alcoholics effect on pancreas.


E27 CA 104 #47948w.

E28 D Bryce-Smith ‘The Zinc Solution’ Century Arrow p51.

E29 J Emsley Designing Sweetness to Order, NS 108 (1480) 22 Robert Shallenberger’s ‘triangle of taste’.


E31 NS 99 (1377) 928 Bottlefeeding correlates with juvenile onset diabetes. NS113 (1553) 28 Infection triggers childhood diabetes Nature 326 p304. NS 177 (1596) Environmental
cause for Type 1 (insulin-dependent) diabetes - Finland incidence 50 times that in Korea, with 3-fold increase over 30yrs. Mid-West Poland epidemic over 3yrs.

E32 C E Casey et al, Trace Elements in man & Animals TEMA 5, Proc Int Symp 5th 1984, p633. Zn in human colostrum. Breast fed infants get 0.13, 0.90, 2.30, 2.46 & 2.54mg on days 1-5 respectively.

E33 E J Underwood, see E18, p227.


E35 K M Kadish, X Q Lin, J O Ding, Y T Wu & C Araullo, A reinvestigation of silver porphyrin electrochemistry. Reactions of Ag(III), Ag(II) and Ag(I) Inorg Chem 1986 25, 3236-42.


E39 H A Harper, ibid, pp462, 495.


E41 CA, mevalonic acid = 3,5-diOH-3Me-pentanoic acid and mevalonolactone = tetraOH-4-OH-4-Me-2H-pyran-2-one. Pharmaceutical patents same classification. Pentanoic acid derivatives include several hypotensive agents.

E42 Heart failure NS 111 (1520) 17, G Rose BMJ ~31/7/86. 10-yr study of 18,000 civil servants suggests benefit of taking less saturated fat.


E44 Aspirin makes the heart grow stronger NS 117 (1598) 24 New Eng J Med 22,000 physician study 325mg aspirin/day halved risk of heart attack. Study stopped. S Kingman Will an aspirin a day keep the doctor away? NS 117 (1599) 26 BMJ 30/1/88 p313 R Doll critical aspirin before first heart attack diverts deaths from heart attack to stroke. FDA checks aspirin claims NS 117 (1603) 23 aspirin manufacturers agree to refrain from making claims on labels. CA 105 #77850w D F Birt, A D Julius. Nutr Cancer 1986 8(2) 117-23 Adding aspirin stops PG production [Sequesters Mn?]. High PG production in colon but not blood or kidney response to high fat and high Se. O Sattaur On the trail of prostaglandins NS 96 (1327) 82 Nobel awards. Aspirin blocks prostaglandin synthesis. [Science] Aspirin
 Prevents hypertension in pregnancy NS 109 (1493) 32 H Wallenburg et al Lancet i, 1
60mg/day from 28th week of pregnancy prevented toxaemia. Aspirin cuts deaths after heart
attacks NS 118 (1607) 22 International Study of Infarct Survival. Aspirin + streptokinase
recommended immediately following heart attack.

E45 A Abbott [Scienoe] The milky way to keep stress at bay NS 117 (1604) 36 L Resnick &
J Laragh suggest calcium can stop people’s blood pressure rising after they eat salty food.
CA 104 #142266f V Erk. Patent Appl 1/3/84. Mn used to treat hypertension and toxaemia
of pregnancy. CA 105 #219172c M S Soloff, Z Grzonka (Ohio). Endocrinology (Baltimore)
1986 119(4)1564-9. 1- 10mM [Mn++] enhances binding of oxytocin to mammary and uterine
cell membranes.

1961 107 (4) 734- 7. Tissue and serum manganese levels in evaluation of heart muscle
damage. A comparison with SGOT. Variations of serum Mn after a heart attack are good
indication of progress.

E47 CA 83 #26631v G A Trapp, J Millam. J Neurochem 1975 24(3) 593-5. Distribution of
selenium- 75 in brains of selenium-deficient rats. High uptake in brain despite low GP
activity. CA 86 #184081g & 86 #134461k SeO3= effective in treating MeHg poisoning in
rats. CA 95 #181728y Health effects of MeHg [MeHg - Se interaction]. 54 CA102
#144419r Sci Tot Env 1985 42(1-2)185-8. Se shown to accumulate in anterior pituitary of
rat.

Roleof selenium in relation to ubiquinone in the rat. Evidence of synergistic action of Se and
or α-tocopherol.

