How many am I – How much is me? Reflections on the leaky boundaries of individuals and its consequences in biology and medicine

Oskar A. Haas, St. Anna Children's Hospital and medgen.at GmbH, Vienna, Austria

Natural Chimerism


Richard David
Precht
WER
BIN ICH
und wenn ja, wie viele?
Eine philo
sophische Reise
GOLDMANN

Definitions

- **Mosaic**
  - two populations of cells with different genotypes in one individual that developed from a single fertilized egg (subset of cells with a mutation)
- **Hybrid**
  - a cross (mix of chromosomes) between parents of two different (sub)species (horse & donkey > mule & hinny)
- **Chimera**
  - fusion of cells from different individuals of same or different species that will develop side by side and form a single organism

Artificial / Iatrogenic Chimera

- Intra-species
  - bone marrow transplantation
  - stem cell transplantation
  - organ transplantation
- Inter-species
  - mouse-human
  - sheep-goat
  - etc

Chimera

(*Χίμαιρα, Chímaira*, "the goat")

… originally a creature of the Greek mythology

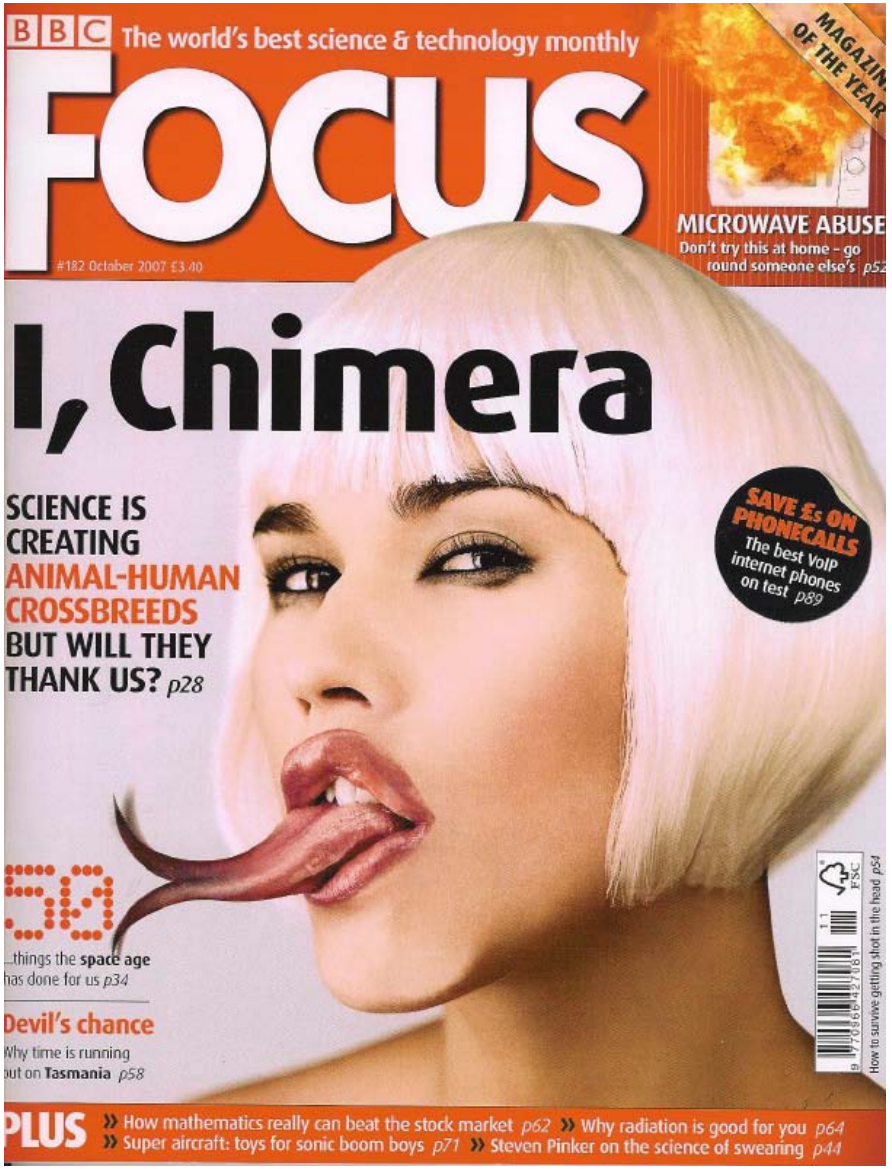
http://en.wikipedia.org/wiki/Chimaera_(mythology)

