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The Emergence of Man: Information from Protein Systems

E. M. Jope

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The emergence of man: information from protein systems

By E. M. Jope, F.B.A.
Archaeology Department, The Queen's University of Belfast, Belfast BT7 1NN, Northern Ireland

Protein amino acid sequences are not directly very informative about the emergence of man from his immediate primate ancestry. But this could be because too little attention has been given to protein systems most relevant to the progress of hominization, those that, through their cell-surface action or enzymatic control of biosynthesis of other key proteins or hormones, can modulate the course of cell and tissue development, and so determine changes in tooth architecture, bone and tissue structure, brain and nerve cell development, etc. There are also the histones and other proteins associated with DNA in the genetic material, which have some modulating influence on gene expression. The whole process of carrying information from the genetic material to a species-reproducible morphology is through a cascade of multiple interlocking systems involving proteins at every turn. It is through changes in balance within these systems, and subsequent selection pressures, that the modulations of primate morphology and behaviour that constitute hominization have proceeded, and the process must be understood in terms of cytobiochemistry to give a fully detailed definition of the evolving human genome.

Human protein data in terms of amino acid sequences† reveal little about the emergence of man from his immediate primate ancestry. They suggest that man and apes are genetically very similar (Nei & Roychoudhury 1974; Nei 1975; King & Wilson 1975; Manueledis & Wu 1978; Bruce & Ayala 1978). Yet different they certainly are in morphology and behaviour patterns. However much the selective pressures have been at work on the polymorphic systems (Bodmer & Cavalli-Sforza 1976), the prime determinants underlying these heritable evolutionary differences must be sought at molecular level, coded in the DNA–protein complexes that make up the genetic material, the genes grouped in the chromatin of the chromosomes. This information is processed through RNA systems into intricate networks of protein and metabolic pathways (figure 1) to emerge as a heritable morphology and behaviour pattern with nuances of variance but astonishing overall species reproducibility (note some forward thinking in Needham (1942)). In this process many protein systems exercise a modulating control. These protein systems must therefore be fully understood, in terms of changes in molecular structure and of biological behaviour, and also in relation to DNA and RNA sequences, if the cumulative processes of hominization are to be defined.

Recent studies of base-pair sequences in DNA (Jeffreys & Barrie, this symposium) have provided a method of inferring protein amino acid sequences, and this has tended to discourage direct protein sequenation. But protein sequencing is still sometimes necessary. First, some amino acid residues of the primary sequence undergo post-biosynthetic modifications that profoundly affect their biological properties, as occurs with post-synthetic modifications of histones (Isenberg 1979) and hydroxylation of many prolines and lysines in the collagens (see

† These data are for many protein systems only available by gel electrophoretic methods, which only reveal about 40 % of the amino acid differences (Ferguson 1970), but this does not greatly alter the above conclusion.