Excretion of dimethyl selenide by the rat. Me2Se found in expired air. CA 70 #94512p I S
Palmer, D D Fischer, A W Halverson & O E Olson. Biochim Biophys Acta 1969 177(2)
336-42. Identification of a major selenium excretory product in rat urine. Me2Se+ found in
rat urine. CA73 #53604p I S Palmer, R P Gunsalus, A W Halverson, O E Olson. Biochim
Biophys Acta 1970 208(2) 260-6. Trimethyl-selenium ion as a general excretory product
from selenium metabolism in the rat. Me3Se+ constituted 20-50% of urine Se.

E50 CA 96 #5226v Animal and epidemiological studies relating selenium to heart disease R
Martin & H E Ganther. CA 105 #189766e R J Shamberger. Front Bioinorg Chem, 2nd 1985
152-9. Se def & cancer, CHD etc in man & animals [R36refs]

E51 Vitamin E mops up dangerous radicals NS 87 (1217) 712 L Corash et al, New England
J Med 303, 416. Hereditary G6PD deficiency - small increase in half life of blood
cells following high Vitamin E supplement attrib free radical effect. R Willson The radical
theory of ageing NS 100 (1388) 837. Tar may not be the killer in cigarettes NS 110 (1514)
Cigarette filters inadequate. Carcinogenicity of cigarette smoke attributed to free radicals.

Reducing the risk of resuscitation. Catalase and SOD reduce free radical damage during resuscitation. Free radicals responsible for deterioration of organs during transplants.


Se-independent GP in rabbit liver detected, characterised.

Se Deficiency in rats → high LDL cholesterol. An old drug has new advantages in heart disease NS 95 (1317) 363 prazosin (α-blocker). LDL represents cholesterol on the way into an atheromatous plaque, while HDLs are cholesterol on its way out. Prazosin raises HDL/ LDL ratio. J Cardiovasc Pharm 4,5222 Cholesterol test for heart disease ‘does not work’ NS 110 (1502) 16 S Pocock & G Shaper Lancet 3/86 HDL/ LDL ratio not diagnostic for CHD. [Science] How to lose cholesterol without even dieting NS 112 (1538) 26 M Martin Lancet ii,934 & J Stamler J Am Med Assoc 256, 2823 controversy on blood cholesterol as risk factor. Lovastatin & synvinolin block cholesterol synthesis. Confusion at the heart of the matter NS 116 (1588) 27 high HDL statistically significant at protecting against CHD in US study, but not in USSR study.

High correlation between Se and GP in sheep. CA 91Q #155719u Hypertensive patients, NZ, had more than usual Se in erythrocytes. Fish → Se↑ +ve correlation GP with Se. cf: CA 91 #138096w Se levels lower in 78-yr-olds than 25-yr-olds. CA 97 #214668a Se Supplementation: plasma GP an indicator of Se intake. E58 C E Curtis Ocean mining and the law of the sea. NS 89 (1245)736 typical nodule content: Mn 35% Co 3% Ni 2% V .01% Cu 2% Mo .01%Fe, Pb & Zn also present. Law of the sea goes down for the third time. NS 103 (1421) 7.
E59 CA 84 #134484d Effect of dietary antioxidant supplementation on the susceptibility to oxygen toxicity in mice. C Schatte, A Swansinger (Dep Physiol Biophys, Colorado State Univ, Fort Collins, Colorado) Aviat Space Environ Med 1976 #47(2),147-50. Simulated US male diet. 0_2 at 1 atm, time to death in mice statistically longer on Se supplement.


E62 CA 77 #148127g Trace elements in tobacco smoke, uptake - no figures given or specific mention made in abstract.


E64 CA 85 #40937x Use of Vitamin E-Se to treat veterinary diarrhoea.

E65 SA Geller Autopsy SA Mar 83 p110. 40% of causes of death refuted at autopsy - only 15% of deaths are autopsied.

E66 California’s polluting fields NS 105 (1446) 5 San Joaquin Valley irrigation. C Caufield Toxic selenium collects in Californian soils NS104 (1427) 8 West of San Joaquin Valley. 2-14ppm Se teratogenic to wildlife. Dumping to wildlife refuge since 1980.

