THE EVOLUTION OF VERTEBRATE FIBRINOGEN. Russell F. Doolittle. Department of Chemistry, University of California, San Diego, La Jolla, California U.S.A.

The fibrinogens of all vertebrates studied to date are comorised of three pairs of non-identical polypeptide chains. Moreover, in all of these cases--whether the molecule is isolated from a primitive fish or an advanced mammal--polymerization is induced by the thrombin-catalyzed cleavage of a specific peptide material from the amino-terminal segments of two of the three chains. Amino acid sequence studies on mammalian fibrinogen molecules have provided convincing support, however, for the notion that the three non-identical polypeptide chains have evolved from a common ancestor and also that the present chains have been elongated by a series of internal duplications. Thus, we are now in a position to speculate on the structure of the primordial fibrinogen molecule and how it could be gelled by a proteolytic event. The molecule must have been comprised of (two) bundles of three identical polypeptide chains, all of which must have been sensitive to the action of thrombin. Furthermore, symmetry arguments suggest that the way the three identical chains would have been bundled together is best approximated by a (disulfide-linked) three stranded rod. Given the multiple restraints on such a molecule, a reasonable scheme can be advanced for polymerization based on the removal of polar material from one end of the rod. The differences in amino acid sequences for the three chains comprising the present day fibrinogen molecules are such that the duplicative events leading to their divergence must have occurred more than 600 million years ago, or long before the origin of vertebrates. It will be of great interest if a primitive molecule can be found in some extant creature which approximates the prototype structure.

PROTOTYPES FOR CLOTTING BY TRANSAMIDATION. R. V. Myhrman and L. Lorand. Department of Biochemistry and Molecular Biology, Northwestern University, Evanston, Illinois, U.S.A.

In the plasma of vertebrates, onset of clotting reflects on the ability of thrombin to hydrolyze fibrinogen; stiffening of the clot network by transamidation is a later event. We will contrast this sequence with two entirely different systems in which clotting occurs apparently by transamidation alone. The formation of the copulation plug from guinea pig seminal vesicle secretion (I) and the coagulation of lobster blood plasma (II) will be considered. Whereas in vertebrate blood the zymogen (Fibrin stabilizing factor or Factor XIII) co-circulates with fibrinogen, the other two enzymes are sequestered from their clotting substrates by being stored in separate tissues (coagulation gland in case I, amoebocyte or muscle in case II). Clotting of guinea pig seminal vesicle secretion (Williams-Ashman et al., Proc. Natl. Acad. Sci., 69, 2322, 1972); purification and properties of a transamidase from the guinea pig prostate (Wing et al., Fed. Proc., 33, 290, 1974); release of the lobster amoebocyte enzyme; its purification from lobster muscle together with its enzymatic properties; and the use of the lobster clotting system in the diagnosis of a human defect of fibrin stabilization (Lorand et al., J. Clin. Inv., 47, 268, 1968) will be reviewed.

HEMOSTASIS IN NONMAMMALIAN VERTEBRATES: AN OVERVIEW. W. Jean Dodds. Division of Laboratories and Research, New York State Department of Health, Albany, New York, U.S.A.

A common feature of comparative hemostasis throughout the animal kingdom is the participation of cell aggregation and plasma coagulation processes in the sealing of wounds. This applies to many invertebrates and all vertebrates. It is tempting therefore to assume a direct evolutionary progression from primitive invertebrates to advanced vertebrates. The major factors contributing to hemostatic plug formation and dissolution (vessel contraction, plasma coagulation, platelet or thrombocyte reactions and fibrinolysis) are present to greater or lesser extent in most nonmammalian vertebrates including Cyclostomes, Elasmobranchs, Bony Fishes, Amphibians, Reptiles and Birds. Of these functions, the thrombin-fibrinogen reaction has evolved as the final stage of the coagulation mechanism of all vertebrates. Prothrombin conversion to thrombin, accomplished by a tissue factor, is also common to all classes of vertebrates although the plasma factors involved in prothrombin activation have not been delineated for many lower forms of vertebrates. Similarly the exact relationship between the various types of cells involved in hemostasis has yet to be established. Although mammalian platelets probably were derived from invertebrate and lower vertebrate thrombocytes, this is yet to be proven. The challenge remains to develop a more thorough understanding of the basic mechanisms of hemostasis and thereby provide additional biochemical evidence for evolutionary progression.