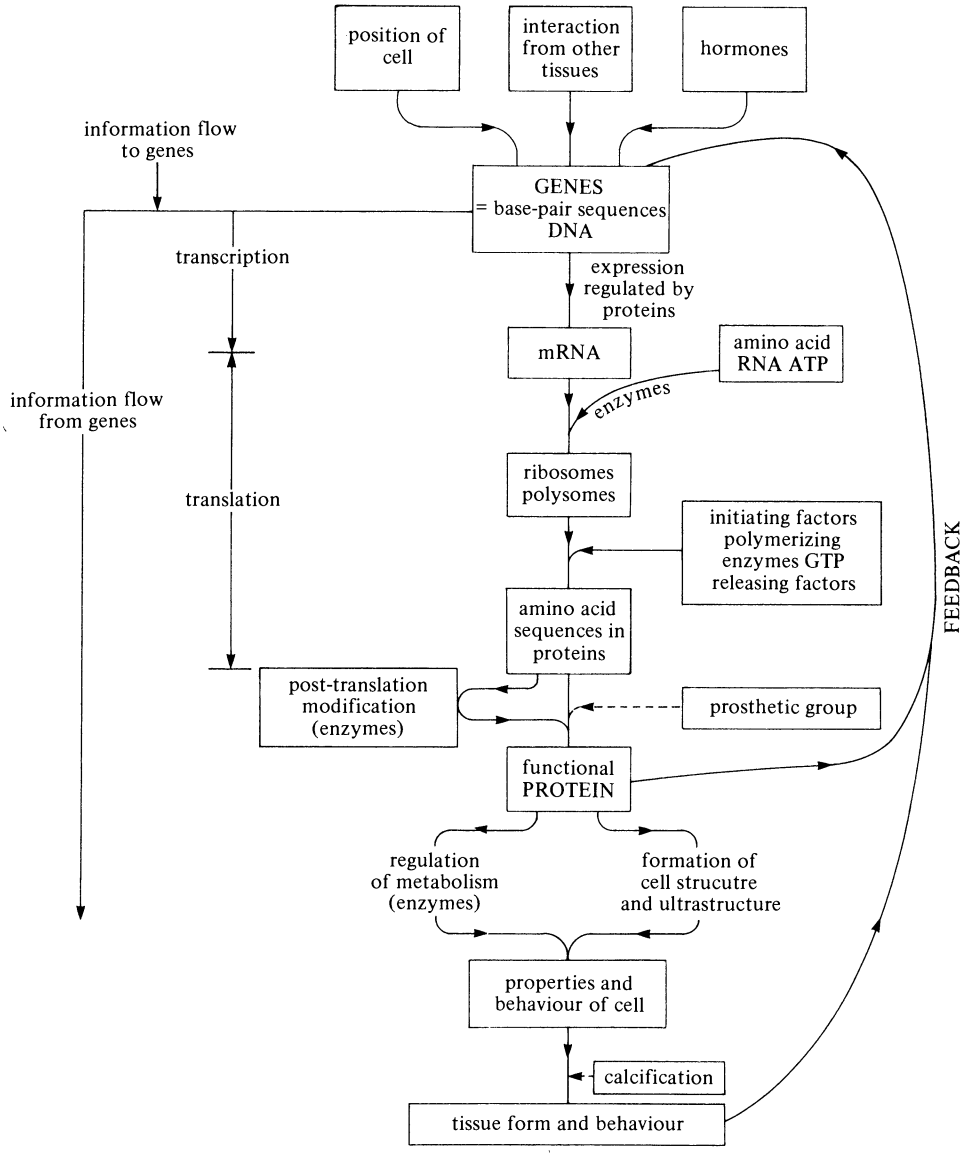

FIGURE 1. The molecular basis of morphogenesis. Summary diagram showing the molecular basis of information flow from the genome DNA, through functional proteins, to cell development and tissue form.

below). Secondly, direct sequencing is necessary with fossil protein material, in which molecular structures can survive even from the distant past (Wyckoff 1972; Jope 1980; cf. below), the DNA material being less fully preserved (Jeffreys 1980).

Study of protein systems is thus an indispensable complement to DNA constitution in tracing the emergence of the hominid genome. There are the proteins of both histone and non-histone type closely associated with the DNA in the primary genetic material, the chromatin of the chromosomes (Bonner *et al.* 1968; Elgin & Weintraub 1975; Kedes 1979). These proteins exercise a strong and cell-type-specific control over the parts of the genome that are transcribed as mRNA (Truman 1974). The simple view that the histones have been invariant through eukaryote evolution is now being subjected to considerable modification (Isenberg 1979). It is becoming clear that specific subunits in the histone molecules are significant, and some mechanisms that

can influence growth are beginning to emerge, such as the post-biosynthetic phosphorylation of specific serine and threonine residues (Isenberg 1979).

The RNAs are themselves complex entities, with some polymorphisms (Newrock *et al.* 1977; Kedes 1979), and have a close and potentially modulating relation with protein molecular units (Harwood 1979; Kedes 1979). Their mechanism of operation with RNA may sometimes be by binding to specific membrane surfaces (Harwood 1979). RNA data have their own contribution to make to genetic distance assessment (Grantham & Gantier 1980).