E67 CA 86 #41368v In majority of women with toxaemia and nephritis of pregnancy, blood Se was down by factor of 4. CA 86 #188001d-2e Bioinorganic Chem 1977 7(1), 23-, 35- Correlation low-Se in diet with cancer of large intestine, rectum, prostate, breast, ovary, lung. Suggest US Se-intake be doubled. CA 89 #74558x Br J Nutr 1978 39(2),391 Low Se British foods. Min Ag study 60μg/day average intake - due low soil level CA 91 #50664u P J Shamberger et al Trace Subst Environ Health 1978 12, 48-52. Se & heart disease II 25-county study. Cerebro-vascular and hypertensive heart disease in relation to intake of Mn. -ve correlation Se with heart disease. Britons lose heart- but keep their livers NS105 (1439) 8 extracts from WHO report deaths from CHD:

<table>
<thead>
<tr>
<th>Country</th>
<th>Deaths/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scotland</td>
<td>300</td>
</tr>
<tr>
<td>West Germany</td>
<td>166</td>
</tr>
<tr>
<td>Italy</td>
<td>129</td>
</tr>
<tr>
<td>France</td>
<td>75</td>
</tr>
<tr>
<td>England &amp; Wales</td>
<td>244</td>
</tr>
</tbody>
</table>

Cf England & Wales lung cancer 56. CA 104 #128726z E J Roekens et al. Z Lebensm-Unters Forsch 1986 182(1) 8-13. Dietary Se intake in Belgium is low to very low. CA 104 #167276x M Abdulla et al. 3rd Proc Int Symp Ind Uses Se & Te 1984 522-7. Se Swedish diets very low compared with the recommended 50-200 μg/day. CA 104 #205807f A Solvang et al. Næringforskning 1985 29(4) 139-41. Norwegian dietary trace elements...Se 84μg/day. CA105 #59755q M Van Caillie-Bertrand et al. Pediatr Res 1986 20(6) 574-6. Very low Se levels observed (Netherlands) Found 10μg/dl in adult, 8 in children, 1-2 in infants but
GP levels OK. CA 105 #190025u I Thornton, C Smith, S van Dorst. Dept Geol, ICL Trace Elem Man Anim TEMA 5, Proc Int Symp 5th 1984 853-5. Soil Se def British livestock 517 samples 0.01… 4.66 μg/g British soils from calcareous and coarse sedimentary rocks lower than … from fine grain sediments … acids soils most suspect.


F1 Sen-itiroh Hakomori Glycosphingolipids SA May 1986 p32

F2 Kimball ‘Biology’ 2nd edn, Addison-Wesley 1968, Fig 22-1, p410

F3 The following assumptions:
* Complex structures:
  
  \[
  \begin{align*}
  \text{Ca}^{++} & | \text{Mg}^{++} : \text{SO}_3^- \\
  \text{Na}^{+} & | \text{K}^{+} : [\text{nor-}] \text{adrenaline} \\
  \text{Na}^{+} & | \text{K}^{+} : \text{codeine} | \text{morphine} \\
  \text{MnCl}_4^- & : \text{NaCl} \\
  \text{I}^- & | \text{Li}^+ : \text{O}_2 . \text{H}_2 \text{O} \\
  \text{SiF}_6^{2-} & : \text{apatite} \\
  \text{Zn}^{++} & : \beta \text{Dglucose} \\
  \text{Zn}^{++} & : \text{ketoLgulonate} \\
  \text{Arg} & \text{analogues} & : \text{PP}_1 \\
  \text{Ag}^+ & : \text{creatin} \\
  \text{Ag}^+ & : \text{serotonin} | \text{melatonin} \\
  \text{Ca}^{++} & | \text{Mn}^{++} : \text{SeO}_3^- \\
  \end{align*}
  \]

* Properties of ice crystallised in liquid N$_2$
* Photophosphorylation of [d]ADP to [d]ATP at ~4μ
* Occurrence, structure and function of tDNA
* N$_2$, O$_2$, CN$^-$ and H$^+$ fixation by a tDNA + NAD[P]
* Aldosterone in creation of MnCl$_4$=
* I$^-$ from thyroxine
* Glucagon in Zn$^{++}$ homeostasis
* Somatostatin in Cu$^{++}$ homeostasis
* Vitamin D in creation of SiF$_6^{2-}$
* Ag-porphyrin + Vitamin A in creation of PP$_1$ & inositol-P$_n$
* Mn$^{++}$ in cholesterol synthesis
* Vitamin E in creation of SO$_3^{-}$| SeO$_3^{-}$ from -S- | -Se-
* Osmoregulation system
* Nucleohistone H-bond chaining
* 9 centriole components determine 9 repeats in nucleohistones
* Late evolution of protein
* 4μ couples energy in grana, mitochondria and muscle
* The 5-hook theorem
F4 J Rivers reviewing Linus Pauling’s ‘How to live longer and feel better’, NS 112 (1528) 53