Gérard de Nerval

CHIMÉRY

LES CHIMÈRES

TRIGON



Typhon

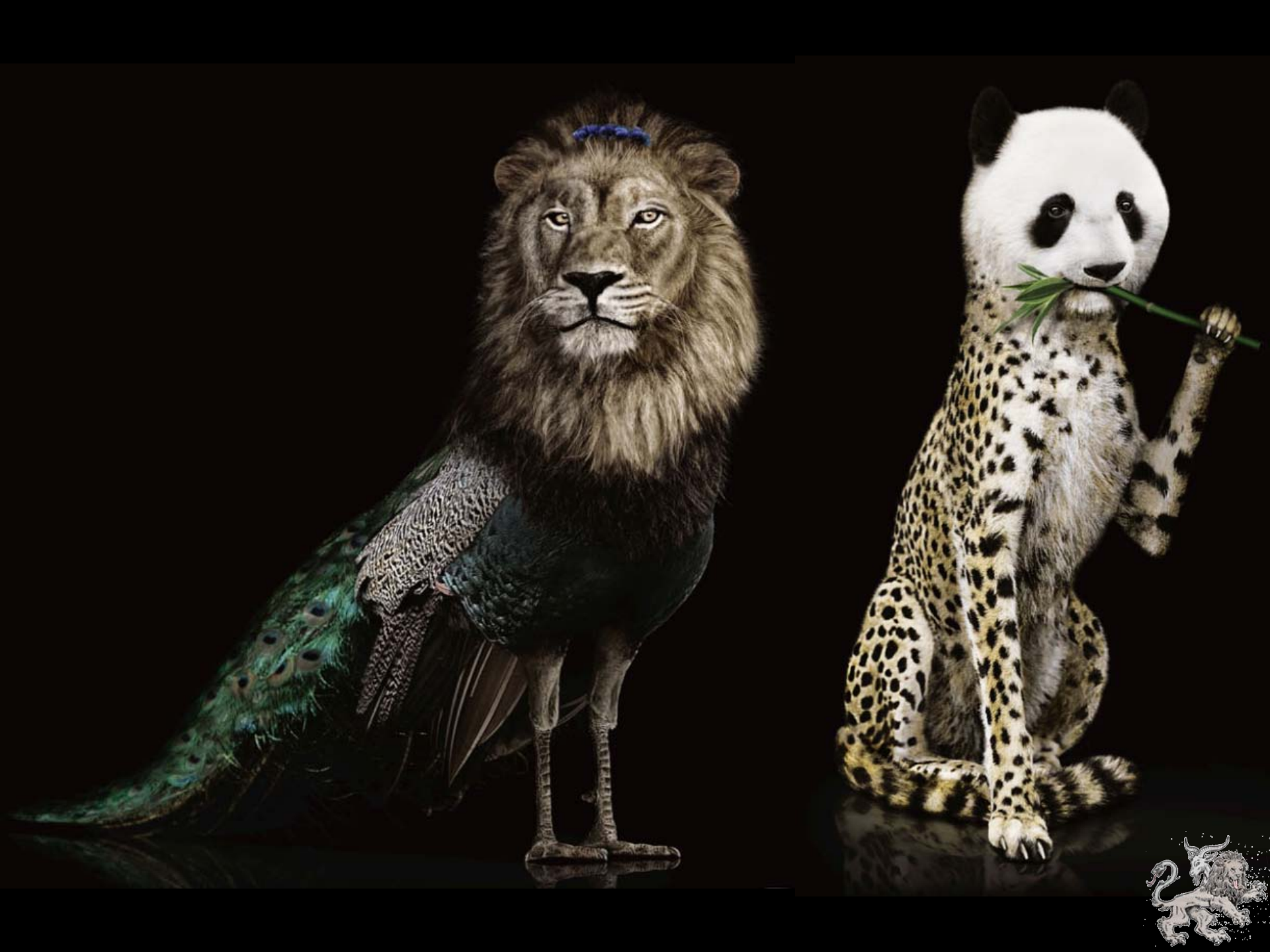
Echidna

Cerberus

Chimera

Hydra

Sphinx

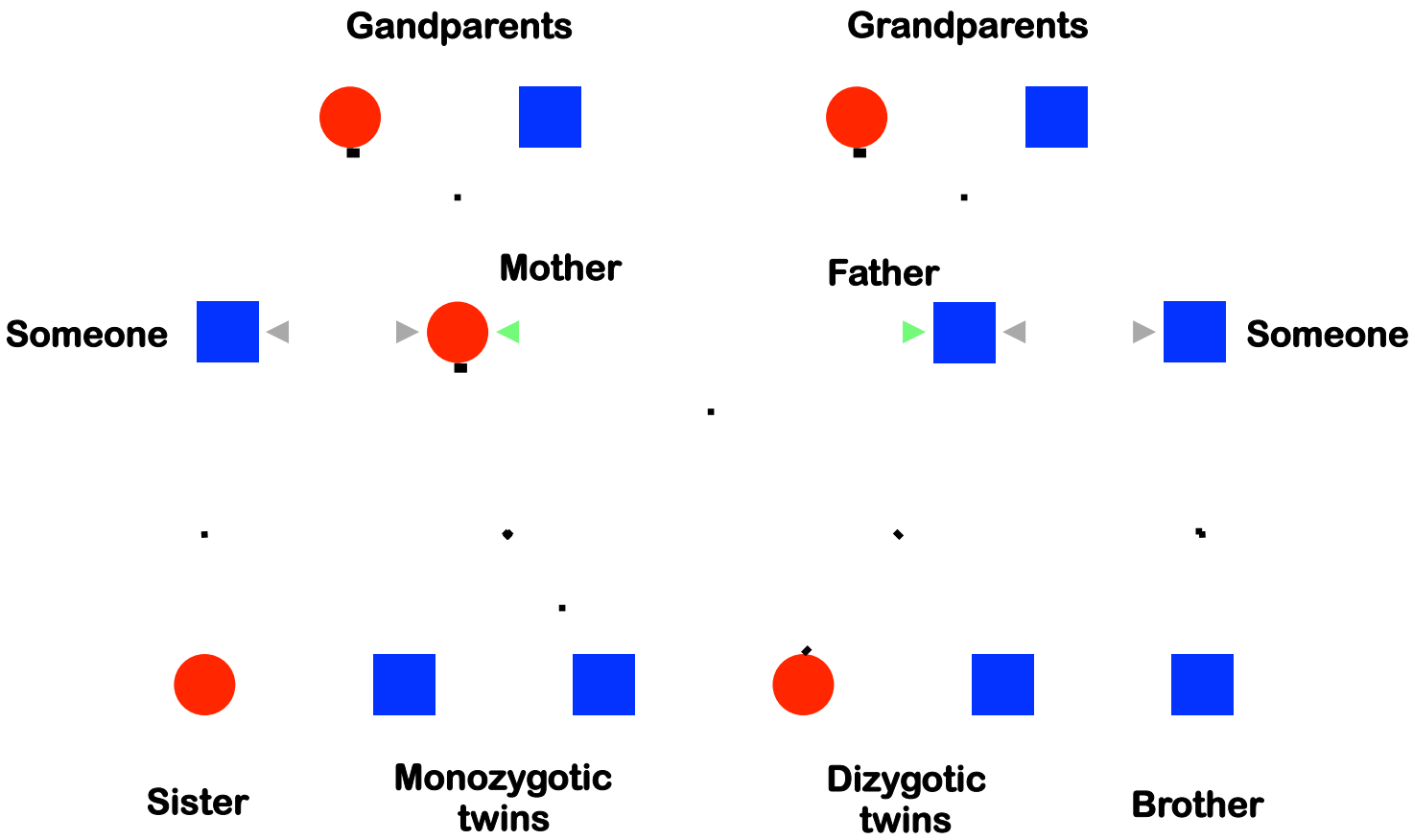


?

Natural Chimera

- Fetal-maternal chimera
- Blood sharing and twin chimera
- Whole body or dispermic chimera
- Tumor chimera
- Germ cell chimera

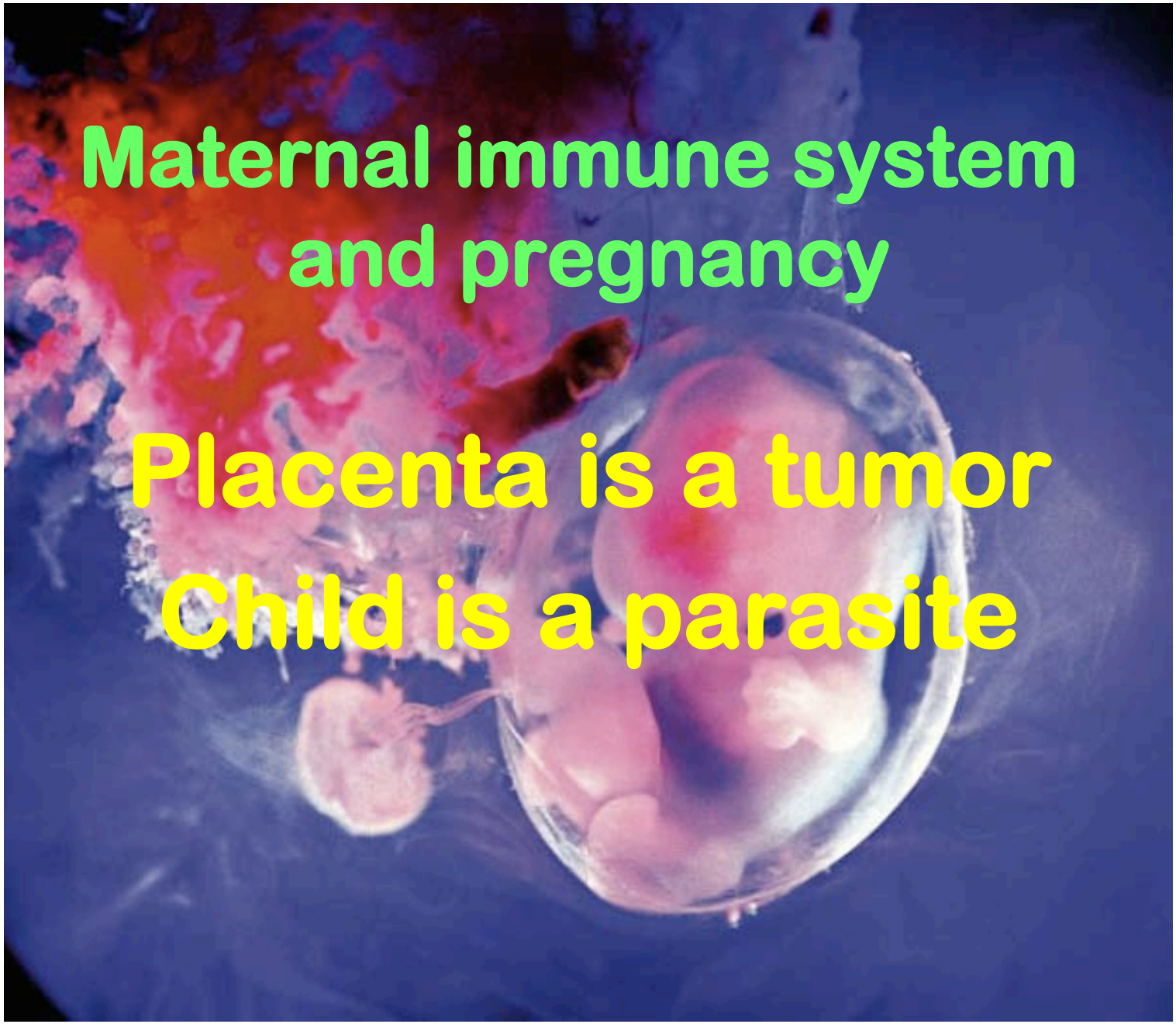
Rinkevich, Human Immunol 62:651 (2001)