Beyond these primary molecular stages of transcription and translation of genetic instructions at molecular level, a mammalian organism develops through the embryonic stages (gastrulation, etc.), and the complexities of cell differentiation and growth, with backfeeding interactions, resulting in specialized tissue formation (always involving proteins), into adult life (Wessells 1977). These processes operate through networks of interacting metabolic systems, largely involving proteins (figure 1), each protein itself needing many other preformed molecules (protein–enzyme transferase systems and hormones) to complete its biosynthesis. The human genome contains at least 10^5 (and probably nearer 10^6) genes coding for biosynthesis of proteins (Bodmer & Cavalli-Sforza 1976). Only by isolating and defining each specific protein can its function in the organism be assessed, and the parts of the genetic material that determine its biosynthesis and control its operation located in the genome.

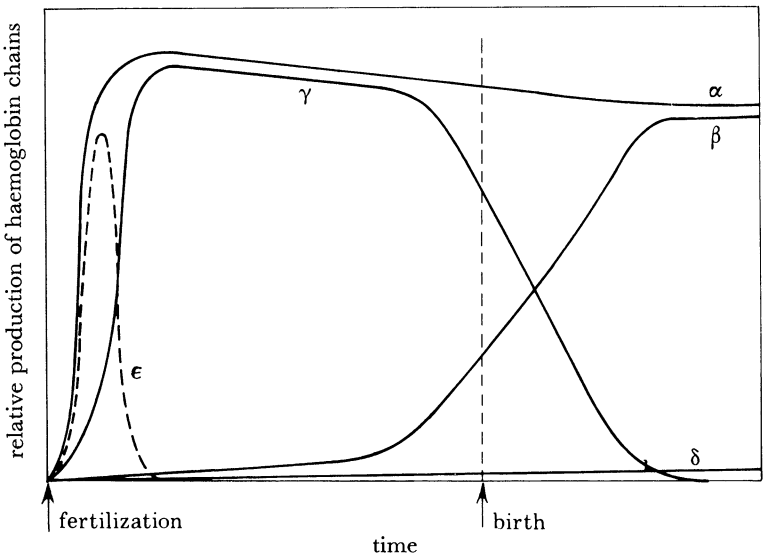

FIGURE 2. The polymorphic forms of human haemoglobin α, β, γ, δ, ε: their place in the development of the living system, from the embryo into adult life. (Adapted from Zuckerkandl (1965)).

In living organisms many proteins are in the form of molecular families of homologous constitution with a graded range of properties. This protein *polymorphism* probably reflects DNA mutations, deletions, gene duplications, and analogous processes in the genetic material. With the genes potentially operable but switched on or repressed by various mechanisms (Ochoa & de Haro 1979) these polymorphisms provide within a population a cumulative heritable reserve of adaptability to varying conditions and constraints, as in environment or the transition from embryonic to adult life, and are the basis of evolution by selective pressure. The haemoglobin family (figure 2) provides an excellent example of the range of variability while still retaining the basic biological function of oxygen transport (Zuckerkandl 1965).