F5 R Dawkins ‘Creation and natural selection’ NS 111 (1527) 34


F7 R B Heslop & P L Robinson, ‘Inorganic Chemistry’ 3rd edition, Fig 192, p319. Structure of Tris(salicyl aldehyato)caesium

δ4Appendix - Software

The software used to prepare this thesis comprised a word processor, SPA and graphics package GRA, derived from originals compiled in 6510 Assembler on a Commodore 64 μ-computer, OKI printer and Watanabe flat-bed plotter. SPA offered: Diagram 32 Assemble 6510 object code in text to relocatable object code. Enhancements included TEXt strings and decimal CONstant definition. The object code is presented in BASIC DATA statements susceptible of serial transmission. Using 15-character lines, object modules 2K long are possible.

Blank text buffer
Copy/Insert sequential file of text.
Directory.
Form fill editor enables data entry to highlighted fields in form
Help error messages
Load/Save disk file to text
Move line range to new position, enabling file merging
Merge files
Upper case/text mode toggle
Width to pad/truncate lines
Edit text. During data entry, full-screen edit, scrolling when the cursor passes the top or bottom line. Single key insertion/delete functions, performing full line operations when
cursor is in right/left margin respectively. All function keys auto-repeat, they have two key-selectable speeds.

The HOME key toggles to the control line, enabling searches for text strings. Hits are displayed reversed in blank lines in the screen, and may be copied there using the CLR key. This enables ‘scissors and paste’ editing without reference to line-numbers or need of positioning markers in the text.

Special characters:
- Above/below super-/sub-script [at print]
- Centre, indent, width [at realign]
- Diagram to include [at print]
- Formatted data end, underline/underline [Format]
- Greek letter [at print]
- @abcdefgh hjklmnop = ÅαβΣδεφγ θκλμΞΩ
- pqrsuvw xyz [ \ ]^_= πνρστΔνω χνℓ {\} ↓→

Page end [at realign]

An unprintable graphic retains collimation and multiple spacing when realigning. Tabulation isn’t implemented. Form-fill editor enables tabulated data entry.

Order: order/select, vide infra

Print, specifying number of columns, line range, page numbering, page heading, line spacing, lines per page, margin indent.

Test spelling against user-created dictionaries.

Demonstration of SPA editor

Diagram 33

Diagram 34

Unprintable blanks for paragraph indentation. \( \text{SO}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+ + \text{HSO}_3^- \).

Second new line implemented at print.

Element radius [Å]

\[
\begin{align*}
\text{S} & \quad 2.3 \\
\text{O} & \quad 2.5
\end{align*}
\]

The two examples below illustrate sort/select option. The enquiry is interactively vetted. Only the first character of any keyword is typed. By realigning to
Graphics editor enables wireframe object preparation with nodes defined:

- X, Y, Z coords
- Symbol, one of 31 elements; X signifies the first two title characters.
- A line type: double bond, dotted line, jump, area fill, fill code # (default single)
- A stack instruction: stack, unstack, draw line, double bond, dotted line, or jump to stack
- Vector Δx Δy Δz amplitudes of sinusoidal movement of node

The example below shows the layout. Editor converts data to GRA file, enabling batch rotation, scaling and translation of source coordinates. SPA also prepares netplot data.

GRA handles 8 objects, 7 wireframes/netplots, a 2D overlay of text and line drawings. Calculations use 9-bit floating-point arithmetic and three screen images 2D, unchanged 3D and main screen image). All 70+ possible operations are single key, achieved by pre-setting an amplitude value, either a scalar or power of 2.

GRA illustrations may be printed either directly or via SPA. GAP converts edited data files to flat-bed plotter instructions. GAP options are: character size, scaling, positioning and feature suppression.

Coordinates from a model of the Ca-salicaldehyde complex\textsuperscript{F7} entered as:

```
pes1  Ca-salicaldehyde
0 16 160 100 0 0 0 32 1 0
  -148 +
  -148 X s
-24 -188 O d s
-52 -152 92 H ju
```
Enable the representation at left; ‘tandem mutation’ using the Graphics editor yielded the views at right: Diagram 36

Object viewable in stereo: Diagram 37
A colour printer, monitor or plotter yields red/green stereo, see Figs 18-20. GAP converts raster graphics to vector graphics for plotting.
Known and proposed structures of ice compared

Ferroelectric transition in ice I$_t$ and ATP-Mn$^{++}$ complex showing relation of purine ring to phosphodiester bond during photophosphorylation, see Figure 18.
Transfer RNA structure related to the unit membrane.

