containing specialized sequences. The authors see this secondary structure as a phenotypic expression of the primary nucleotide sequence and it may be that the properties of these phenotypes in turn provide extra factors that may play their part in the selection of these evolving molecules. Finally, Mills *et al.* intimate that they have sequenced a mutant of their MDV-1 molecule subjected to different selection pressures.

From a Correspondent

PROTEIN SYNTHESIS

In Praise of Controls

from our Molecular Biology Correspondent

THE history of haemin as a regulator of haemoglobin synthesis has transmogrified itself into an absorbing moral fable. When it was discovered that the output of protein by a rabbit reticulocyte system was heftily stimulated by the addition of a *soupoon* of haemin, the scheme of regulation that forthwith leapt unbidden to the mind of molecular biologists, nourished on a lifelong diet of feedback, fell so pleasingly into place in the canon, was so close indeed to the way they would themselves have designed it, as to exclude all doubt of its validity. In such a situation it might have seemed wanton to jeopardize so satisfying a conceit by doing one experiment too many. That experiment has now, alas, been done and in several laboratories at once, and the result is a true Huxleian tragedy — a beautiful and virtuous hypothesis butchered by a gang of ugly facts.

The idea, of course, was that globin, accumulating apace in consequence of stimulation by free haemin, would bind progressively more of this haemin, thereby inhibiting further globin synthesis until new haemin was added to the pool. Mathews, Hunt and Brayley (*Nature new Biol.*, **243**, 230; 1973) have shown, however, that haemin stimulates equally the translation of extraneous messengers in the rabbit reticulocyte system. They have tried this experiment with another globin messenger, from the mouse, with lens crystallin messenger and with a viral RNA. The proteins that were synthesized were fractionated by gel electrophoresis, and were not globin, except when a globin messenger was used, as judged by their electrophoretic mobilities and their autoradiographic tryptic peptide maps.

In the case of EMC virus RNA the control of translation by haemin was less marked, but this is very likely a consequence of reluctant and brief initiation by this messenger and its effect in inhibiting endogenous messenger activity.

The same conclusions were in fact taken a step further by Beuzard, Rodvian and London (*Proc. natn. Acad. Sci. U.S.A.*, **70**, 1022; 1973). In the first place they separated the freshly synthesized proteins from intact reticulocytes by ion-exchange chromatography, and found that haemin engendered essentially the same degree of stimulation on the synthesis of haemoglobin, which makes up the overwhelming bulk of the red cell protein, and that of carbonic anhydrase. They next proceeded to a totally unrelated system, ascites tumour cells, and found that here too the translation of both the endogenous messenger and of added rabbit globin messenger was stimulated by addition of haemin. The effect is not on the initial rate of the synthesis, for the build up of incorporation with time is more or less the same regardless of the presence or concentration of haemin (at least up to a limiting value), but rather on the length of time during which synthesis is sustained, so that the stimulating effect becomes apparent only after some minutes.

Yet another independent demonstration of the lack of specificity of the haemin comes from Lodish (*ibid.*, 1526), whose concern was with the synthesis of the proteins of the red cell membrane, a problem of interest in a number of connexions. The same patterns of amino acid incorporation were found whether the synthesis was observed in whole reticulocytes, or in lysates prepared by cautious procedures, that do not evidently provoke the release of membrane-bound polysomes into the solution. Evidently therefore the membrane proteins synthesized in these cells are not made predominantly on membrane-bound ribosomes (in contrast with extracellular proteins, which are synthesized on membranes for instant export as they come off the assembly line). In fact only three of the fifteen or so principal identifiable membrane proteins, as recognized by electrophoretic analysis, turn out to be significantly labelled, and the labelling patterns indicated that one of them was perhaps a precursor of another. This was confirmed by examination of the tryptic fingerprints of the two products, and by inhibition of the transformation of the one into the other by an active-site reagent specific for serine proteases. Thus only two of the principal membrane proteins are synthesized at the reticulocyte stage, and their molecular weights are estimated by detergent-gel electrophoresis to be about 53,000 and 33,000. The preponderant membrane protein species, therefore, especially the high-molecular-weight spectrins, and the blood-group antigen glycoprotein, are synthesized at an earlier stage of development. As to the effect of haemin, this is just as important for the

synthesis of the membrane proteins as for the globin.

All this does not, of course, deprive the function of haemin in this role of its interest, even though it is presumably not implicated in protein synthesis in most other cells. Mathews *et al.* advert to some observations which indicate that the haemin operates by binding to and inactivating an inhibitor of synthesis. Darnborough *et al.* (*J. mol. Biol.*, **76**, 379; 1973) have, moreover, just come up with some compelling evidence that initiation in the reticulocyte system proceeds in a rather different manner to that of most tacit assumptions. They find that a complex is first formed between formylmethionine-tRNA and 40S ribosomal subunits. This complex then takes up messenger and the 60S subunit, and synthesis now begins. It appears that in the absence of haemin, the concentration of the 40S-tRNA complex runs down rapidly. It seems, therefore, that the mysterious inhibitor intervenes at this point, unless haemin is present. Whether the action of the haemin is purely adventitious is not yet, of course, clear. It is, incidentally, interesting that double stranded RNA, which is a strong inhibitor of initiation of protein synthesis, also according to Darnborough *et al.* interferes with the build up of the tRNA-40S complex. Moreover, Kaempfer and Kaufman (*Proc. natn. Acad. Sci. U.S.A.*, **70**, 1222; 1973) have shown that it works by binding to and inactivating an initiation factor, IF-3 (though their inference is that initiation normally occurs on a base-paired segment of the messenger RNA).

SEED RESEARCH

New Directory

THE publication of a *Directory of Seed Research in Britain* (obtainable from the Scottish Horticultural Research Institute, Invergowrie, Dundee DD2 5DA) should improve communications and reduce unnecessary duplication of research effort. It covers not only agricultural and horticultural crops, but also trees, weeds and wild species. Seed production, processing, quality, storage, dormancy, germination and seedling establishment are among the topics included. The compiler—Dr T. W. Hegarty—has divided the directory into four main sections: (1) an alphabetical list of research establishments; (2) a list of research interests, arranged under name(s) of the individual or group concerned within each institution; (3) a name index; and (4) a subject index.