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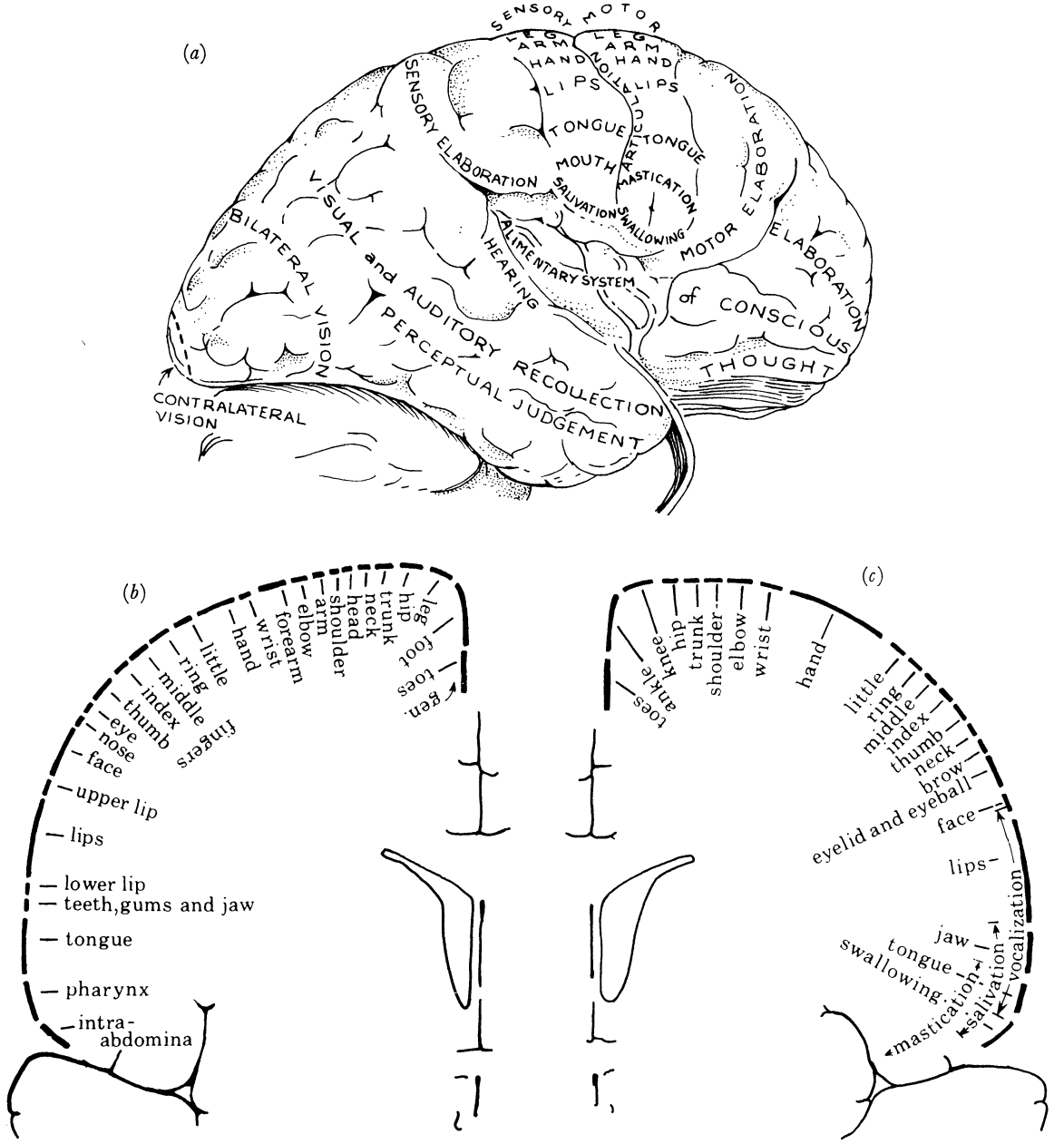

FIGURE 3. Diagram of the lateral aspect of a right human cerebral hemisphere (from Penfield & Rasmussen (1950)). The regions from which somato-sensory and somato-motor responses are evoked by electrical stimulation are shown diagramatically in transverse section in (*b*) and (*c*) respectively. In (*a*) the localization of electrically evoked visual ('vision') and auditory ('hearing') responses are also indicated. The remaining entries in (*a*) are entirely hypothetical and are based on Penfield's interpretations concerning the possible functions of the remaining areas. The functions of speech (see R. E. Passingham, this symposium) are most commonly represented in the left hemisphere. This diagram directs attention to areas of cells particularly apt for detailed cytochemical study.

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One reason why protein data have so far been uninformative about the emergence of man may be because the potentially more informative protein systems in relation to morphogenesis and behaviour have been comparatively little studied. Many of the distinctive hominizing features, such as postnatal increase in brain size, reduction in tooth size, differentiation of power and precision grip, muscular control over nuances of facial expression, sequencing of images, and speech, are concerned with particular cells of the tissues, brain and nervous system, some in specific restricted regions of the cerebral cortex (figure 3). It is the protein systems of these groups of cells that need intensive cytochemical study, especially concerning mitosis induction or inhibition (Thornley & Lawrence 1975), in differentiation processes, and in tissue formation, with all the cell-to-cell surface interactions involved. The microtechniques necessary for identifying and localizing the significant molecules in, on and around the cell are gradually becoming available (see, for example: Elliott & Gardner 1980; Barer & Jope 1950).