Width of tRNAs determines the triplet code, and their ‘hinged’ αα-binding arms introduce the bound αα for transfer to the ribosome. Vitamin A, silver porphyrin and hexadrenaline-sodium complex are shown to the same scale, see Figure 18.
Mechanism of tDNA

The stages enabling, activating and driving directed transport of an uncharged substrate by a charged carrier, and of exchange of charged substrates by uncharged carriers.

---

**Figure 3**

---
Structures related to active transport & ion exchange

Choline controls membrane potential. $SO_3^-$, $SeO_3^-$ & adrenaline rings exchange Ca$^{++}$/Mg$^{++}$/Mn$^{++}$/Na$^+$/$K^+$ control $P_i \sim P_e$ energy release, osmolarity & viscosity → BMR.
Explaining valinomycin action, drug addiction, kidney failure and bipolar disorder, see Figure 19.
Efficient NAD-NADP proton transport and N₂ fixation

Ordered H-bonds eschew Mitchell’s chemiosmosis and Haber’s thermodynamics.
Bone, tooth & plant SiO$_2$ skeletons use apatite$_2$.SiF$_6$.

Adrenaline | noradrenaline, serotonin | melatonin analogues reinstate Ag in biology.

Figure 7

Silicon hexafluoride apatite complex

Builds both bone and silica skeletons

Melatonin

Methoxytryptamine

Silver 5-Serotonin

Silver 5-Methoxytryptamine
Zn and Arg carry glucose, gulonate from vit C and PP$_i$. Zn$^{++}$, Ag$^+$, creatine & arginine carry βD-glucose, 2keto-L-gulonate, inositol & PP$_i$, explaining action of anti-cancer drugs canaverine, imidazole, dacarbazine & chloroplatinate.
Se & vit E help 3-phospho-mevalonolactone pump water

α-tocopherol releases SeO$_3^{2-}$ from vasopressin, carrying Mn$^{++}$, cofactor synthesising cholesterol from mevalonate, controlling H$_2$O transport, see Figure 19.
<table>
<thead>
<tr>
<th>1 MOTILITY</th>
<th>2 SENSITIVITY</th>
<th>3 EXCRETION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca$^{++}$/Mg$^{++}$</td>
<td>Na$^{+}$/K$^{+}$</td>
<td>salt/CO$_2$</td>
</tr>
<tr>
<td>SO$_3^{-}$</td>
<td>catecholamines</td>
<td>MnCl$_4$</td>
</tr>
<tr>
<td>choline</td>
<td></td>
<td>rennin angiotensin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>kidney</td>
</tr>
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Muscular exercise reduces energy reserves needed for producing sufficient tri-phosphates for cell division.

<table>
<thead>
<tr>
<th>4 RESPIRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>O$_2$</td>
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<tr>
<td>thyroid</td>
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</table>

The redox potential within the cell affects the status of the proposed Ag$^{++}$/Ag$^{3+}$ porphyrin switch.

<table>
<thead>
<tr>
<th>5 GROWTH</th>
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<td>KEY</td>
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4 RESPIRATION

<table>
<thead>
<tr>
<th>6 RIGIDITY</th>
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</thead>
<tbody>
<tr>
<td>O$_2$</td>
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<tr>
<td>thyroid</td>
</tr>
</tbody>
</table>

The redox potential within the cell affects the status of the proposed Ag$^{++}$/Ag$^{3+}$ porphyrin switch.

<table>
<thead>
<tr>
<th>7 ASSIMILATION</th>
<th>8 REPRODUCTION</th>
<th>9 OSMOREGULATION</th>
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</thead>
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<tr>
<td>β$_D$glucose</td>
<td>H$_2$P$_2$O$_7^{-}$</td>
<td>H$_2$O</td>
</tr>
<tr>
<td>Zn$^{2+}$</td>
<td>sero/melatonin Ag$^{+}$</td>
<td>P-mevalonate</td>
</tr>
<tr>
<td>insulin glucagon</td>
<td>arginine</td>
<td>vasopressin oxytocin</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>creatine Vit A</td>
<td>Mn$^{++}$SeO$_3^{-}$ Vitamin E</td>
</tr>
<tr>
<td>β-cells</td>
<td>porphyrin pineal</td>
<td>posterior pituitary</td>
</tr>
</tbody>
</table>

Glucose metabolism uses phosphorylated intermediates, reducing available P$_i$ as compared with fat metabolism. Feeding glucose to non-vascularised reserves, reduces P$_i$, inhibiting cell proliferation.