Gandparents
Grandparents
Mother
Father
Someone
Someone
Sister
Monozygotic twins
Dizygotic twins
Brother

Natural Chimera

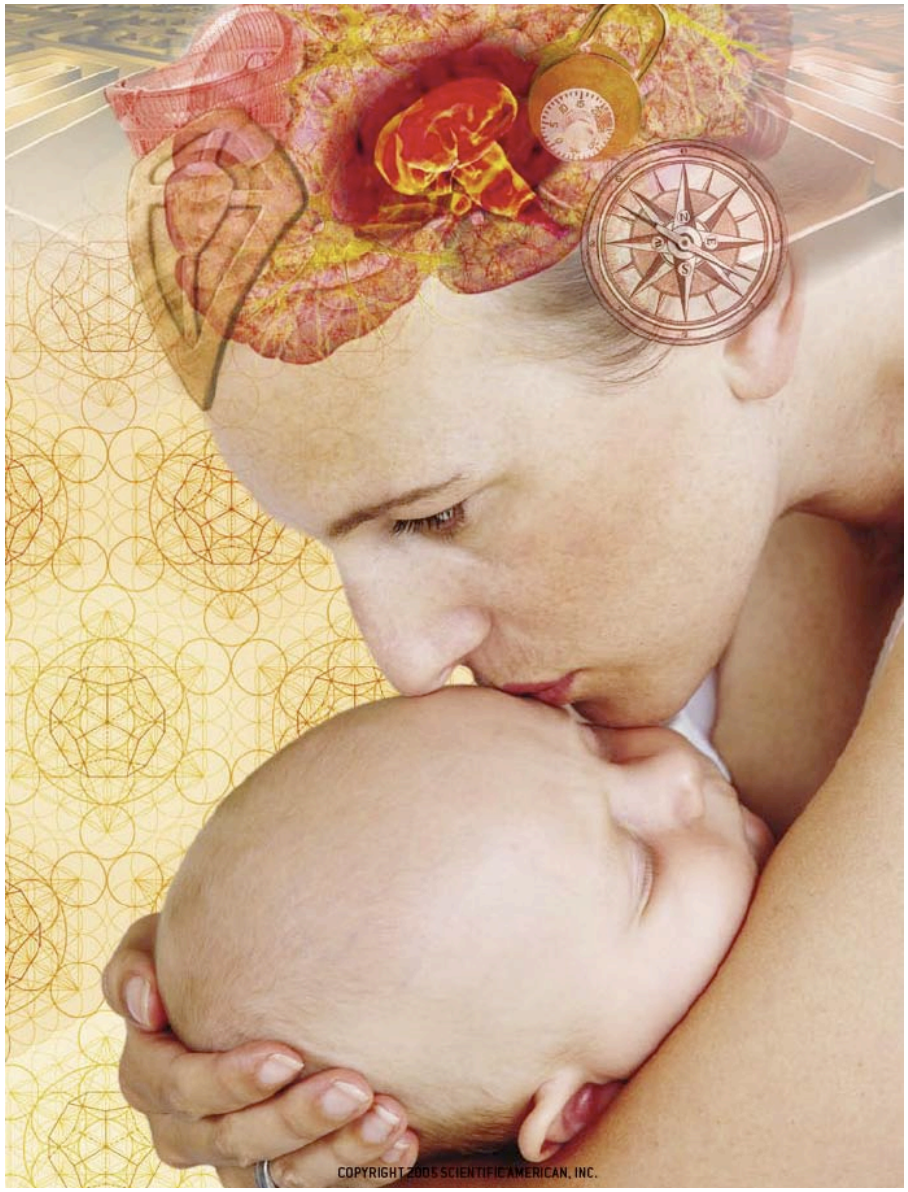
- **Fetal-maternal chimera**
- Blood sharing and twin chimera
- Whole body or dispermic chimera
- Tumor chimera
- Germ cell chimera

Rinkevich, Human Immunol 62:651 (2001)


