of histone IV has the highest degree of specificity. This must be seen as the first really powerful evidence against the argument that histones are merely "glue" and have no function but to package the DNA. Whether the high specificity is demanded by a specific repressor function or by very precise steric requirements which enable the histone to impose a super-structure on the DNA is uncertain. Details of this exciting work will be eagerly awaited. Meanwhile, we will cherish Professor Smith's comment that "we are all brothers under our histones".

Pharmacogenetics

from our Medical Biochemistry Correspondent

SEVERAL inherited differences in human enzymes have been recognized only because the abnormal enzyme alters the metabolism of certain drugs. A dramatic example of this type of reaction can occur with the drug suxamethonium (succinyl choline), used by anaesthetists as a muscle relaxant. Patients who have some abnormal variants of choline esterase cannot hydrolyse succinyl choline as rapidly as usual, and can be paralysed and stop breathing spontaneously for periods up to an hour (Liddell, *Proc. Roy. Soc. Med.*, **61**, 168; 1968).

A deficiency of glucose 6-phosphate dehydrogenase in the red blood cells is commonly found in some populations, and those suffering from this deficiency develop haemolytic anaemias after eating broad beans or after treatment with antimalarial drugs. Deficiency of another enzyme in the red blood cells, glutathione reductase, can also give rise to haemolytic anaemias. Symptoms often arise only when the patient has been exposed to certain drugs such as chloroquine, salicylazo-sulphapyridine, nitrofurantoin, sulphonamides, phenyl-butazone, phenacetin, dicoumarin and chloramphenicol. Blume, Rudiger and Löhr (*Biochim. Biophys. Acta*, **151**, 686; 1968) have now shown that in these patients there is a complete absence of one of the two isozymes of glutathione reductase found in normal red blood cells. On electrophoresis of haemolysates of normal human red blood cells, glutathione reductase activity was found in two distinct bands which have been called GR I and GR II. GR I contained 65 per cent of the total activity and GR II 35 per cent. The haemolysates of patients with glutathione reductase deficiency had only half the enzyme activity found in normals, a pH optimum of 6·4 as opposed to 6·8 in controls and a different affinity for glutathione. On electrophoresis, only one band of enzyme activity was found, corresponding to the GR I band in normal red cells.

Of more general interest is the recent demonstration by Vesell and Page that the rate of loss of phenyl-butazone from the blood in man is genetically determined (*Science*, **159**, 1479; 1968). After a single dose of any drug, the concentration of the drug in the blood usually declines exponentially as the drug is metabolized and excreted. Vesell and Page gave a single oral dose of about 6 mg/kg phenylbutazone to 7 pairs of identical and 7 pairs of non-identical twins, and estimated the blood concentrations to determine the half-life of the drug in each individual. The pairs of identical twins had very similar half-lives for phenylbutazone, but the fraternal twins showed much more variation in half-life between individuals. Statistical analysis showed that the difference between the two types of

twins was significant, and the intra-pair correlation coefficients (excluding one pair of fraternal twins where one individual had a very abnormal half-life) were those to be expected when the factor under examination is genetically determined. The investigation was repeated on two sets of identical twins 9 days after the first dose, and the same values were found as in the first investigation. This suggests that the half-life is not influenced to any great extent by environmental factors such as prior administration of the drug.

Before excretion, phenylbutazone is hydroxylated by a liver microsomal system which is believed to metabolize a number of other drugs. If the genetic variation is in this enzyme system, the rate of metabolism of the other drugs will also vary considerably. In Vesell and Page's study the half-life of phenyl-butazone varied between 1·2 days and 7·3 days although the mean was $3·0 \pm 0·3$ days. This means that the toxicity and effectiveness of these drugs can vary greatly in different individuals.

Prebiotic Synthesis of Nucleic Acids

by our Biochemical Genetics Correspondent

THE question of how life may have evolved is certainly fraught with problems. Some small biological molecules, such as several of the common amino-acids and some nucleic acid components, can be made relatively easily under mild neutral conditions given the required reactive reagents. Such reagents, plausibly enough, may have been generated by radiation or thermal processes. But in order to create a complex which can evolve by the forces of natural selection requires the construction of molecules in which information can be carried and expressed. In life today these functions are carried out by nucleic acids—DNA and RNA—and by proteins. DNA is usually the repository of genetic information. It is most likely that, when natural selection began to operate, either DNA or RNA molecules were present: it is also likely that these molecules arose in the first place by spontaneous chemical synthesis. How closely the nucleic acids, as we see them today, resemble those which were around one or two thousand million years ago is an open question.

To investigate the conditions which might be required for spontaneous nucleic acid synthesis, Sulston, Lohrmann, Orgel and Miles (*Proc. US Nat. Acad. Sci.*, **59**, 726; 1968) have attempted to build a polyadenylic acid molecule using a template of poly-uridylic acid; the complex of poly-A and poly-U is, in fact, a triple helix of two poly-U chains and one poly-A chain. Sulston *et al.* used conditions under which two poly-U chains and 5′ adenylic acid could form a triple helix in which the adenylic acid monomers are simply held in place by the two poly-U chains. Under similar conditions a double poly-U : adenosine helix can also be formed. They then tried to see whether coupling reagents, such as carbodiimide, could link up the monomer adenylic acid or adenosine units to form oligo-nucleotides. Their control experiments lacked poly-U. They found that the poly-U does indeed "catalyse" the formation of oligoadenylic acids; the presence of poly-U accelerated the rate of formation of oligomers by a factor of about ten. Furthermore, the presence of poly-U is specific for adenosine and does not affect either uridine or cytidine nucleosides.