

Fig. 3. High-powered photomicrograph of the mononuclear infiltrate about a small blood vessel in the cerebellum of an agammaglobulinemic chicken; this is similar to lesions in control animals except for the absence of plasma cells.

the development of EAE. In that the intensity of the disease was equivalent in the bursectomized and irradiated animals to that in both the control irradiated and unirradiated chicks, it could not be demonstrated that circulating antibody was protective. Complement-fixing antibodies to brain antigens were not measured. Our study confirms the findings of Janković that thymectomy in the newly hatched chick inhibits the ability of the animal to manifest EAE, and it adds support to the contention that EAE is a manifestation of delayed hypersensitivity.

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Immunological Time Scale for Hominid Evolution

Abstract. Several workers have observed that there is an extremely close immunological resemblance between the serum albumins of apes and man. Our studies with the quantitative micro-complement fixation method confirm this observation. To explain the closeness of the resemblance, previous workers suggested that there has been a slowing down of albumin evolution since the time of divergence of apes and man. Recent evidence, however, indicates that the albumin molecule has evolved at a steady rate. Hence, we suggest that apes and man have a more recent common ancestry than is usually supposed. Our calculations lead to the suggestion that, if man and Old World monkeys last shared a common ancestor 30 million years ago, then man and African apes shared a common ancestor 5 million years ago, that is, in the Pliocene era.

It is generally agreed that the African apes are our closest living relatives. However, the time of origin of a distinct hominid lineage has been a subject of controversy for over 100 years (1). The absence of an adequate fossil record has forced students of hominid evolution to evaluate the phylogenetic significance of anatomical and behavioral characteristics in the living primate species in order to attempt a solution to that controversy. The nature of the problem is such, however, that no definitive answer has yet been given. Current estimates range from a date in the late Pliocene (2) to one in the late Oligocene or early Miocene (3) for the origin of the hominids. This great range (4 million to 30 million years) effectively negates any meaningful discussion of the nature of our pre-Australopithecine ancestors, for the early dates bring us near to a primitive prosimian stock, while the late ones would suggest that a common ancestor for man and the African apes might well resemble a small chimpanzee.

One solution to this question lies in the measurement of the degree of genetic relationship which exists between man and his closest living relatives. As it has recently become clear that the structure of proteins closely reflects that of genes, it is to be expected that quantitative comparative studies of protein structure should aid in providing this measure of genetic relationship (4).

Proteins appear to evolve over time, as do the organisms of which they are a part. Thus, we may speak of the common ancestor of, for example, the human and chimpanzee serum albumin molecules, this ancestral molecule being present in the common ancestor of man and the chimpanzee. From the time that the human and chimpanzee lineages separated, their albumins have had the opportunity of evolving independently until today they are recognizably different, but homologously related, molecules. Such homologies may be studied by immunological techniques, the magnitude of the immunological cross-reaction serving as a measure of the degree of structural similarity between the two kinds of albumin (5).

The immunological methods used in this investigation were similar to those described earlier (5, 6). Serum samples were obtained from all the living genera of apes and from six representative genera of Old World monkeys and stored at -10°C (7). Albumin was purified from individual chimpanzee, gibbon, and human serums by the method of Hoch and Chanutin (8). Groups of three or four rabbits were immunized by three courses of injections with each of the purified albumins. The antisera were tested for purity by immunodiffusion, immunoelectrophoresis, and microcomplement fixation (MC'F) with whole serum and purified albumin. Antibodies to components of serum other than albumin were always detectable with the first two methods, but they were too low in concentration to interfere with the MC'F analysis of the cross-reactions discussed below (9). Pooled antisera were made by mixing the individual antisera in reciprocal proportion to their MC'F titers (10). The degrees of cross-reaction were expressed quantitatively as the index of dissimilarity or immunological distance (ID) that is, the relative concentration of antiserum required to produce a complement fixation curve whose peak was as high as that given by the homologous albumin.

These antisera were used to obtain the data summarized in Table 1. Some of these results have already been published (5, 6). With the antiserum pool prepared against human serum albumin, the albumins of the African apes (gorilla and chimpanzee) reacted more strongly than those of the Asiatic apes (orang, siamang, and gibbon). The antiserum pool directed against chimpanzee (*Pan troglodytes*)

albumin showed the albumin of the pygmy chimpanzee to be immunologically identical to that of the homologous species. Human and gorilla albumins reacted somewhat less well but more strongly than did the albumins of the Asiatic apes. The antiserum pool directed against gibbon (*Hylobates lar*) albumin reacted most strongly with that of the siamang. The albumins of the other apes and man were appreciably less reactive.