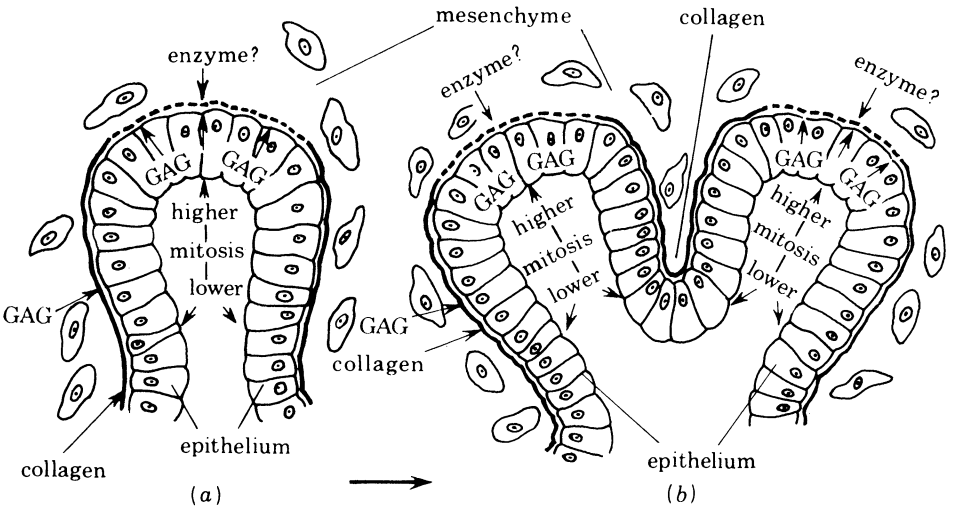

FIGURE 4. Schematic diagram illustrating the localized surface activity of specific molecular species (GAG, collagen) during lobe formation. (Adapted from Wessells (1977).)

The collagen family (and their associated post-translational enzymes, so essential in remodelling) give an instructive example of protein molecules through which some genetic control seems to be exercised, during embryonic and at later stages, over cellular development, grouping and remodelling, thus regulating the tissue architecture and function (such as is discussed below for the brain), that is, morphogenesis. The collagens are a varied polymorphic family of homologous structures (e.g. the closely packed helical domains of repeated -Gly-Pro-X-). Collagens are very versatile in function, the result of long cumulative gene duplication (Miller 1977; Tanzer 1978). Their monomers assemble outside the cell into trimers, and then into microfibrils and fibrils, to give a fibrous tensile structure to a tissue (skin, tendon, bone, etc.); they can also provide a necessary firm matrix (e.g. basal lamina) for differentiated cell and tissue development (Wessells 1977). Yet internally the collagen molecular structure is in a continually dynamic state of 'breathing' (Torchia & Vander Hart 1976; Piez & Trus 1978). Collagen molecules have many active sites on the surface, and through these are involved in interactions with other molecular complexes, such as the proteoglycans (made up of glycosaminoglycan (GAG) and some protein), to give an immense diversity of macromolecular structures (Wessells 1977;

Hascall & Heinegard 1974; Scott 1980). The GAGs (polymers of acetylated aminosugars and uronic acids, often sulphated) are themselves vital factors in determining the progress of complex tissue growth, such as lobe formation (figure 4), being removable by hyaluronidases in remodelling. The proteoglycan GAG complexes appear to be a necessary factor at the outermost actively growing part of a lobe in cleft formation, whereas the collagens provide fibre formation for binding within the inner folds of a cleft; each is removable enzymatically in remodelling where no longer required (figure 4; Smith *et al.* 1975; Wessells 1977). These complex heterogeneous polysaccharides (GAG) illustrate the way in which a class of substances of the utmost importance in controlling morphogenesis can lurk unrecognized for a long time (Wessells 1977; Bernfield *et al.* 1973; Bannerjee *et al.* 1977; Cohn *et al.* 1977).