Apart from cell division, the management of sleep, fat/carbohydrate metabolism, energy reserves, and photoperiodism.

Cell vol. or nuclear vol. X conc$^a$ = available quantity. Failure of fluid control or of cell wall maintenance changes volume; may result in excess dATP.
Silver controls phosphate transport as pyrophosphate

Vitamin A transfers energy from Ag-porphyrin, esterifying P_i to PP_i, carried by arginine.

Silver porphin mediates this process:

\[
\begin{align*}
\text{Ag}^{3+} & \rightarrow \text{Ag}^{2+} \\
\text{Oxidised} & \rightarrow \text{Reduced} \\
\text{Arginine (A) is carrier for pyrophosphate}\n\end{align*}
\]

Vitamin A esterifies phosphate to pyrophosphate (P_i + P_i → PP_i) when its redox state enables soliton transfer across the membrane:

\[
\begin{align*}
\text{Vitamin A} & \rightarrow \text{Vitamin A} \\
\text{Blocked} & \rightarrow \text{Conducting} \\
\text{Arginine (A) is carrier for pyrophosphate}\n\end{align*}
\]
Nucleohistone structure enables efficient replication

Anti-parallel β-pleated proteins with alternate neutral & basic ααs hold DNA flat. Pro forms asymmetric bends, creating coils of 21x 9-base pair units. 9 coils form ‘minions’, explaining chromatin packing & directional transcription. See Figure 20.
Protein synthesis on DNA and memory storage on DNA

Transfer RNAs feed ααs to ribosomes for protein synthesis, proton-ordered arrays of H-bonds connecting Lys | Arg ω-amines to DNA phosphates enable memory storage.

Amino-acid binding arm enables pre-elecction of amino acid in protein synthesis

```
    aa   aa   aa   aa
    /    /    /    /
    /    /    /    /
pp(dddd)(dddd)(dddd)(dddd)p
```

```
    |(H:H):(H:H):(H:H):(H:H)|
    |(H:H):(H:H):(H:H):(H:H)|
dd(pppp)(pppp)(pppp)(pppp)d
```

```
    /   /   /   /
    /   /   /   /
c-c-c  c-c-c  c-c-c  c-c-c
-COD-COD-COD-COD-
```

Width of pump pore determines triplet code.

```
    Aa   aa   aa
    /    /    /
    /    /    /
pp(dddd)(dddd)(dddd)(dddd)p
```

```
    |(H:H):(H:H):(H:H):(H:H)|
    |(H:H):(H:H):(H:H):(H:H)|
dd(pppp)(pppp)(pppp)(pppp)d
```

```
    /   /   /   /
    /   /   /   /
c-c-c  c-c-c  c-c-c  c-c-c
-COD-COD-COD-COD-
```

The paired (tRNA)n-mRNA / (tDNA)n-dDNA strands

```
c-c-c  c-c-c  c-c-c
-COD-COD-COD-
```

are straight, not in double helical, bound by histones, see Fig 12.

**Nucleohistone H-bonding**

As in ice It, the H-bonds holding nucleic acid to protein are ordered, SIDE view of nucleohistone structure:

```
base pairs
```

```
P  P  P  P
```

β-sheet & sugar-P

```
H-bond positions
```

```
/ \ / \ / \ / \ N N N N N
```

ω-amine of lysine

```
Ordered H-bonds
```

```
P  P  P  P
```

Switched H-bonds

```
/ \ / \ / \ \ N N N N N
```

```
Ordered H-bonds on two decks
```

```
P  P  P  P
```

```
Inter-deck H-bond connection
```

```
P  P  P  P
```

```
/ \ / \ / \ \ N N N N N
```

```
P  P  P  P
```

```
/ \ / \ / \ \ N N N N N
```
Nine centriole pins send energy to chromosomes along conjugated H-bonds in the nine α-helices of a keratin spindle.

Each of three α-helices in spindle fibres affords three pathways of alternate double- & H-bonds, transmitting energy (accelerating chromosome protons along the cytoskeleton al features retained from early life. See Figure 20.
Differentiation & eukaryotes evolve from prokaryotes

Prokaryotic chromosomes insert incorporated transport pumps to their membranes, eukaryotic exons and introns are nouns and verbs in transport genetics.