Conclusions about genetic relationships among the albumins of apes and man may be drawn from these data. The albumins of the orang, gorilla, chimpanzee, and man stand as a unit relative to those of the gibbon and siamang. This is evident from the data obtained with the antiserum to *Hylobates* albumin (Table 1). The close relationship between the albumins of the gibbon and siamang is consistent with the fact that these two genera of apes are usually placed together in a separate family or subfamily (Hylobatinae). It is also evident that the albumins of the gorilla, chimpanzee, and man stand as a unit relative to the albumins of the Asiatic apes. Moreover, the albumins of the gorilla, chimpanzee, and man appear to be equidistantly related; the gorilla and chimpanzee albumins are no closer to each other than either is to human albumin. These relationships are consistent with those suggested by Goodman on the basis of qualitative immunodiffusion data (11).

Table 1 also shows that with each antiserum pool the Old World monkey albumins gave markedly weaker reactions (mean ID = 2.3) than those given by any hominoid albumin. The size of the immunological gap between the albumins of hominoids and Old World monkeys is illustrated by the fact that, at an antiserum concentration where all hominoid albumins give strong reactions, Old World monkey albumins give no reaction with antisera to hominoid albumins. Thus, the albumins of all the living apes are much more similar to each other than any of them is to nonhominoid albumins.

The phylogenetic significance of the above findings, however, is not unequivocal. For example, at least two explanations are possible for the extremely close structural similarity of ape and human albumins. On the one hand, albumin evolution may have been retarded in the ape, human, or both lineages since their separation. Goodman (11) and Haelegh and Williams

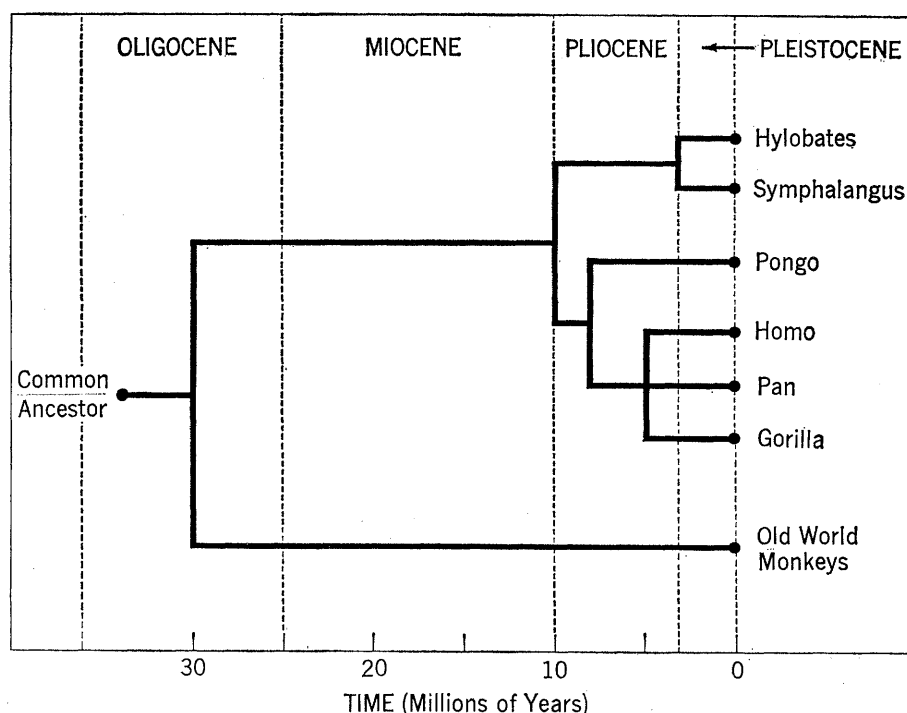


Fig. 1. Times of divergence between the various hominoids, as estimated from immunological data. The time of divergence of hominoids and Old World monkeys is assumed to be 30 million years.

(12) have tended to favor this explanation. Alternatively, the close molecular relationship may reflect a more recent common ancestry between ourselves and the living apes than is generally supposed, albumin evolution having proceeded at the usual rate for primates.

