is before the increase in ribosome content—ribosomes must be used more efficiently during this period; this is consistent with models in which the frequency of initiation of protein synthesis is established simply by the amount in the cytoplasm of messenger RNA.

Amounts of ribosomal and transfer RNA seem to be perfectly coordinated in fibroblasts, unlike the situation in bacteria in which the ribosome/tRNA content may vary over a ten-fold range. But since these two classes of RNA display different stabilities in the fibroblast, their coordinate amounts cannot be established at the level of synthesis; neither rRNA nor tRNA is stable in resting cells, where their half lives are different, and rRNA is stable in growing cells whereas tRNA is not—details of the stabilities of different classes of RNA, a critical parameter in constructing models for the regulation of their activity, are reported by Johnson *et al.* to be in preparation. But the apparent coordination of the relative contents of tRNA and rRNA must clearly require noncoordinate synthesis. And the general response of the cell to conditions which stimulate growth is to increase its capacity for protein synthesis, the level of mRNA relative to that of the ribosomes and tRNA itself increasing so that the cell makes a more efficient use of the protein synthetic apparatus. Establishing the mechanisms implicated in the control of and response to the different states of the cell represented by the division cycle is clearly fundamental to any understanding of cell development, emphasising the importance of studies such as these which cast a light on the general systems that regulate RNA production.

Role of terminal sugars in biological events

from a Correspondent

DURING the past few years glycoproteins have moved dramatically from the ignominious position they long occupied of taking up the last forlorn session on the last day of international scientific meetings, to the glory of fully fledged symposia. There is scarcely a biological phenomenon that has not been bombarded with every laboratory's collection of lectins. Another obligatory reagent for research at present is neuraminidase, the effects of which are legion: on the immunogenicity of tumour cells; on receptor sites for viruses, hormones and certain lectins such as wheat germ lectin which has weak affinity for N-acetylneuraminic acid residues or other lectins having sialic acid specificity, for example, from *Limulus polyphemus*; on cell-

cell interactions; on lymphocyte transformation, and so on.

The clear demonstration of a causal relationship between these various events and terminal sialic acid residues of glycoproteins or gangliosides is unfortunately less commonly obtained, though notable exceptions are binding of myxoviruses and certain lectins that clearly recognise this sugar and bind to it. Another candidate is the interaction of the natural peptide, tuftsin with polymorphonuclear leukocytes (Constantopoulos and Najjar, *J. biol. Chem.*, **248**, 3819–3822; 1973). The enhanced phagocytic capacity induced by tuftsin is abolished when cells are first treated with neuraminidase so raising the possibility that membrane sialic acid is the receptor site.

Perhaps the most convincing demonstration of a direct role of terminal sugar residues in the control of biological activity comes from Ashwell and his colleagues, who have shown that neuraminidase treatment of a large variety of soluble glycoproteins (including hormones) redirects these components from a normal circulatory pattern to one in which they are quickly cleared from the blood stream by sequestration in the liver. Ashwell and his collaborators have clearly identified receptor sites present on hepatocytes that recognise another terminal sugar, D-galactose, which is exposed as such after removal of sialic acid residues.

A possibly analogous situation is described by Sandford and her colleagues (*J. Immunol.*, **111**, 1071–1080; 1973) and may provide the explanation for earlier observations that the ability of a transplantable murine tumour to grow in certain foreign strains of mice is significantly reduced by prior treatment of the tumour cells with neuraminidase. Tumour cells treated with neuraminidase are rapidly killed by a naturally occurring antibody (probably 19S IgM) in the serum of resistant mice with specificity for newly exposed oligosaccharide terminals containing galactose residues.

The apparently widespread involvement of sialic acid terminals in biological activities, either directly or by virtue of a protective effect in 'hiding' other recognisable sugar terminals (galactose for instance), is a consequence of the ready availability of neuraminidases. Similar experiments using other glycosidases to point out possible functions of terminal sugars such as fucose have been hampered by the relative inaccessibility of active glycosidases of the required specificity. The recent report of Remold (*J. exp. Med.*, **138**, 1065–1076; 1973) suggests that it is only a question of time before other sugar residues are involved in biological events. Remold has studied the effect of the enzyme, L-fucosidase, on the interaction of macrophage inhibition factor (MIF) with its target cell.

MIF is a soluble glycoprotein of moderate size that is secreted by sensitised lymphocytes on exposure to antigen. It is so-called because of an ability to immobilise macrophages *in vitro*; macrophages are prevented in culture from migrating from the orifice of a capillary tube. The factor also performs other duties in enhancing the effector activity of macrophages in the immune response: for instance, in increasing their stickiness and phagocytic capability. It is relevant to point out that the carbohydrate unit of MIF seems to play a part in its activity since neuraminidase treatment inactivates MIF as shown 3 years ago by Remold and David. The unknown mechanism of action of MIF certainly involves as the first step, interaction of MIF with the macrophage surface. It is this step that Remold has now found to require intact fucose terminals on the glycoproteins of the surface membrane of the target cell.

First, guinea pig peritoneal macrophages, incubated *in vitro* with MIF in the presence of L-fucose at 100mM, fail to migrate as well as a control cell population and several other sugars have no effect. The inhibition by fucose is easily reversed by removing the sugar by dialysis. Second, when macrophages are treated with a specific glycosidase to remove L-fucose terminal residues from the surface, these cells do not respond to MIF but migrate normally. Clearly then the necessary fucose residues are part of cellular surface glycoproteins and are not part of MIF itself. Indeed MIF exposed to fucosidase in contrast to neuraminidase (or proteases) retains full biological activity. The inhibitory effect of fucosidase on macrophages is transient and the cells regain their ability to respond to MIF within a few hours, probably by replacement of the fucose-deficient surface membrane glycoproteins with complete molecules. The inference therefore is that the molecules containing receptor sites for MIF on the macrophage surface contain L-fucose residues and are manufactured by the macrophage population. Since L-fucose alone is inhibitory only at high concentrations, it seems likely that MIF recognises an extended oligosaccharide sequence terminating in an L-fucose residue in the receptor site on the macrophage surface.

The identification of this sequence and the question of whether it exists on a unique glycoprotein species of the macrophage surface, or alternatively if MIF will recognise a terminal L-fucose residue attached to any penultimate sequence remains to be determined. The competitive effect of L-fucose binding lectins on the activity of MIF would also be of interest and no doubt is under active study.