**Primitive**

Tandem mutations

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**Key**

D = differentiation DNA, dDNA
E = exon e=RNA copy
I = intron i=RNA copy
m = messenger RNA, mRNA
t = transfer RNA, tRNA
T = transport DNA, tDNA

**Prokaryote DNA**

Transcribed

bind form

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<tbody>
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<td>cell membrane</td>
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<tr>
<td>protein synthesis</td>
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**Eukaryote DNA**

Transcribed

bind form form bind

tRNA mRNA exons introns dDNA tDNA
t|m | e | E |   |
| t|m | e | E |   |
| t|m | e | E |   |
| t|m | I | I | D | DT |
| t|m | I | I | D | DT |
| t|m | I | I | D | DT |
| t|m | e | E |   |
| t|m | e | E |   |
| t|m | I | I | D | DT |
| t|m | I | I | D | DT |

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</tr>
<tr>
<td>reticulum e</td>
<td>E</td>
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<tr>
<td>protein e</td>
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<td>synthesis e</td>
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visit cell membrane

for active transport

residents on

cell membrane

for active transport

80
Oxidative phosphorylation

Oxidative phosphorylation reinterpreted, using 4μ infrared quanta as intermediates.

**Redox transfer to mitochondria**

<table>
<thead>
<tr>
<th>Outside</th>
<th>NADH</th>
<th>→</th>
<th>NAD⁺</th>
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<tr>
<td>P P P</td>
<td>N</td>
<td></td>
<td>N⁺</td>
</tr>
<tr>
<td></td>
<td>C C N</td>
<td></td>
<td>C C N</td>
</tr>
<tr>
<td></td>
<td>C C –C</td>
<td></td>
<td>C C–C</td>
</tr>
<tr>
<td></td>
<td>C O</td>
<td></td>
<td>C O</td>
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<tr>
<td></td>
<td>H H</td>
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<td>H H</td>
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<tr>
<td></td>
<td>C N</td>
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<td>C C –C</td>
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<td></td>
<td>C C O</td>
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<td>C C O</td>
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**Cytochrome oxidase**

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<td>H⁺</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>C C–C–N</td>
<td></td>
<td>C C–C</td>
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<tr>
<td></td>
<td>C C H</td>
<td></td>
<td>C C H</td>
</tr>
<tr>
<td></td>
<td>N⁺</td>
<td></td>
<td>N⁺</td>
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<td>d d d</td>
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<td>d d d</td>
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</table>

<table>
<thead>
<tr>
<th>Inside</th>
<th>NADPH</th>
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<th>NADP.O⁺</th>
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**Cytochrome chain coupled to phosphorylation**

<table>
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<tr>
<th></th>
<th>ADP + P_i</th>
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</thead>
<tbody>
<tr>
<td>NADH + Cyt₂⁺ → NAD⁺ + Cyt₂H + 〜〜〜〜〜〜↓</td>
<td>ATP</td>
</tr>
<tr>
<td>Cyt₂H + Cyt₁⁻ → Cyt₂⁺ + Cyt₁H</td>
<td>ADP + P_i</td>
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<tr>
<td>Cyt₁H + Cyt₂⁻ → Cyt₁⁺ + Cyt₁H</td>
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<td>Cyt₃H + Cyt₄⁻ → Cyt₃⁺ + Cyt₄H</td>
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<tr>
<td>Cyt₄H + Cyt₅⁻ → Cyt₄⁺ + Cyt₅H</td>
<td>ADP + P_i</td>
</tr>
<tr>
<td>Cyt₅H + Cyt₆⁻ → Cyt₅⁺ + Cyt₆H</td>
<td>ADP + P_i</td>
</tr>
</tbody>
</table>

**Mitochondrial (cytosol) contribution**

**Redox transfer:**

2NAD + [2NADH] → 2NADH + [2NAD⁺]

**Cytochrome oxidase:**

NADPH + [O₂ + H⁺] → NADP.O⁺ + [H₂O]

**Cytochrome chain:**

2NADH + NADP.O⁺ + H⁺ + 6ADP + 6P_i → 2NAD + NADPH + H₂OPH + 6ATP

**Overall:**

6ADP + 6P_i → 2H₂O + 6ATP

[2NADH + O₂ + 2H⁺] → [2NAD⁺ + H₂O]

Overall:

NADH + ½NADP.O⁺ + ½H⁺ + 3ADP + 3P_i

→ NAD⁺ + ½NADPH + ½H₂O + 3ATP
Solids produced by neighbour binding

Cell-cell binding determines tissue topology, five cell-cell connections are acceptable, a sixth allows tumours and cancers to form. The ‘five hook’ theorem, 3D equivalent of the 4-colour mapping theorem, if proven, would support this contention.
Ice It phase transition and width of adjacent tRNAs