Rates of albumin evolution in primates have recently been investigated (6). The evidence appears to rule out the first explanation. No conservatism was detected in the evolution of any particular hominoid albumins relative

to any other, nor, indeed, in the evolution of hominoid albumin relative to those of any other primate group. Albumin evolution appears to have proceeded to the same extent in the various ape, human, and monkey lineages. Therefore, it seems likely that apes and man share a more recent common ancestry than is usually supposed.

The data presented above enable us to calculate how recently this common ancestor lived. We have recently shown that albumin evolution in primates is

Table 1. Reactivity of various primate albumins with antisera prepared against hominoid albumins. Antiserum to *Homo* albumin was a pool obtained by mixing three antisera in reciprocal proportion to their MC/F titers. The three antisera and their titers were 5₁ (1/7000), 6₁ (1/11,000), and Haelegh and Williams' pool II (1/5000). Titer of pool equaled 1/7000. Data taken from (5) and (6). Antiserum to *Pan* albumin was a pool obtained by mixing four antisera [9₂ (1/5000), 10₂ (1/3000), 97₂ (1/2500), 99₂ (1/2500)] in reciprocal proportions to their MC/F titers. Titer of pool equaled 1/3000. Some of these data are taken from (6). Antiserum to *Hylobates* albumin was a pool obtained by mixing three antisera [82₄ (1/1500), 83₄ (1/4500) and 84₄ (1/1900)] in reciprocal proportion to their MC/F titers. Titer of pool equaled 1/2000. The six species of Old World monkeys tested were *Macaca mulatta*, *Papio papio*, *Cercocebus galeritus*, *Cercopithecus aethiops*, *Colobus polykomos*, and *Presbytis entellus*.

Species of albumin	Index of dissimilarity		
	Antiserum to <i>Homo</i>	Antiserum to <i>Pan</i>	Antiserum to <i>Hylobates</i>
<i>Homoidea</i> (apes and man)			
<i>Homo sapiens</i> (man)	1.0	1.09	1.29
<i>Pan troglodytes</i> (chimpanzee)	1.14	1.00	1.40
<i>Pan paniscus</i> (pygmy chimpanzee)	1.14	1.00	1.40
<i>Gorilla gorilla</i> (gorilla)	1.09	1.17	1.31
<i>Pongo pygmaeus</i> (orang-utan)	1.22	1.24	1.29
<i>Symphalangus syndactylus</i> (siamang)	1.30	1.25	1.07
<i>Hylobates lar</i> (gibbon)	1.28	1.25	1.00
<i>Cercopithecoidea</i> (Old World monkeys)			
Six species (mean \pm S.D.)	2.46 \pm .16	2.22 \pm .27	2.29 \pm .10

a remarkably regular process (6). Lineages of equal time depth show very similar degrees of change in their albumins. The degrees of change shown would therefore seem to be a function of time, and a mathematical relationship between ID and the time of divergence of any two species must exist. Thus, albumin molecules can serve as an evolutionary clock or dating device. The calibration of that clock, that is, the elucidation of the relationship between ID and time, would allow us to calculate the time of divergence between apes and man (13).

This relationship is likely to be rather simple. If the amino acid sequences of proteins also evolve at steady rates, and there is evidence that they often do (14), then the relationship between ID and time of divergence should be of the same form as the relationship between ID and structural difference (number of amino acid replacements). Direct evidence for a simple correlation between immunological cross-reactivity and structural relatedness is available from complement fixation studies of hemoglobins (15, 16) and cytochromes *c* (17) of known amino acid sequence. Indirect evidence for such a correlation is provided by the correspondence between cross-reactivity and phylogenetic relatedness which has been demonstrated for a variety of proteins (15, 18).

It appears likely that log ID is approximately proportional to the time of divergence (T) of any two species, that is, $\log ID = kT$, where k is a constant. This relationship is evident from several sets of MC/F data obtained with various purified dehydrogenases of fishes, amphibians, reptiles, and birds whose times of divergence can be estimated from the fossil record (15, 19). Let us suppose that a similar relationship is appropriate for albumin evolution in primates (for an extended discussion of this, see 20).

