PROTEIN SYNTHESIS

The Captive Messenger

from our Molecular Biology Correspondent

WHETHER the particles of rapidly labelling RNA and protein that have been seen in the cytoplasm of mammalian cells are fact or artefact is still regarded in the more sober quarters as an open question, and so indeed is their relation to the complexes containing messenger RNA that are released when polysomes are dissociated. That labelled RNA comes away in sizable particles of high buoyant density has been known for some time, but the possibility that the RNA picks up basic proteins when dunked in the cytoplasm cannot be disregarded. Such random association was indeed shown to occur last year by Baltimore and Huang.

The nature of the complexes present in rat liver polysomes has now been re-examined by Lee and Brawerman (*Biochemistry*, **10**, 510; 1971), who report as follows: Treatment with EDTA releases pulse labelled RNA in the form of a highly polydisperse population of particles. The same effect could be produced in other ways—by raising the *p*H at defined potassium and magnesium concentrations and by treatment with urea. Free messenger cannot be liberated by urea or by high ionic strength, and the particles differ in this respect from the non-specific, and presumably adventitious, complexes described by Baltimore and Huang. Treatment with sodium dodecyl sulphate, which is one of the most efficient reagents for breaking up complexes between proteins, is the only satisfactory method so far known for extracting the free messenger. The latter has a much smaller sedimentation coefficient than the complex, which moreover is the same no matter from which fraction of the broad sedimentation profile of the complex it has been extracted.

The question remains whether the associated material consists of proteins torn out of the ribosomes on dissociation, or of components that the messenger carries into the cytoplasm. The first and more obvious explanation is supported by an observation of Nolan and Arnstein, who found that a poly U messenger carries ribosomal protein away with it on dissociation of the ribosomes. On the other hand, Lee and Brawerman refer to work of their own, as yet unpublished, according to which ribonuclease-treated ribosomes, when exposed to EDTA, release that part of the messenger which is shielded against the nuclease, in uncomplexed form. They also report that in a similar mammalian system, the complexes are found after the ribosomes are allowed to run off the messenger.

It may be remarked that it has not even been properly demonstrated that the associated material is protein, and there is at this stage little that one can say about the possible purpose of this luggage that the messenger seems to carry around the cell. Lee and Brawerman suggest that it is unlikely to be anywhere but at the end of the molecule if it is not to impede the translation process, and that it may be nothing more than a part of the cell membrane to which the polysomes are normally tethered. It will be recalled, however, that descriptions have been published of ribosomal proteins that attach the ribosome to the membrane.

Another unexpected feature of a eukaryotic messenger is reported by Gaskill and Kabat (*Proc. US Nat. Acad. Sci.*, **68**, 72; 1971). They have prepared rabbit haemoglobin messenger from polysomes, and examined it electrophoretically in polyacrylamide gels. In this medium it separates from various contaminants and degradation products and can be unequivocally identified by its labelling properties. There follows something of a leap of faith in that the authors determine the molecular weight from the electrophoretic mobility in the gel. This method in general seems to give reliable results, but would be expected to fail for species with very different degrees of base-pairing from those of the standards in terms of which the calibration is set up. A graphic example of such an effect is to be found in a recent article by Groot, Aaij and Borst (*Biochem. Biophys. Res. Commun.*, **41**, 1321; 1970), who find that with mitochondrial RNA the measured molecular weight changes by 40 per cent relative to calibration standards, according as the measurements are made at 2 or 28° C. This reservation aside, however, Gaskill and Kabat's results at least suggest that the messenger is more than half as long again as it need be to code for the globin chains. This may relate to the battery of stop and start and perhaps other signals that Sanger and his colleagues found in the polycistronic R17 viral RNA.

Heterogeneity of Antigenicity in Malignant Cells

CANCER research wends a tortuous path reflecting the many basic uncertainties in our understanding of the genetic control of differentiation of metazoan cells. Relatively recently, studies in which malignant and normal cells were hybridized revealed that a malignant genotype could apparently be masked in the presence of a normal complement of genetic material (Harris *et al.*, *Nature*, **223**, 363; 1969). The same series of experiments suggested that certain malignant cells had the ability to hide the transplantation antigens of the normal cell constituent of hybrids. The inference from this second finding was that tumours which had been transplanted a long time could enhance their capacity to grow malignantly by effective reduction of antigenicity. Such a mechanism could be thought of as involving antigenic simplification by genetic deletion or, alternatively, a modification process could be implicated by which the activity of these genes, which determine the transplantation antigens, could be quantitatively reduced. Modifier genes are familiar to botanists as a common feature of the genetic changes involved in speciation.

A further set of experiments described in next Wednesday's *Nature New Biology* is relevant to this theme. Negroni and Hunter have amplified an earlier finding (E. J. Walls and G. Negroni, *Europ. J. Cancer*, **2**, 221; 1966) that a clone of cells, isolated from a polyoma induced fibrosarcoma, though itself non-malignant can effectively immunize against the growth of a similar but malignant cell population. The evidence is compatible with the notion that the non-malignant cell population is more antigenic than the malignant cell clone but has a qualitatively similar antigenicity. Negroni and Hunter go on to show that malignant cell clones can be derived from the "non-malignant" cell line by selection with an immune antiserum (produced in C3H mice by immunization with the non-malignant cell lines). The same antiserum applied to certain malignant cell populations effectively reduced immunosensitivity among the survivors.

The phenomenon of tumour progression, by which is implied a change in growth potential with time, has been recognized for many years and a summary of its ramifications has recently been published (L. Foulds, *Neoplastic Development*, **1**, Academic Press, London and New York, 1969). It seems possible that the heterogeneity of antigenicity among malignant cell populations such as that described by Negroni and Hunter is an aspect of tumour progression and a singularly interesting corollary is that, if non-malignant variants could be selected and grown from among a tumour cell population, it is possible that they could be used as a means of immunizing against the truly malignant cells. It is also tempting to wonder whether the "non-malignant" characteristic which, according to the earlier information, involves a lack of the capacity to liberate virus in culture and normal contact inhibitory behaviour really is non-malignant. Would these cells which display such meek characteristics in normal adult mice betray a malignant nature in immunologically deprived recipients? If they did, it would be necessary to define malignancy as a state resulting from a particular tumour–host relationship; a long overdue alteration in immunologists' thinking.