Maternal immune system
and pregnancy
Placenta is a tumor
Child is a parasite

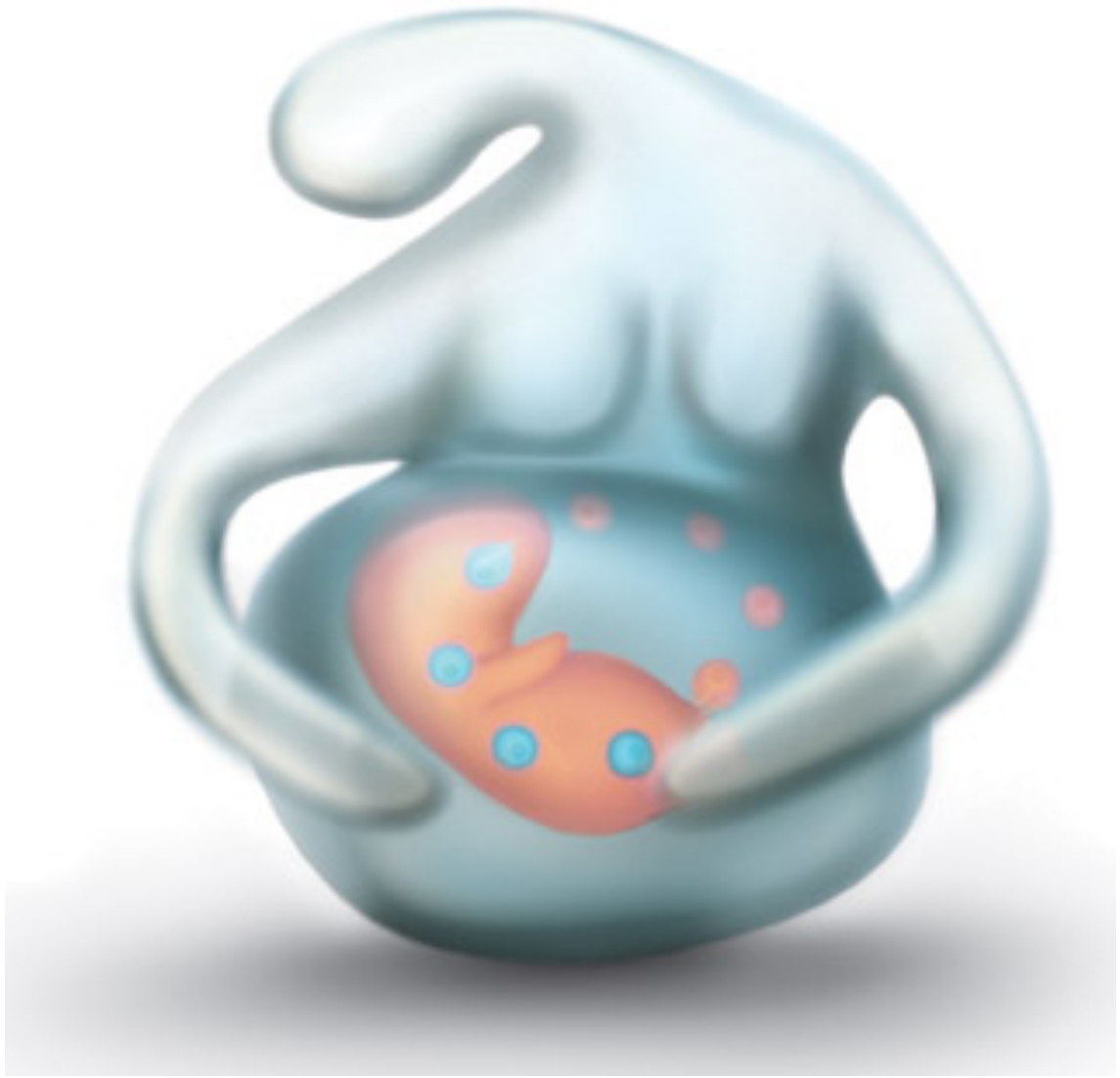
THE MATERNAL BRAIN

Pregnancy and motherhood change the structure of the female mammal's brain, making mothers attentive to their young and better at caring for them



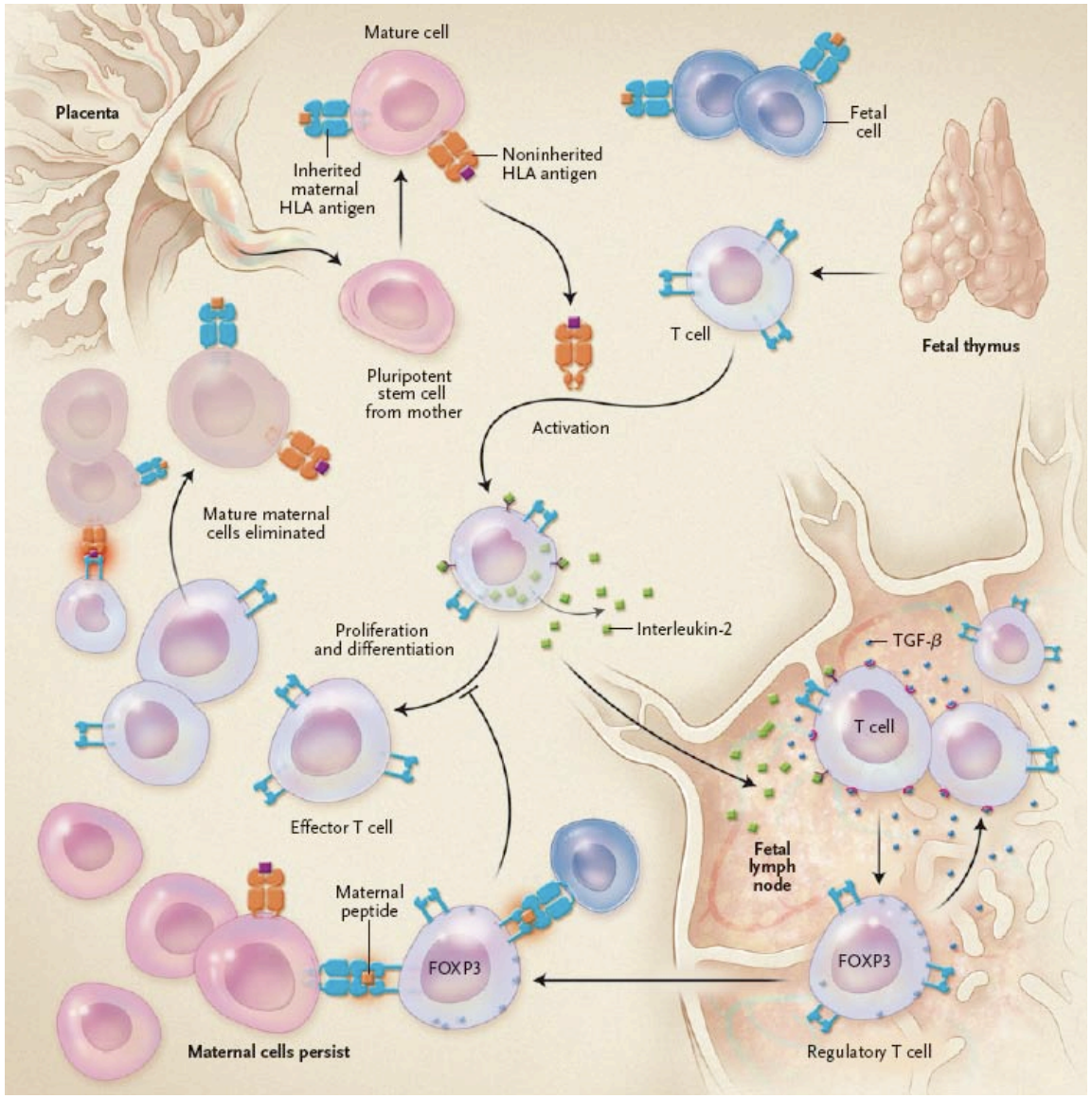
Mother rats nearly always beat virgins in competitions that involve multitasking.

