Human Hemoglobin

INVESTIGATIONS in our laboratories on human hemoglobin during the past four years have shown that the erythrocytes of an individual may contain two, and even three, different molecular species of hemoglobin. Ten genetically distinct conditions that may be characterized by the hemoglobin composition of the erythrocytes have been observed. Some of these conditions are associated with severe anemias, but others are difficult, if not impossible, to detect on the basis of clinical observations. It is therefore of importance in physical and chemical studies on human hemoglobin that the investigator utilize individual rather than pooled specimens.

It has been known for many years that the fetus of a given species produces a hemoglobin which differs from that produced by an adult member of the same species. The discovery of an electrophoretically abnormal hemoglobin in sickle cell disease in 1949 (Pauling, Itano, Singer, and Wells) provided the first positive evidence that adult hemoglobin may exist in more than one molecluar form. The following year a second abnormal adult hemoglobin was discovered, again by the use of electrophoretic mobility measurements. A third abnormal adult hemoglobin was detected last year by the combined use of electrophoretic mobility and solubility measurements. No abnormal fetal hemoglobin is known to exist, but recent investigations in this country and in Europe have shown that in certain anemic states the diseased individual may produce normal fetal hemoglobin beyond the age at which it is present in healthy individuals.

The available evidence indicates that an individual inherits a genetically controlled mechanism for the synthesis of hemoglobin from each of his parents. The great majority of individuals have inherited a normal mechanism from each parent, and their erythrocytes contain only normal adult hemoglobin except in the first few months of postnatal life, when fetal hemoglobin is also present. Whenever an abnormal adult hemoglobin is present in an individual, investigation of his parents has demonstrated the presence of the same abnormal form in one or both of them. Matings of two individuals who possess different abnormal adult hemoglobin may result in children who have either or both the abnormal forms. On the other hand, many individuals with chronic, inherited anemias have fetal hemoglobin in addition to one or two of the adult hemoglobins, but their parents have no fetal hemoglobin. The hypothesis has been advanced that the production of fetal hemoglobin beyond early postnatal life may represent a compensatory response to the anemic state.

Among individuals who have the sickle cell trait—i.e., those whose erythrocytes contain both normal adult and sickle cell hemoglobins—a wide variation in the ratio of concentrations of the two forms has been observed. The results of familial studies of this ratio are consistent with a hypothesis that different normal alleles may exist in the human population which control the production of normal hemoglobin at distinctive rates.

Simple, rapid tests for the detection of the different normal and abnormal hemoglobins and their mixtures are needed, both for chemical and genetic studies. Fetal hemoglobin is most readily differentiated from all the adult hemoglobins by its high resistance to denaturation in aqueous alkaline solutions. The presence of sickle cell hemoglobin is indicated by the sickling of erythrocytes upon deoxygenation. Recent investigations here have demonstrated the usefulness of solubility determinations in the detection of the second abnormal hemoglobin.

The study of abnormal hemoglobins undoubtedly will continue to be a fruitful field for collaboration among chemists, geneticists, and hematologists. It has not been feasible in this brief report of recent work in these laboratories to acknowledge the contributions of the many laboratories elsewhere that are engaged in human hemoglobin studies.

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