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Further observations on the Birmingham chimaera

Summary. The appropriate ABH-gene specified glycosyltransferases in the plasma of the Birmingham chimaera were estimated. These observations and the demonstration of A₁Le^b blood group specific glycosphingolipid in the plasma indicate that the minority population of red blood cells probably represents the true blood groups of the patient.

We recently reported (Battey *et al*, 1974) a human female chimaera with two red cell populations and an overwhelming preponderance of lymphocytes which were of the normal male karyotype 46,XY. We have further investigated this patient in the light of new knowledge.

Case report

Blood group gene products in plasma

The patient has a mixture of about 93% O and 7% A₁ red cells. We, therefore, investigated the patient's plasma for A- and H-gene specified transferases, with the undermentioned results:

α-N-acetylgalactosaminyltransferase (the primary product of the blood group A gene) activity at pH 6	28%
α-2'-fucosyltransferase (the primary product of the blood group H gene) activity at pH 7.2	11%

The percentages represent the amount of radioactivity transferred to a low molecular weight acceptor from UDP-[¹⁴C]-N-acetylgalactosamine and GPD-[¹⁴C]-fucose. A normal A₁ control plasma gave 29% incorporation when tested under the same conditions with UDP-[¹⁴C]-N-acetylgalactosamine. The 2'-fucosyltransferase activity fell within the range expected for an A₁, and was rather high for an O donor. A few O sera

do have activities as high as the figure given above; we find, however, that the average for A donors is higher than for O or B donors (M. A. Chester and W. M. Watkins, unpublished observations). It can, therefore, be claimed that the patient behaves, as far as her transferases are concerned, like a normal A₁ person.

A₁Le^b blood group specific substance

The hybrid A₁Le^b blood group specific substance is a glycosphingolipid present in the plasma of a person who has inherited the A₁, Le, H, and Se genes (Swanson *et al*, 1971; Tilley *et al*, 1975). The A₁Le^b substance coats red cells in the same way as ordinary Le^a and Le^b substances.

Red cells coated with A₁Le^b are agglutinated by an antibody anti-A₁Le^b which does not agglutinate cells coated with either A₁ or Le^b alone (Seaman, Chalmers, and Franks, 1968; Crookston, Tilley, and Crookston, 1970; Gundolf, 1973).

In twin or bone-marrow transplantation chimaeras, A₁Le^b substance coats the subject's true red cells as well as those derived from grafted bone-marrow (Crookston *et al*, 1970; Swanson *et al*, 1971; Wrobel *et al*, 1974).

The red blood cells of our patient were tested with an anti-A₁Le^b serum kindly provided, through Dr K. L. G. Goldsmith, by Dr Carolyn Giles, who had obtained it from Mrs Marie Crookston. All the red cells were agglutinated by this reagent; this showed that her O red cell population was also 'stamped' with her true genetic marker, A₁Le^b. Tests with a potent anti-A also showed that her O cells were coated with A-substance.

Discussion

Although our patient was said not to be a twin, her twin may have been aborted or assimilated. We were unable to obtain firm evidence that dispermy was responsible. If she is really a twin (and we suspect she is), the true blood groups of our patient are those represented by her minority red cell population, as indeed her true sex is that represented by her minority lymphocyte population (46,XX). Similar observations have been made by Wrobel *et al* (1974). The presence of normal amounts of A-gene transferase and of A₁Le^b blood group specific substance in our patient's plasma does not necessarily indicate that she is really a twin. A final opinion must await the results of similar studies in dispermic chimaeras. If she is really a dispermic chimaera, she would of course have two 'true' red cell populations.

In our patient and in other chimaeras, there is much disproportion between the relatively small numbers of red cells which constitute the minority population and the normal levels of the corresponding serum transferase. It is, therefore, highly likely that a large proportion of the ABH-blood group gene specified transferases in plasma are derived from sources other than the bone-marrow.

Furthermore, it is also obvious, from the presence of a population of circulating red cells (group O in our patient) which are not modified by transferase present in plasma (A-transferase in our patient), that the final step in the formation of ABH-active sites on the red cell surface does not occur in the external environment of the cells (Race and Watkins, 1972), and is therefore mediated in the bone-marrow by a process yet to be elucidated.

We gratefully acknowledge the keen interest and valuable advice of Dr Ruth Sanger and Mrs Marie Crookston.

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by endocrine investigation and a testicular biopsy) with anosmia, a number of other unusual features are present including gynaecomastia, agenesis of the anterior brachial muscles, some dental abnormalities, and dyschromatopsia. The karyotype, studied on peripheral lymphocytes, shows, in the proband as well as in his mother, the presence in all mitoses of an extra small metacentric chromosome; its derivation is uncertain.

The association of anosmia with hypogonadotrophic hypogonadism is a rare, but now well-recognized condition, also known as Kallmann's syndrome (Kallmann *et al*, 1944) or olfactory-genital dysplasia (de Morsier, 1954). The condition appears to be heterogeneous, both because of the different patterns of inheritance, and also with respect to response to clomiphene. The syndrome has been described in both sexes, and, as several members of a kinship can be affected, it has been suggested that it is genetically determined. However, the mode of inheritance is still uncertain; in fact, behaviour consistent with X-linked dominant inheritance, X-linked recessive inheritance, and autosomal dominant inheritance have all been reported (McKusick, 1971). Santen and Paulsen (1973) reported a clinical study of six families which suggests an autosomal dominant pattern of inheritance with variability in expressivity, but the authors did not exclude a genetic heterogeneity.

Whereas most investigators report no response to short- or long-term administration of clomiphene in Kallmann's syndrome, Hamilton *et al* (1973) obtained a different response according to the severity of anosmia: in Type I anosmia (no response to vapours at the primary olfactory area) clomiphene was ineffective, whereas some subjects with Type II anosmia (subnormal response to vapours at the primary olfactory area; olfactory responses can be made in an attenuated manner) responded adequately to prolonged treatment. In the view of the authors, the two types of anosmia imply a more or less severe defect of the olfactory lobe; this, in turn, is associated with a different degree of 'maturation' of the hypothalamus, which could explain the positive or negative response to clomiphene. No chromosomal abnormality has so far been described in this syndrome. We therefore report a case where, in addition to the typical features of hypogonadotrophic hypogonadism with anosmia, other abnormalities and an extra small chromosome have been observed; the latter was also present in the maternal karyotype.

A case of hypogonadotrophic hypogonadism with anosmia (Kallmann's syndrome) in a male, with familial incidence of a small metacentric chromosome (47,XY,mat ?+)

Summary. A case of Kallmann's syndrome in a male is reported. Besides the classical picture of hypogonadotrophic hypogonadism (demonstrated both