Kinsley & Lambert, Scientific American p.72 (01/2006)



Nelson, Scientific American p.72 (02/2008)

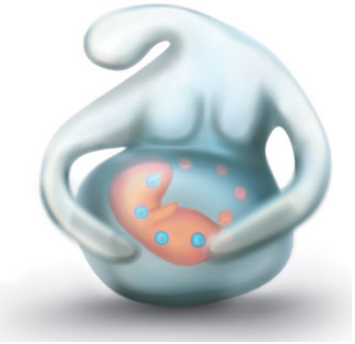
Maternal Instruction to Fetal Cells
Self-defense versus immune tolerance

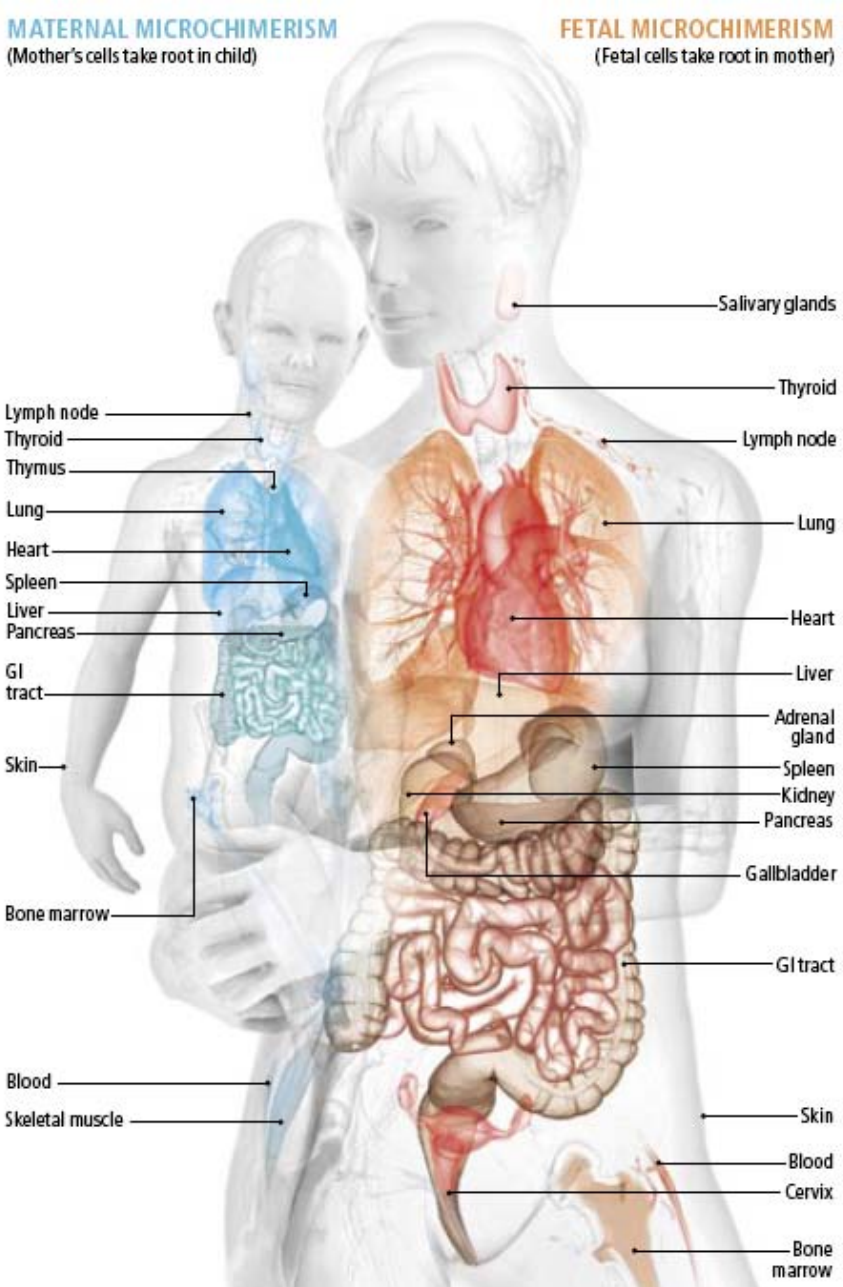


Too much restraint of immunity:
Infection

Too little:
autoimmunity

Mold et al, Science 322:1562 (2008); Burlingham, New Engl J Med 360:1355 (2009)





Nelson, Scientific American p.72 (02/2008)

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 705–708, January 1996
Medical Sciences

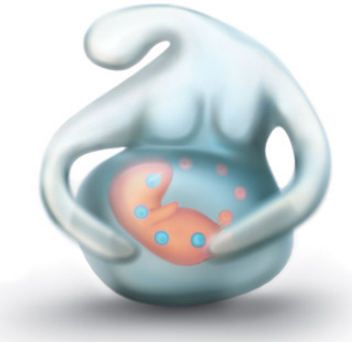
Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum

(pregnancy/chimerism/CD34/CD38)

DIANA W. BIANCHI*†‡, GRETCHEN K. ZICKWOLF*†, GARY J. WEIL*†, SHELLEY SYLVESTER*, AND MARY ANN DEMARIA†

Divisions of *Genetics and Newborn Medicine, Children's Hospital and Harvard Medical School, Boston, MA 02155; and †Departments of Pediatrics, Obstetrics, and Gynecology, New England Medical Center and Tufts University School of Medicine, Boston, MA 02111

Communicated by Leonard A. Herzenberg, Stanford University School of Medicine, Stanford, CA, October 11, 1995
(received for review June 5, 1995)



Fetus-to-mother transfer has been found in:

- Breast cancer
- Cervical cancer
- Multiple sclerosis (immune attack on neurons of central nervous system)
- Preeclampsia (pregnancy-induced hypertensive disorder)
- Polymorphic eruption of pregnancy (inflammatory skin condition)
- Rheumatoid arthritis (immune attack on joints)
- Scleroderma
- Systemic lupus erythematosus (immune attack on multiple organs)
- Thyroid diseases (Hashimoto's, Graves' and other diseases)

Nelson, Scientific American p.72 (02/2008)

Mother-to-child transfer has been found in:

- Biliary atresia (fetal liver disorder)
- Juvenile dermatomyositis (immune attack on skin and muscle)
- Neonatal lupus (immune attack on various tissues in fetus)
- Scleroderma (immune attack that thickens skin and can damage other tissues)
- Type 1 (insulin-dependent) diabetes (immune attack on pancreas)
- Pityriasis lichenoides (inflammatory skin condition)

Nelson, Scientific American p.72 (02/2008)

Multi-lineage potential of fetal cells in maternal tissue: a legacy in reverse

Kiarash Khosrotehrani[1] and Diana W. Bianchi[2,*]

[1]Department of Dermatology, Tenon Hospital and UPRES EA2396, Saint-Antoine School of Medicine, Pierre et Marie Curie (Paris VI) University, 75020 Paris, France
[2]Division of Genetics, Tufts-New England Medical Center, 750 Washington St, Boston, MA 02111, USA
*Author for correspondence (e-mail: dbianchi@tufts-nemc.org)

Journal of Cell Science 118, 1559-1563 Published by The Company of Biologists 2005
doi:10.1242/jcs.02332

Summary

Fetal cells circulate in pregnant women and persist in blood and tissue for decades post-partum. The mother thus becomes chimeric. Factors that may influence such fetal cell microchimerism include histocompatibility, fetal or placental abnormalities, or a reproductive history that includes miscarriage or elective termination. Fetal cell microchimerism is associated with some maternal autoimmune diseases, such as systemic sclerosis. Moreover, a novel population of fetal cells, the pregnancy-associated progenitor cells (PAPCs), appears to differentiate in diseased or injured maternal tissue. The cellular origin of these cells is at present unknown but could be a hematopoietic stem cell, a mesenchymal stem cell, or a novel cell type. Pregnancy therefore results in the acquisition of cells with stem-cell-like properties that may influence maternal health post-partum. Rather than triggering disease, these cells may instead combat it.