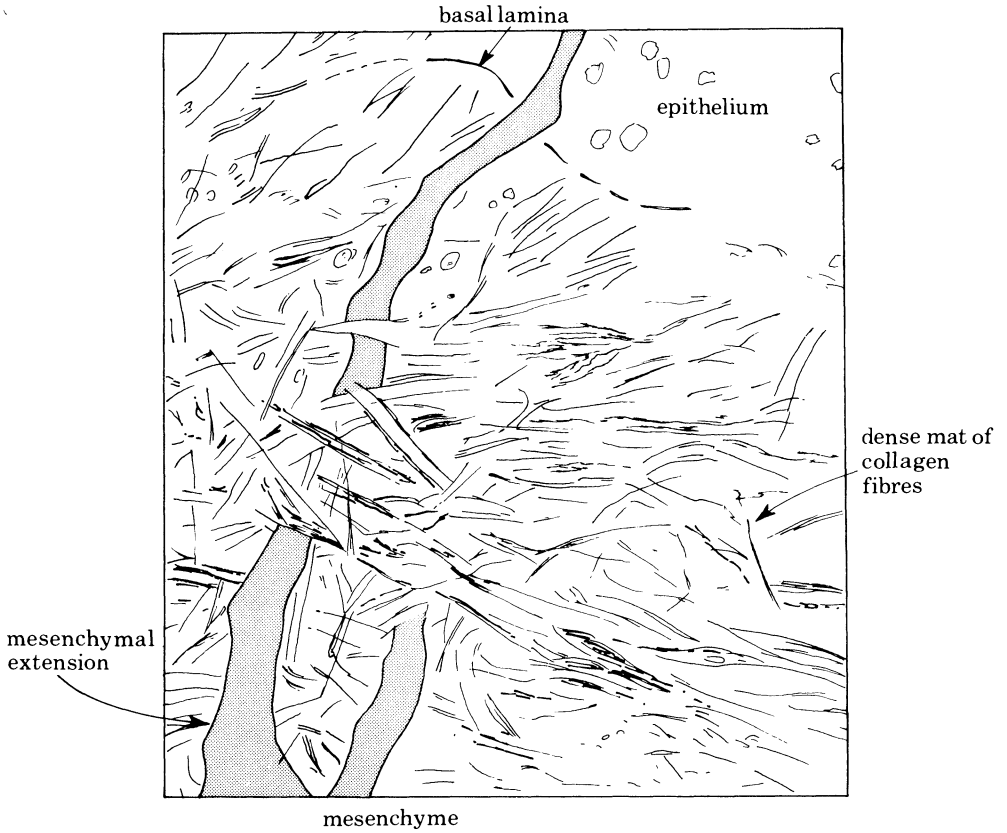

FIGURE 5. Diagram drawn from an electronmicrograph of a developing tooth germ. The shaded area shows a mesenchymal cell extension penetrating through the mat of collagen fibres and the basal lamina, to make the contact that is needed for the development and growth of the tooth itself. The cytobiochemistry of this diagram underlies the determination of dental architecture. (Adapted from Slavkin & Bringas (1976) and Wessells (1977).)

A matrix to hold cells, during cell grouping and remodelling, is a necessary background to tissue formation. Collagens (type IV) are very active in basement membrane surfaces lying at the interface between the extracellular matrix and the cell plasma membrane (Harwood 1979). In some basal laminae, however, there proves to be comparatively little collagen. More work is still needed on the great variety of tissue types and organs, and it is clear that the precise locations of many of these proteins and protein-like substances (whose biosynthesis is largely genetically controlled) can exert a strong influence on the progress of tissue formation. It is this

precise directing and location of these molecules that underlies morphogenesis, and protein molecules play a role at every turn.

Collagens provide also the complex layered substance of teeth (Volpin & Veis 1973). The reduction in size of canines and other teeth is another significant hominizing trend, progressing around 5–2 Ma ago. This can be seen against the molecular background of odontological cytodifferentiation, in which collagen has played a considerable part. Tooth architecture is already being determined with the development of tooth germs at the embryonic stage (figure 5; Slavkin & Bringas 1976). These tooth germs are extrusions of mesenchyme cells, some of which manage to penetrate a dense mass of collagen fibres to make contact with the epidermal cells (figure 5), which stimulates the actual tooth formation. This selective penetration may be due to selective proteolysis of the collagenous fibres, controlled perhaps by cell–cell or tissue–tissue interactions, and must be a main determinant for dental architecture. Tooth architecture can be a sensitive marker in following the emergence of man, and even revealing distinctions among the living races of man (Turner 1976).

