while most of the sequences represented in the cDNA probe were also found in the transcript some aberrant transcription also occurred. While it is possible to demonstrate a fair degree of the *in vivo* transcription pattern *in vitro* by this approach it has to be conceded that some genes, like the 5S gene, may be subject to finer levels of control which may not be recognised by heterologous polymerases. Gross controls such as heterochromatisation, acting at the structural level, might determine which tissue-specific genes are transcribed from chromatin *in vitro* and may require little discrimination on the part of the polymerase for the selective transcription of these genes.

Difficulties in solving heparin structure

from Edward A. Johnson

HEPARIN has now been in clinical use for 40 years, but the achievement of anything like a complete understanding of its anticoagulant action still seems a long way off. The difficulties centre on our ignorance of the structure of heparin; or perhaps one should say structures, for it is clear that not only is the most thoroughly purified material a mixture of many compounds, but various components of the mixture exert different effects within the coagulation 'cascade'—that insecure sequence of enzyme reactions which may sometimes begin with the activation of Hageman factor and (with more confidence) may be said to end with the cross-linking of fibrin by activated fibrin stabilising factor to form an insoluble clot.

A matter in dispute since the discovery of heparin is its native form in tissue; more specifically, in the granules of mast cells which are its only certain source, although Jaques and coworkers (*Lancet* **i**, 411; 1977) have recently suggested that it may be present in other kinds of cell. Silbert, Austen and coworkers (*J. biol. Chem.* **252**, 518; 1977) have now consolidated earlier work by Horner (*J. biol. Chem.* **246**, 231; 1971), confirming that, in some tissues at least, native heparin has a high molecular weight of the order of 750,000 to 1,000,000. These large molecules are made up of a number of chains more nearly the size of commercial heparin (5,000–40,000) linked to a common core of uncertain character by polypeptides which, surprisingly, are resistant to all the proteases to which they have so far been exposed. However, treatment with aqueous alkali, a procedure often used in commercial heparin extraction, readily releases the chains from the core to give a product which is presumably the equivalent of the heparin of commerce.

Heparin, as a strongly anionic polysaccharide, exerts its effects by binding specifically to basic regions of certain proteins, in particular to antithrombin III (see Seegers, Rosenberg and other workers in *Adv. exp. Med. Biol.* **52**, 1975), the inhibitory action of which on serine esterases in the coagulation cascade is thereby greatly accelerated. It is reasonable to suppose that binding will depend on the presence of appropriate sequences peculiar to the heparin chains, since related acidic glycosaminoglycans and other polysaccharides, whether artificially sulphated or not, are all far less effective than heparin in the test systems used. The difficulties of identifying these sequences are very great, principally because heparin is always heterogenous, a complete obstacle to the quasi-statistical methods used in sequencing proteins. Also, hydrolytic degradation is invariably accompanied by far more damage to the released fragments than occurs with peptides, and enzymic methods have to be used.

Useful initial fractionation may be carried out by making use of protein–heparin binding, and, by adsorption on matrix-bound antithrombin or by related procedures, several groups of workers (Lam *et al. Biochem. biophys. Res. Commun.* **69**, 570; 1976, Höök *et al. FEBS Lett.* **66**, 90; 1976; Andersson *et al. Thromb. Res.* **9**, 575; 1976) have concentrated heparin fractions with strong antithrombin binding from various commercial preparations. Such high-affinity material has been called, too loosely, 'active' heparin in contrast to the more weakly bound inactive' heparin (which seems to be indistinguishable in its general physicochemical properties), but it has yet to be proved that antithrombin-binding capacity *in vitro* is the only significant criterion for anticoagulant activity in heparin. It may be important; but there is certainly evidence that, at least *in vitro*, the antithrombin-binding capacity of certain heparin fractions does not follow their activity in other and presumably unrelated stages in the coagulation cascade (Andersson *et al. Thromb. Res.* **9**, 575; 1976). High-affinity heparin is still very heterogeneous, but Lindahl's group, with Linker (*FEBS Lett.* **69**, 51; 1976), has taken a further step by adsorbing heparin fractions on antithrombin–Sepharose and incubating the complex with heparinase. The segments of the heparin chains bound to the protein were not attacked, but could be displaced in the usual way by increasing the ionic strength. The material isolated in this way had molecular weights of 2,000 to 5,000 (6–16 monosaccharide units), depending on the heparin starting material, but was still heterogeneous.

This kind of approach, ultimately identifying and comparing the heparin segments that are most strongly bound to various proteins involved in coagulation, is difficult and laborious; few of the other relevant proteins are as easy to isolate or as stable as antithrombin III. Nevertheless, it is probably the best hope so far of gaining a proper understanding of heparin anticoagulation. Additional help can come from fluorescence and circular dichroism effects of heparin–protein interactions and also from X-ray diffraction studies on heparin salts—which may give some

Triassic extinction or Jurassic vacuum?

IN his article "Triassic extinction or Jurassic vacuum?" (*News and Views* **265**, 402; 1977), Milner refers briefly to my work on a Middle Jurassic microvertebrate locality in Oxfordshire. (*Science* **194**, 1053; 1977). He expresses hope that it and other new localities in Queensland, India and the Isle of Skye may provide data on the times of extinction of the procolophonids, rhynchosaurs, thecodonts, dicynodonts and temnospondyl labyrinthodonts, all of which are conventionally supposed to have died out at the end of the Triassic.

The Oxfordshire site has yielded isolated bones and teeth of mammals, therapsids, theropods, ornithischians, ?sauropods, pterosaurs, crocodilians, lepidosaurs, chelonians, anurans and actinopterygians, but in spite of a deliberate search, no teeth of labyrinthodonts have yet been found. The fragmentary condition of the material would not permit ready identification of the other Late Triassic groups to which Milner refers even if these were present. The diversity of the vertebrate fossils from Oxfordshire indicates that a wide range of vertebrate palaeoenvironments fell within the catchment area of the deposit, and that therefore the absence of the labyrinthodonts in the Late Bathonian is real rather than apparent.

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