Although the primate fossil record is fragmentary, it does, in combination with the available immunological evidence, provide sufficient evidence to suggest that the lineages leading to the living hominoids and Old World monkeys split about 30 million years ago (21). That is, the ID of 2.3 which is the mean ID observed between the albumins of hominoids and Old World monkeys corresponds to a T value of about 30 in the above equation. If $\log 2.3 = k \times 30$, then $k = 0.012$. Since the mean ID between the albumins of man and the African apes

is 1.13, the time of divergence of man from the African apes is $\log 1.13$ divided by 0.012, that is, 5 million years. Proceeding similarly, we calculate that the lineage leading to the orang separated from that leading to the African apes 8 million years ago, and that the time of divergence of the gibbon and siamang lineage from that leading to the other apes and man is 10 million years (Fig. 1).

There are, of course, at this stage in our investigation, uncertainties in these calculations. We may possibly be making erroneous assumptions about (i) the time of divergence of apes and Old World monkeys, and (ii) the nature of the relationship between ID and time of divergence. We feel, however, that these possible errors are unlikely to be of sufficient magnitude to invalidate the conclusion that apes and man diverged much more recently than did the apes and Old World monkeys. In our opinion, the albumin data definitely favor those who have postulated that man and the African apes shared a common ancestor in the Pliocene.

If the view that man and the African apes share a Pliocene ancestor and that all the living Hominoidea derive from a late Miocene (22) form is correct, a number of the problems that have troubled students of this group are resolved. The many features of morphology, particularly in the thorax and upper limbs, which man and the living apes share in varying degrees, but which were not present in the Miocene apes, such as *Dryopithecus* (Proconsul), *Limnopithecus*, and *Pliopithecus* (23), are then seen as due to recent common ancestry and not, as generally accepted, to parallel or convergent evolution (24).

We suggest that the living apes and man descended from a small member of the widespread Miocene dryopithecines, which became uniquely successful due to the development of the locomotor-feeding adaptation known as brachiation. The adaptive success of this development and the subsequent radiation of the group possessing it may have made this group the only surviving lineage of the many apes present throughout the tropical and subtropical Miocene forests of the Old World. Possibly the African members of this radiation, in the Middle Pliocene (due perhaps to pressure from the developing Cercopithecinae), began varying degrees of adaptation to a terrestrial existence. The gorilla, chimpanzee, and man appear to be the

three survivors of this later radiation. According to this hypothesis, some 3 million years are allowed for the development of bipedalism to the extent seen in the earliest fossil hominid, *Australopithecus*.

The concept of an immunological time scale is a logical extension of the finding that the immunological properties of serum albumin have undergone regular changes during primate evolution. The utility of that concept can be tested in several ways. First, extensive immunological studies of proteins of known amino acid sequence are needed in order to make sure of the nature of the relationship between cross-reactivity and degree of sequence resemblance. Second, albumin evolution should be investigated by the use of immunological methods in other mammalian groups, such as the ungulates, where an extensive fossil record is available. Third, a search must be made for other primate proteins that exhibit constant evolutionary rates. This will permit an independent calculation of the time of origin of hominids.

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21. This date will probably appear relatively recent to many. There is, however, certainly no fossil material to contradict it. The first fossil Old World monkeys (*Mesopithecus*, *Prohylobates*) are found in the middle-to-early Miocene of Africa [E. L. Simons, in *Evolutionary and Genetic Biology of Primates*, J. Buettner-Janusch, Ed. (Academic Press, New York, 1963), vol. 1, pp. 65-129; *Nature* **205**, 135 (1965)]. On the other hand, it can fairly reliably be assumed that all living primates derive from a common ancestral form living no earlier than the late Cretaceous. At least one of the living prosimians, *Tarsius*, represents a lineage already distinct in the early Eocene (see Simons). As there is no reason to believe that any other prosimian group shows closer relationship to the higher primates, these suborders (Anthropoidea and Prosimii) were already distinct no less than 50 and no more than approximately 70 million years ago. Although no upper limit on the time of origin of a separate Old World monkey line is available, there would probably be general agreement with the suggestion, which is entirely consistent with the immunological evidence, that appreciable periods of common ancestry characterize both the Catarrhini (apes, man, Old World monkeys) after their separation from the ancestors of the New World monkeys and the living Anthropoidea after their separation from the Prosimii. To contain these periods within the 50-to-70 million year limits set above would seem to require that a reasonable upper limit on the time of divergence of apes and Old World monkeys be set at 30 to 45 million years. We feel that the lower end of this time scale is more probable. If this were not so, the relationship between ID and time of divergence for primates as a whole would be extremely complex. We feel that on immunological grounds this is unlikely (20).
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24. The availability of antisera to *Pan* and *Hylobates* albumins allows a partial answer to a caveat that might be made against these conclusions. It could be argued that the similarities among, for example, hominoid albu-