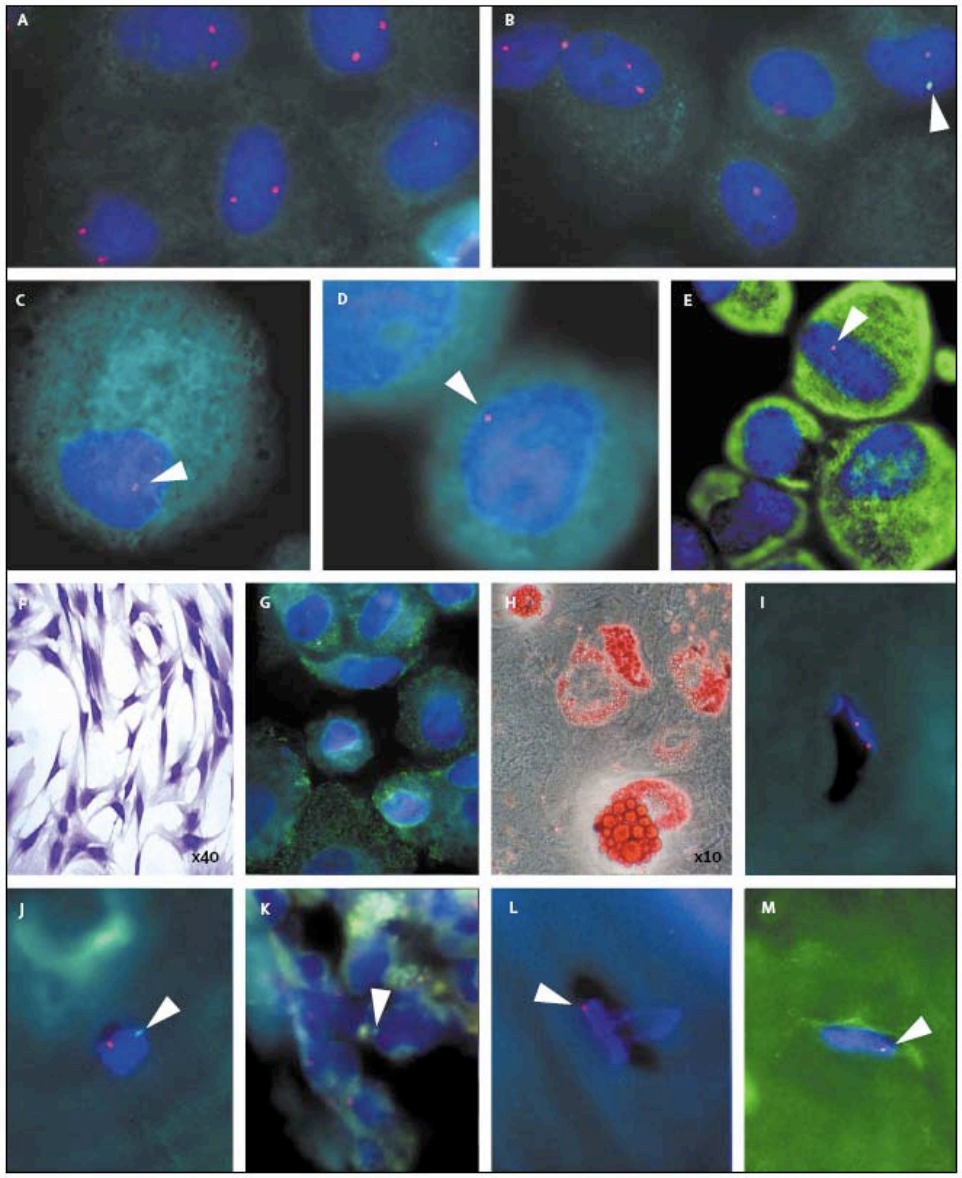
Key words: Stem cells, Pregnancy, Fetus, Fetal cell microchimerism, Pregnancy-associated progenitor cells

Fetal Cells Traffic to Injured Maternal Myocardium and Undergo Cardiac Differentiation

Rina J. Kara, Paola Bolli, Ioannis Karakikes, Iwao Matsunaga, Joseph Tripodi, Omar Tanweer, Perry Altman, Neil S. Shachter, Austin Nakano, Vesna Najfeld and Hina W. Chaudhry

Circ Res. 2012;110:82-93; originally published online November 14, 2011;

Michrochimerism in female BM
13 - 51 years after male pregnancies

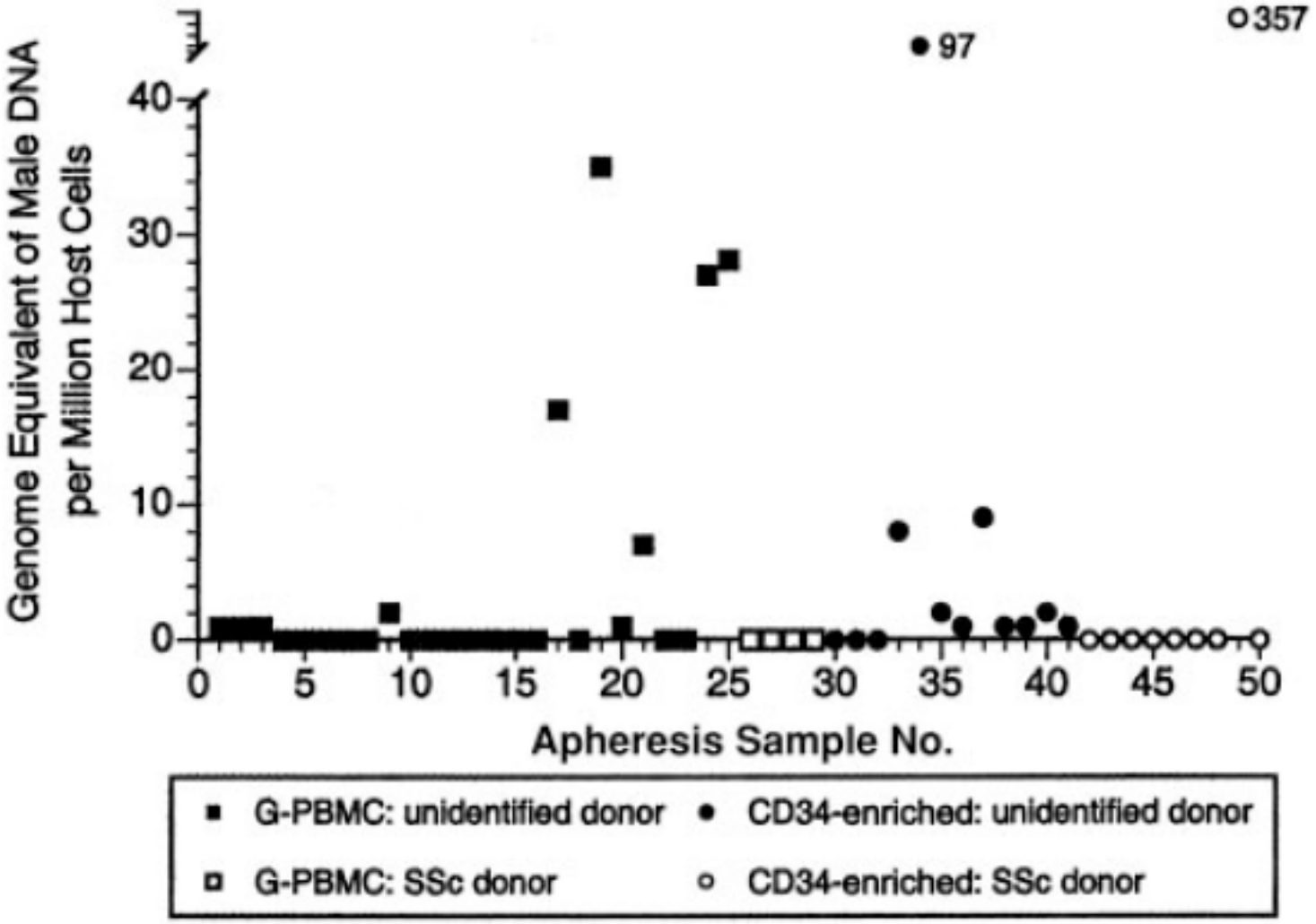


Technical Challenges

- Chimeric cells are rare
- Only male/female cells distinguishable
- FISH only method for identification

