

*AN XX/XY HUMAN HERMAPHRODITE
RESULTING FROM DOUBLE FERTILIZATION**

BY STANLEY M. GARTLER, SORRELL H. WAXMAN, AND ELOISE GIBLETT†

DEPARTMENTS OF MEDICINE, GENETICS AND PEDIATRICS, UNIVERSITY OF WASHINGTON AND THE
KING COUNTY CENTRAL BLOOD BANK, SEATTLE, WASHINGTON

Communicated by Curt Stern, January 17, 1962

Genetic mosaicism may result from one or more post-zygotic mitotic irregularities. Mosaicism may also occur when an organism derives its heredity from more than a single sperm and/or egg nucleus. For the latter type of mosaicism, several different mechanisms have been described. Thus, there may be single or double fertilization of a binucleate egg, known to be responsible for the formation of insect gynandromorphs,^{1, 2} or possibly polyspermy, as has been suggested for color mosaicism in pigeons.³ Alternatively, two fertilized eggs or early embryos may fuse to form a single organism, as has been demonstrated experimentally in the sea urchin⁴ and Triton⁵ and claimed in the rat.⁶ Finally, transplantation of tissue between embryos can occur such as is known to take place in the mammalian twin blood group chimeras.⁷⁻¹⁰ Only this latter mechanism is known to occur in human subjects, the transplantation being apparently limited to blood-forming tissue. We have recently studied a human hermaphrodite who exhibits mosaicism for all tissues sampled and who probably represents an example of double fertilization. This individual is the subject of the present report.

The patient, a white girl, was first seen at two years of age for surgical correction of an enlarged clitoris. It was observed at this time that she had heterochromia simplex, the left eye being hazel and the right eye brown. No other obvious asymmetries were noted. Cytological examination of a peripheral leucocyte culture performed by the method of Moorhead, Nowell, Mellman, Battips, and Hungerford¹¹ revealed a normal chromosome count of 46 in the 33 cells examined. However on karyotyping, two classes of cells were found, seven cells having XX and six cells having XY chromosomal complements (Fig. 1). A second culture confirmed the presence of these two types of cells.

At laparotomy, a normal ovary was found on the left side and an ovotestis on the right side (clinical details and preliminary cytological results have been published elsewhere).¹² At this time, biopsies were taken from the skin on both sides of the abdomen, from the testicular and ovarian parts of the ovotestis, from the clitoris, and from the normal ovary. The biopsies were cultured, and cytological observations were made on the resulting cell lines (Table 1). The results demonstrate that: (1) in addition to blood, other tissues are also XX/XY mosaics, and (2) there is some topographical segregation of the various cell types.

Paralleling this cytological investigation were blood and serum group studies on the propositus and her family. The blood and serum studies included the ABO, MNSs, P, Rh, Kell, Duffy, Lewis, Lutheran, Kidd, secretor, Hp, Tf, and Gm groups. Pertinent results are shown in Table 2. The propositus has two red blood cell populations in approximately equal numbers as indicated by differences in two autosomal genes which are known to show independent assortment.¹³ One population is MS^u/MS, CDe/cDE (R¹/R²), while the other population is MS^u/Ns,