Collagenous polypeptides are sometimes involved in enzymic activity, as, most significantly, when they form subunits of an acetylcholinesterase in synaptic membranes of electric fish (Lwebuga-Mukasa *et al.* 1976), and they are found in other unexpected contexts, such as part of a link protein in a protease of the complement system, which is a vital protector of the life of the individual animal and so of the continuation of the species (Porter 1980).

Collagens provide the main fossil protein material that is relevant to the emergence of man, as their molecular structures can survive fairly well (Jope 1980). Too little is yet known of the sequences of their amino acid chains 1055 residues in length (Hulmes *et al.* 1973; Piez & Trus 1978), but they must have only limited evolutionary substitutions as the functional requirements impose a structural conservatism. Immunological distinctions among primate collagen appear to be possible, but until more is known of the molecular structural basis of such sensitive discriminations they cannot be fully interpreted (Furthmayr & Timpl 1976). It has been noted that the immunological recognitions occur largely in the non-helical teleopeptide tails (Bornstein & Hesse 1970). Herein, however, lies a paradox; in collagen all the tyrosine is found in these non-helical teleopeptides (Hulmes *et al.* 1973) and it is tyrosine that is most readily lost in fossil bone material, indicating degradation in these tails (Jope 1976). More data on the molecular mechanisms of these immunological observations is clearly needed.

Blood groups, histocompatibility complexes, and other immune reaction systems are sensitive phylogenetic markers at subspecies level and should be informative in charting the emergence of man. The HLA system, for instance, clearly distinguishes between man and apes (Balner, this symposium), and the blood groupings (A, B, O and Lewis) give useful classifications among the races of man (Nei & Roychoudhury 1974). Their evolutionary significance, however, still remains uncertain (Bodmer & Cavalli-Sforza 1976), though they do provide a containing barrier for population groupings, even within the species. The molecular mechanisms by which they operate are only partially understood, though it is clear that protein molecules are widely involved; they are now being investigated by biophysical techniques (Dwek *et al.* 1977; Amzel & Poliak 1979). The molecular background of the A, B, O and some other blood group systems is now reasonably worked out (Watkins 1972; Crumpton 1979; Porter 1979). In the A, B, O groups the operative determinant group is polysaccharide, carried on a protein–branched-chain polysaccharide supramolecule, with the small key determinant groups *N*-acetylgalactosamine or galactosamine attached to a specific position by specific protein–enzyme transferase systems

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(protein enzymes) (figure 6; Crumpton 1979). These complexes are heritable and should therefore be detectable as small changes in the genome DNA sequence. Each complex depends upon a chain of interacting protein systems, and once again the underlying protein biochemistry has to be fully explored to define the developing human genome.

Postnatal increase in brain size and in functional integration in specific regions is distinctive to man; how did these changes actually come about in molecular terms? Tobias (this symposium) has discussed the anatomy and timing of the hominizing brain size increase; we must now examine the cytomolecular processes involved. The trend could have been due to selection of slight modifications within the metabolic systems controlling the processes of mitosis, cell differentiation, cell cloning and cell-to-cell surface interactions in specific parts of the cerebral neocortex (figure 3; see above) in the postnatal regime (giving longer continuing mitosis, yielding larger clones of brain cells of the same type (cf. Truman 1974), with a more complex convoluted topology). These processes are better understood for other organs, such as kidney (cf. Wessels 1976). These cellular events could have been brought about by changes in balance between stimulation and restriction of production of particular enzyme or other protein or hormone systems, and have become stabilized in morphological evolution due to selection pressures, size being sometimes advantageous (cf. Pilbeam & Gould 1974). With this cellular modulation must also have been linked the corresponding modulation of control of postnatal bone growth to give a more capacious cranium.