O'Donoghue et al, Lancet 364:179 (2004)

Male DNA in 34 % G-PBMC and 48% CD34-enriched apheresis products of 46 female donors



Adams et al, Blood 102:3845 (2003); Adams & Nelson, JAMA 291:1127 (2004)

Long-term feto-maternal microchimerism revisited

Microchimerism and tolerance in hematopoietic stem cell transplantation

Tatsuo Ichinohe
Department of Hematology and Oncology; Graduate School of Medicine; Kyoto University; Kyoto, Japan

Chimerism 1:39 (2010)

Non–T-cell–depleted HLA haploidentical stem cell transplantation in advanced hematologic malignancies based on the feto-maternal michrochimerism

Chihiro Shimazaki, Naoya Ochiai, Ryo Uchida, Akira Okano, Shin-ichi Fuchida, Eishi Ashihara, Tohru Inaba, Naohisa Fujita, Etsuko Maruya, and Masao Nakagawa

Feto-maternal microchimerism suggests that immunologic tolerance exists between mother and fetus. Based on this hypothesis, we performed haploidentical stem cell transplantation (SCT) without T-cell depletion (TCD) in 5 patients with advanced hematologic malignancies. HLA incompatibilities for graft-versus-host disease (GVHD) direction included 3-loci mismatches in 4 patients, and 2-loci mismatches in one patient. Recipient chimeric cells were detected in all patients. The prophylaxis against GVHD was tacrolimus with minidose methotrexate. Engraftment was obtained in all patients. An acute GVHD of less than or equal to grade 2 developed in all patients except one who developed tacrolimus encephalopathy. Two patients died, 1 from fungal pneumonia and 1 from disease progression. The other 3 patients survived, with one patient in complete remission. These observations suggest that haploidentical SCT based on the feto-maternal microchimerism without TCD is possible. (Blood. 2003;101:3334-3336)

Shimazaki et al, Blood 101:3334 (2003)

Fetal Cell Microchimerism and Cancer: A Nexus of Reproduction, Immunology, and Tumor Biology

Lisa R. Kallenbach, Kirby L. Johnson and Diana W. Bianchi

Cancer Res 2011;71:8-12. Published online January 2, 2011.

Indirect evidence that maternal microchimerism in cord blood mediates a graft-versus-leukemia effect in cord blood transplantation

PNAS 109:2509 (2012)

Jon J. van Rood[a,1], Andromachi Scaradavou[b], and Cladd E. Stevens[b,2]

[a]Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands; and [b]National Cord Blood Program, New York Blood Center, New York, NY 11101

blood

2010 116: 2706-2712
Prepublished online July 13, 2010;
doi:10.1182/blood-2010-02-270942

Effect of parity on fetal and maternal microchimerism: interaction of grafts within a host?

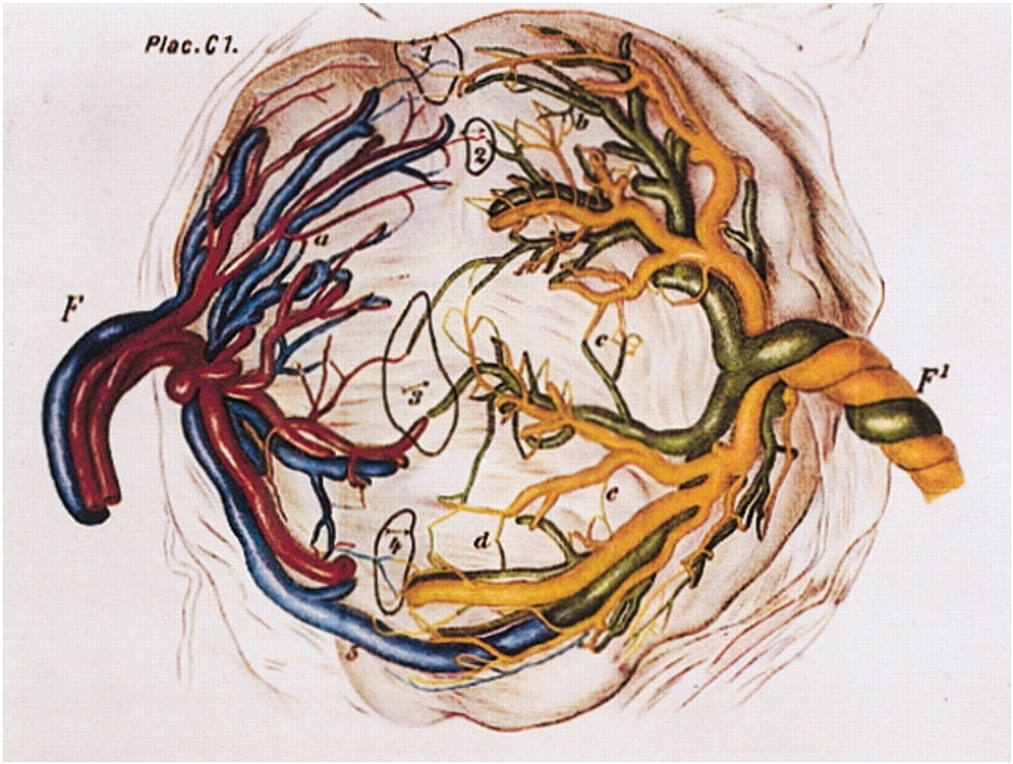
Hilary S. Gammill, Katherine A. Guthrie, Tessa M. Aydelotte, Kristina M. Adams Waldorf and J. Lee Nelson

Natural Chimera

- Fetal-maternal chimera
- **Blood sharing and twin chimera**
- Whole body or dispermic chimera
- Tumor chimera
- Germ cell chimera