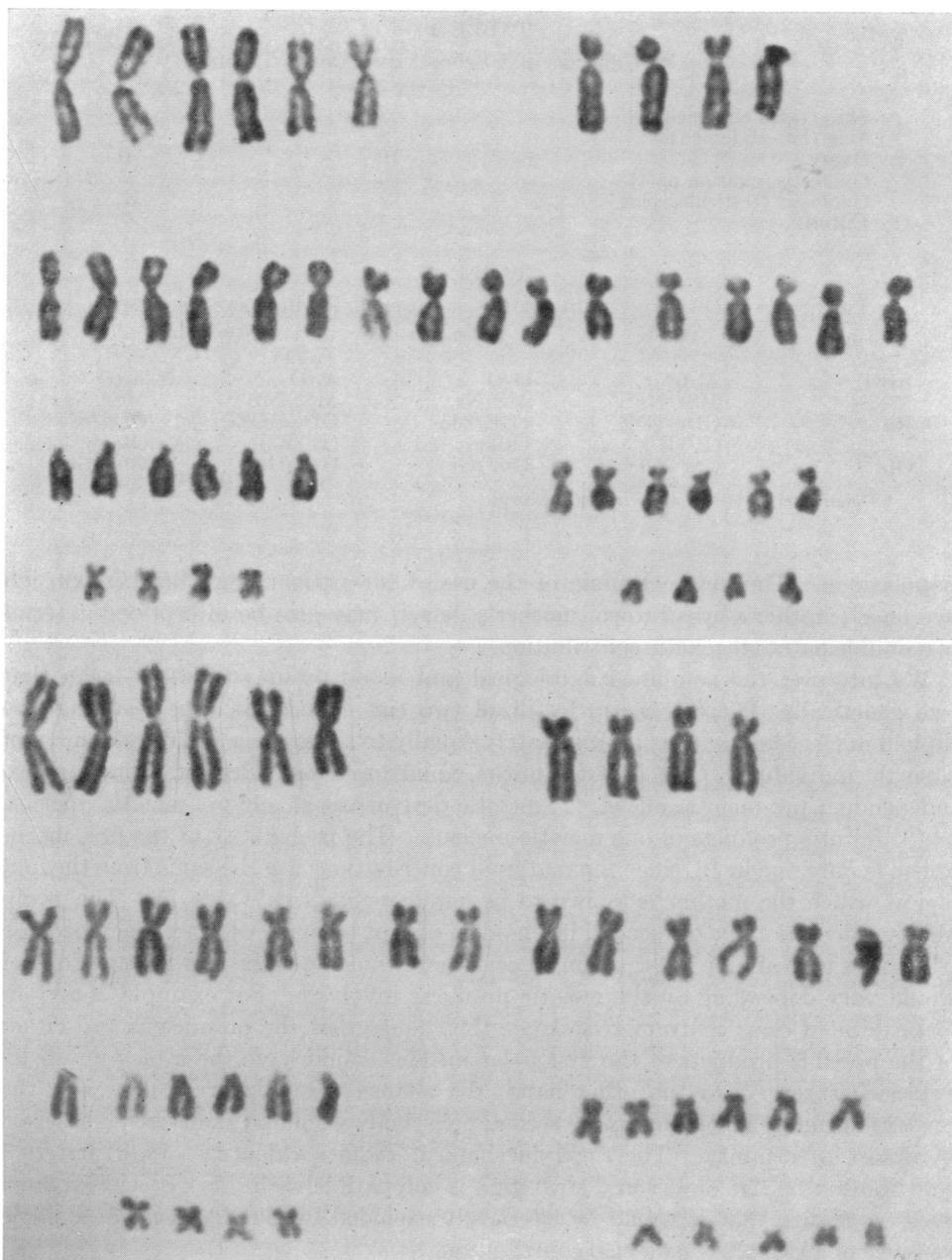


FIG. 1. Karyotypes of the two kinds of cells found in the patient: Upper XX, lower XY.

CDe/cde (R^1/r). (More detailed observations on the blood and serum groups of the entire family will be reported elsewhere.) From the pedigree, it can be determined that the father (MS/Ns, cDE/cde or R^2/r) contributed both his genes at the MNSs locus and both his genes at the Rh locus to this child. On the other hand, the maternal Rh and MNSs contributions are the same in both red blood cell

TABLE 1
RESULTS OF CHROMOSOMAL STUDIES ON VARIOUS TISSUES

Tissue	XX cells	XY cells
Skin (right abdomen)	3	10
Skin (left abdomen)	8	1
Ovary	10	0
Ovotestis (ovarian part)	9	2
Ovotestis (testicular part)	2	12
Clitoris	4	7

TABLE 2
PERTINENT BLOOD AND SERUM GROUPS OF MOTHER, FATHER, AND PROPOSITUS

Group	Mother	Father	Propositus	
			(1)	(2)
ABO	A ₁ /O*	O/O	A ₁ /O	A ₁ /O
MNSs	MS ^u /N _s *	MS/N _s	MS ^u /MS	MS ^u /N _s
Rh	CDe/cDE (R ¹ /R ²)	cDE/cde (R ² /r)	CDe/dDE (R ¹ /R ²)	CDe/cde (R ¹ /r)
Gm	Gm ^a /Gm ^b	Gm ^b /Gm ^b	Gm ^b /Gm ^b	Gm ^b /Gm ^b

* Determined by testing other family members.

populations. The heterochromia of the iris of the patient (right eye brown, left eye hazel; father's eyes brown, mother's, hazel) may also be interpreted in terms of a double paternal genetic contribution.

We interpret the combined cytological and blood group studies to mean that two genetically different sperm fertilized two egg nuclei, with the resulting two diploid nuclei contributing approximately equally to the growth and development of a single individual. The two-egg nuclei could have been derived from (1) two independent pre-meiotic nuclei, (2) meiotic derivatives of one pre-meiotic nucleus, or (3) mitotic products of one meiotic nucleus. The probability of the first mechanism is only one in 16, since the maternal contributions are the same from the four loci at which the mother is known to be heterozygous (see Table 2). The probability calculation for the second mechanism cannot be made with accuracy because it requires unavailable information on centromere linkage of the four loci and further would vary depending on the meiotic products involved. For example, if all four loci exhibited close centromere linkage, the chance that the pronucleus and either of the possible products of the first polar nucleus would have the same four alleles approaches zero. On the other hand, the chance that the pronucleus and the nucleus normally belonging to the second polar body would be identical at these loci is almost a certainty. The third mechanism requires identity of all maternal contributions. The observed distribution is compatible with this hypothesis; however, we realize that it would be effectively excluded by the discovery of a single instance of a two-allele maternal contribution.

