are not exposed (within the ribosome) to attack by kethoxal, a reagent which specifically attacks non-paired guanine bases (Noller and Herr, *J. molec. Biol.*, **90**, 181; 1974). This difficulty can of course be overcome by postulating appropriate conformational changes (Schwarz *et al., Biochem. biophys, Res. Commun.*, **56**, 807; 1974).

Kethoxal has been successfully used as a probe for the accessibility of G-residues on the surface of the 30S ribosomal subunit (Noller, *Biochemistry*, **13**, 4694; 1974), and these studies have also provided information regarding the vexed question of the secondary structure of the rRNA. There is still no proven secondary structure for the 5S RNA, and, while a secondary structure has been proposed for *E. coli* 16S RNA (Ehresmann *et al., Nucleic Acids Res.*, **2**, 265; 1975), there is at present little evidence to support it. Indeed the kethoxal data are to a considerable extent at variance with the proposed structure, and a further complication has recently arisen with the finding that specific regions of the 16S RNA are involved in stable long-range interactions with other parts of the molecule (Mackie and Zimmerman, *J. biol. Chem.*, **250**, 4100; 1975). This suggests that secondary structure model-building based on a simple linear array of hairpin loops may be *a priori* invalid.

Many questions concerning both secondary structure and function of the rRNA will perhaps become clearer with a better understanding of the interactions between RNA and protein within the ribosome. This is one of the most important problems of ribosomology, but again it has not proved an easy one to approach. Most of the available data has been obtained by Garrett and Zimmermann and their co-workers from synthetic complexes between single ribosomal proteins and RNA (reviewed by Zimmermann, *Ribosomes*, 225, Cold Spring Harbor Monograph, 1974). These complexes are subjected to a mild nuclease digestion, following which the RNA region "protected" by the protein can be identified. The approach is of course limited to a study of those proteins which can individually form specific complexes with RNA, the "RNA binding" proteins, but it has nevertheless provided a great deal of information in a number of cases. The size and complexity of the RNA regions involved varies considerably; at one end of the scale are proteins such as S8 and S15 which are found in association with short regions of 16S RNA of the order of 50 nucleotides long. Similar short regions of 5S RNA have been found corresponding to proteins L18 and L25. At the other end of the scale are proteins S4 and L24, both of which interact with very large sections of 16S or 23S RNA approximately 400 nucleotides in length. How far these "binding sites", in particular the very large ones, reflect the situation within the intact ribosome remains to be seen.

For the examination of RNA–protein interactions within the ribosome itself, especially those involving proteins which are unable to bind individually to RNA, another approach is necessary. One method has been to isolate fragments from the complete ribosome following nuclease digestion, and to analyse those RNA sequences which interact with particular groups of proteins in the fragments (for example, Yuki and Brimacombe, *Eur. J. Biochem.*, **56**, 23; 1975); further development of this approach has however been severely limited by the ease with which the specificity of the RNA–protein interaction is lost. A more promising approach, now being undertaken by a number of laboratories, involves the development of suitable RNA–protein cross-linking techniques. One example has been the cross-linking of proteins to the 3′-terminus of the 16S RNA, by way of the periodate oxidation of the 3′-terminal ribose. The proteins concerned are S1 and S21 (Czernilofsky *et al., FEBS Lett.*, **58**, 281; 1975), which is interesting in view of the foregoing discussion of initiation, since both these proteins are involved in mRNA binding. S1 has also been shown to bind to an RNA fragment from the 3′-terminus of the 16S RNA (Dahlberg and Dahlberg, *Proc. natn. Acad. Sci. U.S.A.*, **72**, 2940; 1975).

Cross-linking of protein to RNA within the bulk of the rRNA requires more general methods, but here also a measure of success has been recorded, such as the identification of some peptides of protein S4 which are in contact with the 16S RNA (Ehresmann *et al., FEBS Lett.*, **58**, 106; 1975), or the identification of a region of 16S RNA which is in contact with protein S7 (Rinke *et al., Eur. J. Biochem.*, in the press), in both cases after cross-linking induced by ultraviolet irradiation. These techniques clearly need a lot of refinement, but an extension of this type of study, coupled with the development of more sophisticated cross-linking reagents, seems at the moment to hold the most promise for the immediate future. The recent application of various physicochemical techniques to the protein topography problem is very rapidly giving us a firmer knowledge of the spatial distribution of the ribosomal proteins; it will not be too long before we have at least a first approximation as to how the rRNA is threaded through this protein matrix. This would be invaluable in studies of both structure and function.

A hundred years ago

We cannot see the force of some of the arguments with which Captain Moresby supports his plea for annexation [of New Guinea]. His strong attachment to the natives and his desire for their welfare we think mislead him as to how this is to be accomplished. If New Guinea is to be colonised by white men, all previous experience teaches us that the natives will inevitably suffer, will be demoralised, and ultimately extinguished. It is inexpressibly sad to think of such a fate overtaking these gentle and altogether superior natives of New Guinea; but how can it be helped, unless it is resolved to put a stop to the increase in the white portion of the world's population.
from *Nature*, **13**, March 9, 365; 1876.

Models from maps

from S. D. Dover

Analysis of the electron density maps which are the results of an X-ray crystallographic investigation is the last stage in protein structure determination.

In the initial development of the subject maps were analysed by placing markers in regions of density corresponding to an identifiable feature, measuring the marker co-ordinates, and adding to or adjusting a wire model of the structure accordingly. The interpretation of a new part of the map frequently relied on the existing portion of the model. This feedback was facilitated by the Richard's box (*J. molec. Biol.*, **37**, 225; 1968) a construction which enabled an image of the model in a half-silvered mirror to be superimposed on a stack of perspex sheets on which were drawn the electron density contours. Alterations or additions to the model were then seen directly in the context of the map and any unexplained or poorly fitted features were made obvious.

The use of computers as aids in the building of models started with Diamond's automatic procedures to fit a model to coordinates read from the map (*Acta Cryst.*, **21**, 253; 1966). This approach has been extended to the refinement of a model to fit an electron density map itself ("real-space" refinement), rather than guide coordinates (*Acta Cryst.*, **A27**, 436; 1971). Refinement is an essential part of the structure-solving process and Diesenhofer and Steigmann (*Acta Cryst.*, **B31**, 238; 1975) have taken Diamond's method farther by improving the phasing of the