For this increasing trend in brain size and the heightened organization to be heritable there must have been genomic variety in the DNA base-pair arrays through the population, controlling a change of balance in amounts of various proteins assembled at particular points in the metabolic cascade (Tsuboi *et al.* 1979). These would hardly be detectable (as between apes and man) at molecular level except in base-pair sequences, but the significant lengths can only be localized in the genome from a full basic knowledge of the cytochemistry of the brain cells involved. For this reason we await with great interest the expansions of the primate DNA sequencing work and correlations with the human genome reported by Jeffreys (this symposium).

The problems of defining the hominizing of the brain, however, must lie ultimately in studying the increasing synaptic organization of the multiple connections of the diverse cortical neurons; it is precisely these that are most difficult to systematize (Shepherd 1979). Recent work stresses the role of the hippocampus in learning processes and is beginning to reveal morphological changes in the dendritic spines (Shepherd 1979). The molecular basis of functioning of these highly specialized cell groupings now needs to be defined. It is not so much with the molecular neurotransmitters (nearly all small molecules that can penetrate membranes e.g. γ-aminobutyric acid, GABA) that we are concerned here, but with the processes of molecular, cell and tissue organization that can lead to the marshalling of neurosynaptic connections. These operations must be programmed by biomolecular systems, in which proteins will play a leading part (Krnjevic 1974; Shepherd 1979). Their detailed study in these tissues could be significant in mapping the emergence of the human genome.

The effects of *hormones* in the hominizing process must not be neglected; once again their biosynthesis is intimately dependent upon protein systems. The peptide hormones are particularly instructive. Neurohypophysial peptide hormones *vasopressin* and *oxytocin* are active in regulating memory consolidation and retrieval (de Wied 1980), and comparatively small modifications in their production rate in specific cerebral cell groups could have contributed to heightened ability to set and retain the image of given items in a particular sequence; this

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ability is stressed by Brown (this symposium) as a major higher hominizing capability. The evolution of such peptide molecules as vasopressin or oxytocin has proceeded by a complex series of interactions between the processes of precursor biosynthesis, with intermediate stages of modification, and proteolytic enzymes producing the final active hormone from the precursors. Duplication (with or without fusion) may also have been a strong influence in giving the necessary small required modulation to some protein operative in the system (Acher 1980). In such interplay between multiple systems small changes at one point could have had profound effects, giving evolutionary consolidation through selective pressures.

Professor Young (this symposium) draws attention to the long period of pre-puberty as a characteristic of man and its importance in giving a long childhood for learning. He then notes the possibly vital role of the pineal gland, and one of its hormone products, melatonin, is now known to regulate the onset of puberty (Niv *et al.* 1978). Production of melatonin (4-acetoxytryptamine) is controlled by specific protein systems.

We return once more to the higher activities of the human brain, which mark off man from other primates. Of these, the capability for sequential thought, and perhaps the fine nuances of muscular control that give the communicative potential of speech and of facial expression, are perhaps the most significant. Enhanced integration of signals, and particularly the ordered seriation and storage of responses, integrated with an equally efficient signal retrieval system, must underlie the processes of sequential thought. It is the detail of cellular and molecular processes through which these operate that we must try to understand. Twenty years ago Humphrey & Coxon (1963) wrote a book entitled *The chemistry of thinking*, and many of the problems there described still remain.. But it is the avowed aim of the neurosciences to provide a coherent account of the total performance and behaviour of an animal or man in cellular and molecular terms (McGeer & Eccles 1978). Enhanced integration of signals and particularly the ordered storage of responses and integrated retrieval are the facilities of the versatile brain capable of sequential thought. These must operate through an increasingly ordered synaptic neuron connections network. The biochemistry of the synaptic neuron connections will be basically the same; all the more highly marshalled grouping of responses and retrieval at will must operate ultimately through molecular processes. This could be through local surface concentration patterns of significant active substances (de Weid 1980), which could control cell-to-cell recognition. It is perhaps such cloned molecular groupings that should be sought in pursuing the molecular biology of sequential thought.

This overview of some aspects of the biochemistry of hominization, particularly stressing the role of proteins, is intended to suggest new lines of enquiry worth more concentrated attention in programming future research in human palaeobiology.

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