In view of these uncertainties, we prefer to keep the question of the exact nature of the maternal contribution open, hoping that the eventual discovery of similar cases or newer techniques may provide more definitive information.

Summary.—Cytological and blood group studies on a human hermaphrodite with widespread mosaicism are reported, and possible explanations for the data are considered. It is concluded that the mosaicism found in this subject can best be interpreted as resulting from double fertilization.

The authors are indebted to Mrs. J. H. Crookston for quantitation of the two red-cell populations, to Dr. A. G. Steinberg for determining the Gm groups, and to Prof. C. Stern for critical review of the manuscript.

* Supported in part by grants from the National Science Foundation (G-14825) and the National Institutes of Health (2A-51901 and H-5780).

† With the technical assistance of Barbara Burt.

¹ Goldschmidt, R., and K. Katsuki, *Biol. Zentralbl.*, **51**, 58-74 (1931).

² Whiting, P. W., and A. R. Whiting, *Biol. Bull.*, **52**, 89-117 (1927).

³ Hollander, W. F., *J. Hered.*, **40**, 271-277 (1949).

⁴ Bierens de Haan, J. A., *Roux' Arch. Entw. Mech.*, **37**, 420-432 (1913).

⁵ Mangold, O., and F. Seidel, *Roux' Arch. Entw. Mech.*, **111**, 593-665 (1927).

⁶ Nicholas, J. S., and B. V. Hall, *J. Exptl. Zool.*, **90**, 441-459 (1942).

⁷ Owen, R. D., *Science*, **102**, 400-401 (1945).

⁸ Dunsford, I., C. C. Bowley, A. M. Hutchison, J. S. Thompson, R. Sanger, and R. R. Race, *Brit. Med. J.*, **2**, 81 (1953).

⁹ Booth, P. B., G. Plaut, J. D. James, E. W. Ikin, P. Moores, R. Sanger, and R. R. Race, *Brit. Med. J.*, **1**, 1456-1458 (1957).

¹⁰ Nicholas, J. W., W. J. Jenkins, and W. L. Marsh, *Brit. Med. J.*, **1**, 1458-1460 (1957).

¹¹ Moorhead, P. S., P. C. Nowell, W. J. Mellman, D. M. Battips, and D. A. Hungerford, *Exptl. Cell Research*, **20**, 613-616 (1960).

¹² Waxman, S. H., S. M. Gartler, and V. C. Kelley, *J. Pediat.* (in press).

¹³ Race, R. R., and R. Sanger, *Blood Groups in Man*, 3rd ed. (Oxford: Blackwell Scientific Publications, 1958).

DUAL EFFECTS OF STRUCTURAL GENES IN *ESCHERICHIA COLI**

BY NANCY LEE† AND ELLIS ENGLEBERG

DEPARTMENT OF BIOLOGICAL SCIENCES, UNIVERSITY OF PITTSBURGH

Communicated by Milislav Demerec, January 3, 1962

L-arabinose isomerase, L-ribulokinase, and L-ribulose 5-phosphate 4-epimerase are the first three enzymes involved in the sequential breakdown of L-arabinose by *Escherichia coli*, strain B/r.^{1, 2} Twenty-two L-arabinose negative mutants have been isolated and shown to be closely linked in a linear order between the markers threonine (thr) and leucine (leu) and divisible into four functional and genetically discrete groups or genes (A, B, C, D).¹⁻⁴ Gene A mutants are deficient in the enzyme L-arabinose isomerase and have higher L-ribulokinase activity than the wild type. Gene B mutants are deficient in L-ribulokinase activity and have either increased or decreased inducible levels of both L-arabinose isomerase and L-ribulose 5-phosphate 4-epimerase activities. Gene C mutants are deficient in all three enzymes. Gene D mutants are deficient in L-ribulose 5-phosphate 4-epimerase.^{1, 2} (see Fig. 1). Since L-arabinose is apparently the inducer of all three enzymes, it has been proposed that this entire arabinose region probably represents an operon,^{1, 2, 5, 6} with the C gene the operator gene,¹ and genes A, B, and D the structural genes for L-arabinose isomerase,¹ L-ribulokinase,¹ and L-ribulose 5-phosphate 4-epimerase,² respectively.

This paper will present evidence that the A and B genes are indeed the structural