We are designing and building a program package oriented to this new generation of micro-computers, incorporating advanced direct methods, raster graphics, real-time micro-computers with 32-bit registers and 32 Mbytes task virtual address space, providing the power, scope and ease of programming of a mainframe while retaining the closely-interactive features of a mini.

The system has been tested by using the ORTEP system. It is, however, important to note that this is only a partial test, as detailed real-time conformational calculations, with maximally precise positioning, have not yet been made using a separate energy-minimisation program. Further details of our system have recently been reported (North et al., in Molecular Structure, Conformation, Function and Evolution, Vol. 1, ed. Srinivasan, R.) 59-72, Pergamon, Oxford, 1980).

The system has been tested by using the known binding energies between 2,3-diphosphoglycerate and normal and a variety of mutant forms of human haemoglobin, and between several synthetic analogs of 2,3-diphosphoglycerate and normal adult deoxy-haemoglobin. There is good agreement between calculation and experimental measurement.

In another test, the different proportions of the four isomers formed by the auto-catalytic breakdown of the haem group in oxy-myoglobin and in the α and β chains of oxy-haemoglobin are accurately predicted by calculating the relative accessibility of the four methene bridges to the attacking haem-bound oxygen molecule (Brown, Chabot, Enderby and North, Nature, 1980), 289, 92-95.

Current work is concerned with a study of the possible modes of binding of a variety of inhibitors to the enzyme dihydrofolate reductase. The initial structure of the enzyme is taken to be that which occurs in its complex with the anti-cancer agent methotrexate, for which crystallographic data are available. The predicted mode of binding of the heterocyclic trimethoprim agrees well with available NMR data and we have designed analogs of trimethoprim which are calculated to bind more tightly to the enzyme. Similar studies are in progress with the anti-malarial compounds pyrimethamine and cycloguanil which also act by inhibition of dihydrofolate reductase. These studies provide a rational 3-dimensional structural basis for the synthesis and testing of a number of compounds of potential clinical importance.