Red-green stereos created with Watanabe flat-bed plotter

Figure 18
Hex-adrenline & Vitamin E interacting with vasopressin Figure 19
Red-green stereos created with Watanabe flat-bed plotter
α-helices in keratin & β-sheet binding uncoiled DNA

Red-green stereos created with Watanabe flat-bed plotter
Periodic table showing availability of biological elements

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<thead>
<tr>
<th>H#</th>
<th>Periodic Table</th>
<th>He</th>
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<tbody>
<tr>
<td>8K</td>
<td>100K</td>
<td>-</td>
</tr>
<tr>
<td>Li</td>
<td>Be</td>
<td>Element</td>
</tr>
<tr>
<td>65</td>
<td>6</td>
<td>Crust ppm</td>
</tr>
<tr>
<td>8K</td>
<td>300</td>
<td>Biosphere ppm</td>
</tr>
<tr>
<td>Na</td>
<td>Mg</td>
<td># Major</td>
</tr>
<tr>
<td>26K</td>
<td>39K</td>
<td># Minor</td>
</tr>
<tr>
<td>K</td>
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<td>Rb</td>
<td>Sr</td>
<td>Y</td>
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<tr>
<td>Cs</td>
<td>Ba</td>
<td>La</td>
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<tr>
<td>Roles of ‘Minor’ elements</td>
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<td>Wrole</td>
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<td>Si</td>
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<tr>
<td>I</td>
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C Carrier described in this thesis
P Known protein cofactor:
1 Hemovanadin
2 Glycosyl transferases, Cholesterol synthesis
3 Haemoglobin
4 Vitamin B12
5 Ceruloplasmin
6 Alcohol dehydrogenase
7 Glutathione peroxidase
8 Xanthine oxidase
R Redox agent (eg in cytochromes)
? Not established

Z1K Schwarz & D B Milne, Bioinorg Chem 331(1972)
Z4K Schwarz & W Mertz, Arch Biochem Biophys 72 515 (1967)
Z5 D M Greenberg, H D Copp & E M Cuthbertson, J Biol Chem 147 749 (1943)
Z8 C F Mills & J Murray, J Sci Food Agric 9 547(1960)
Z9 W R Todd, C A Eivehjem & E B Hart, Am J Physiol 107 146 (1934)
Z11 J N Thompson & ML Scott, J Nutr 97 335 (1969)
Z14 Baumann (1895) M Young, M G Crabtree & I M Mason, MRC, Spec Rep Ser SES217 (1936)
R.J.P. Williams

By Joachim Krebs

Professor R.J.P. Williams, FRS, is Emeritus Fellow at Wadham College and Emeritus Professor, University of Oxford. He studied Chemistry at Merton College, Oxford, graduating in 1948. During the course of his Part II work the Irving-Williams series of the stabilities of complex ions, which is of paramount importance in both non-living and living systems, was discovered. He took his doctor's degree at Oxford in 1950 working with Professor H.M.N.H. Irving. With Professor A. Tiselius (Uppsala, Sweden) 1950-51, he developed certain (gradient elution) chromatographic methods of analysis. He then became lecturer and tutor in Chemistry at Wadham College, 1955-65.

After a year at Harvard University, 1965-66, with Professor B.L. Vallee, he changed to teach biochemistry until 1974, and was Napier Royal Society Research Professor at the University of Oxford from 1975-1991. In 1961 he proposed proton-gradient-driven ATP formation as the driving force of bio-energetics. He pioneered the field of Bio-Inorganic Chemistry, especially concerning the role of calcium as a biological messenger, and contributed substantially to our understanding of the evolution of life. Together with J.J.R. Frausto da Silva he just published a book on the Chemistry of Evolution. He was elected Fellow of The Royal Society in 1972 and is a Foreign Member of the Swedish, Portuguese, Czechoslovakian and Belgian science academies. He received various medals of the Biochemical Society, the Royal Society, the Royal Society of Chemistry, the European Biochemical Societies and of the International Union of Biochemistry. He has honorary degrees from Louvain, Leicester, Keel, Lisbon and East Anglia Universities. Bob Williams was a founder member of the Oxford Enzyme group in which he and his colleagues devised many new methods for the study of in vitro and in vivo biological systems, especially using nuclear magnetic resonance spectroscopy.