mins are a result of parallel evolution and not recent common ancestry. That is, immunologically similar albumin structures have evolved in genetically separated lineages. It can be seen that this would, in the case of apes and man, require a most improbable set of coincidences, for the ID's of other apes and man obtained with antisera to gibbon albumin are very nearly equal (obviously except for the siamang), indicating these albumins have changed to much the same degree since their separation from the gibbon; yet the antisera to human and chimpanzee albumins show that human, chimpanzee, gorilla, and orang albumins are quite different from one another. To support the idea of parallelism, then, one would have to postulate that gibbon albumin evolved in parallel to those of the other apes until the radiation of these lineages began, and then diverged from all of these (clearly gibbon albumin cannot have evolved in parallel

to all four nonhylobatid lineages at the same time). We see that to reconcile the immunological data with many of the current views concerning hominoid evolution (3) we are forced to postulate a remarkable series of coincidences. In the same way those who would attribute the morphological similarities in the trunk and upper limbs, among all the living apes and man, to parallelism must make a similar appeal to coincidence.

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Visceral Tissue Vascularization: An Adaptive Response to High Temperature

Abstract. Electrical heat sources implanted in the abdominal cavities of sheep were heated to give initial temperatures of 42° and 45°C at the surfaces of the heaters. During 18 days of constant heating, a vascularized connective-tissue envelope encapsulated the heat sources, and the temperatures at the surfaces of the heaters declined 0.8° and 1.8°C, respectively. The degree of vascularization and the magnitude of the decrease in the surface temperature appeared to be related to the proximity of the tissue's initial temperature to 45°C, a temperature ordinarily considered detrimental to cell structure. The vascularization thus appears to be adaptive.

While studying the effects of additional endogenous heat in animals, we implanted aseptic, electric heat sources covered with medical-grade silicone rubber in the abdominal cavities of sheep. Two of these devices (5.1 cm wide, 15.1 cm long, and 0.64 cm thick) were implanted end to end in the dorsal abdominal cavity and extended from the renal artery caudally to the aortic bifurcation. After recovery of the animals, voltage (direct-current) was applied to each heater through insulated wire leads from an external electronic circuit capable of sensing the heater-coil temperature and maintaining it within $\pm 0.05^\circ\text{C}$. Another ewe with identical implants to which no heat was applied served as a control.

The temperature at the surface of the heater was calculated from the measured temperature of the heater coil and a predetermined conductance factor for the silicone rubber covering each heater.

Power input was continuously recorded, and calculated temperatures at the heater surfaces were tabulated. Data from one of these experiments are plotted in Fig. 1. The two strip heaters were designated anterior and posterior, according to their positions relative to each other in the dorsal abdominal cavity. The initial surface temperature

of the anterior heater (T_{sa}) was 45°C; that of the posterior heater (T_{sp}) was 42°C. Both temperatures were in the noxious range (1). As heating continued, a decline in both temperatures occurred in spite of the increase in power to each heater required to keep heater-coil temperatures constant.

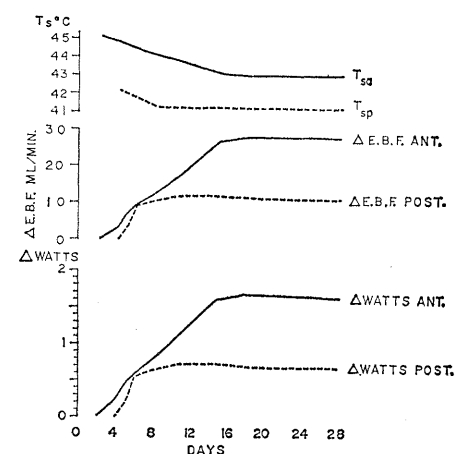


Fig. 1. Differential heating of anterior and posterior dorsal abdominal heat-exchangers in a sheep. T_{sa} , Surface temperature of anterior heater; T_{sp} , surface temperature of posterior heater; Δwatts , increase in power necessary to maintain the heater coil at a constant temperature; $\Delta\text{E.B.F.}$, increase in effective blood flow equivalent to increase in power (0.85 assumed to the specific heat of blood).