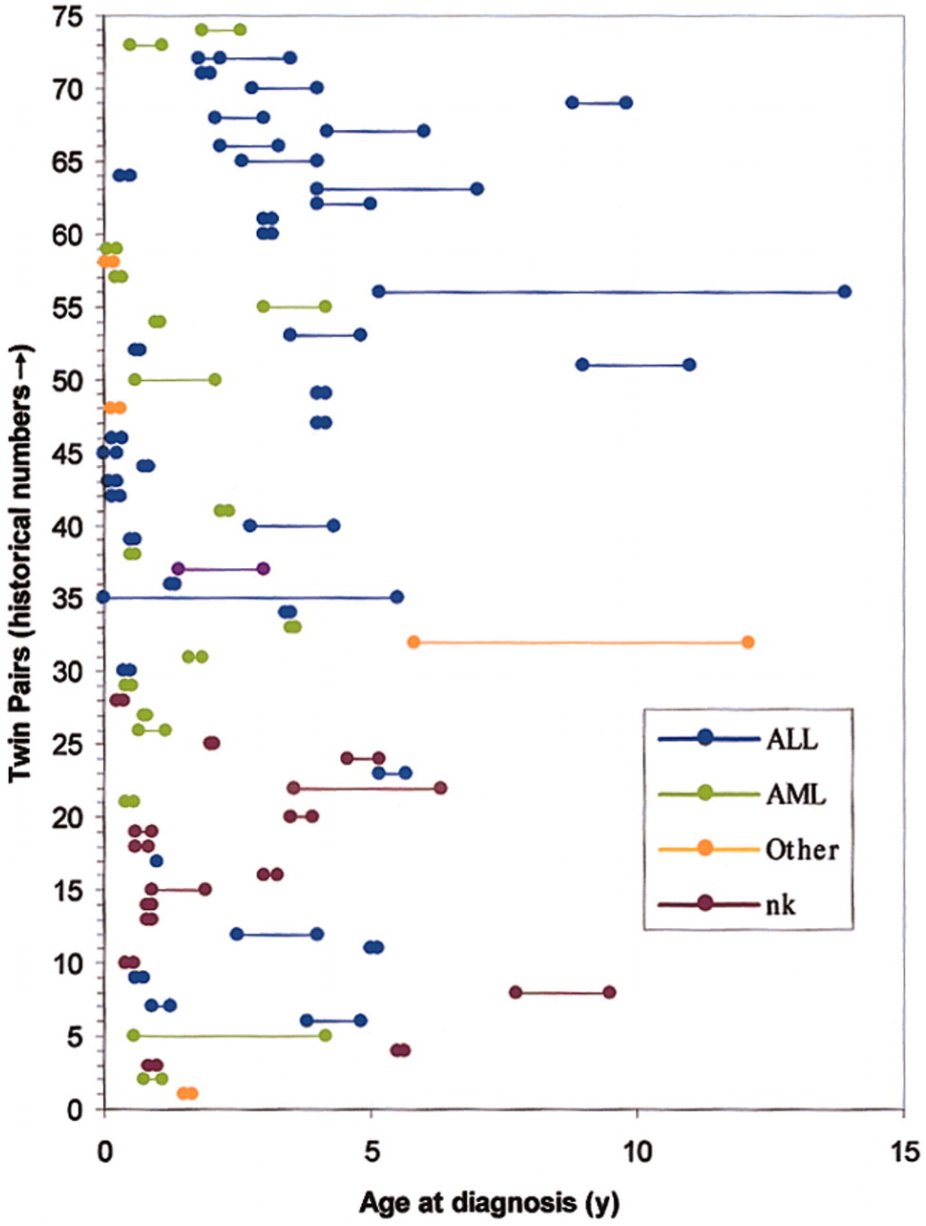
Rinkevich, Human Immunol 62:651 (2001)

de Wikkelkinder (1617)
Children of the Major of Amsterdam



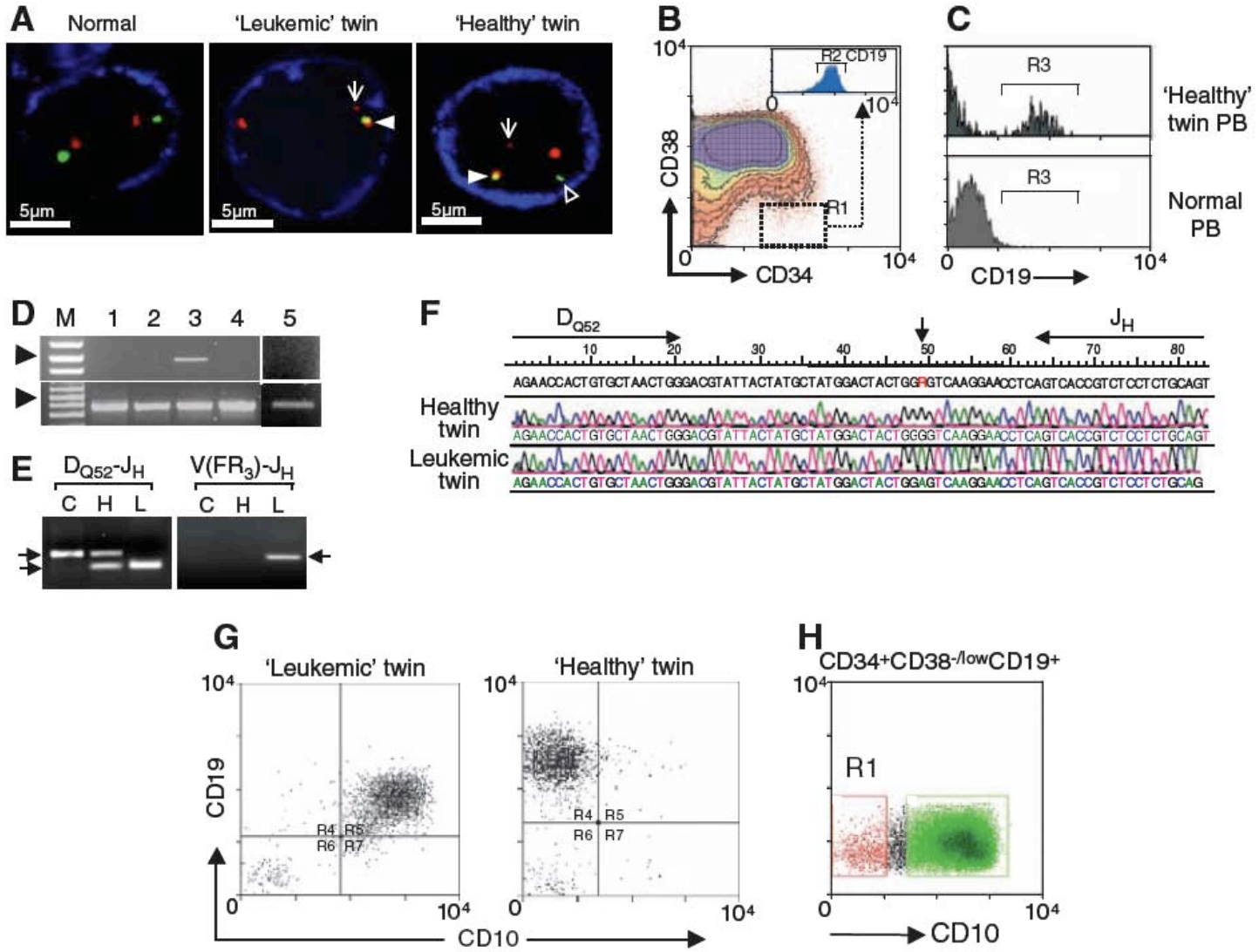
Greaves et al, Blood 102:2321 (2003) Fg 1 & 5

Concordant leukemia in twin children



Greaves et al, Blood 102:2321 (2003)

Initiating and Cancer-Propagating Cells in TEL-AML1-Associated Childhood Leukemia



Dengli Hong et al, Science 329:336 (2008)

Natural Chimera

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- Blood sharing and twin chimera
- **Whole body or dispermic chimera**
- Tumor chimera
- Germ cell chimera

Rinkevich, Human Immunol 62:651 (2001)

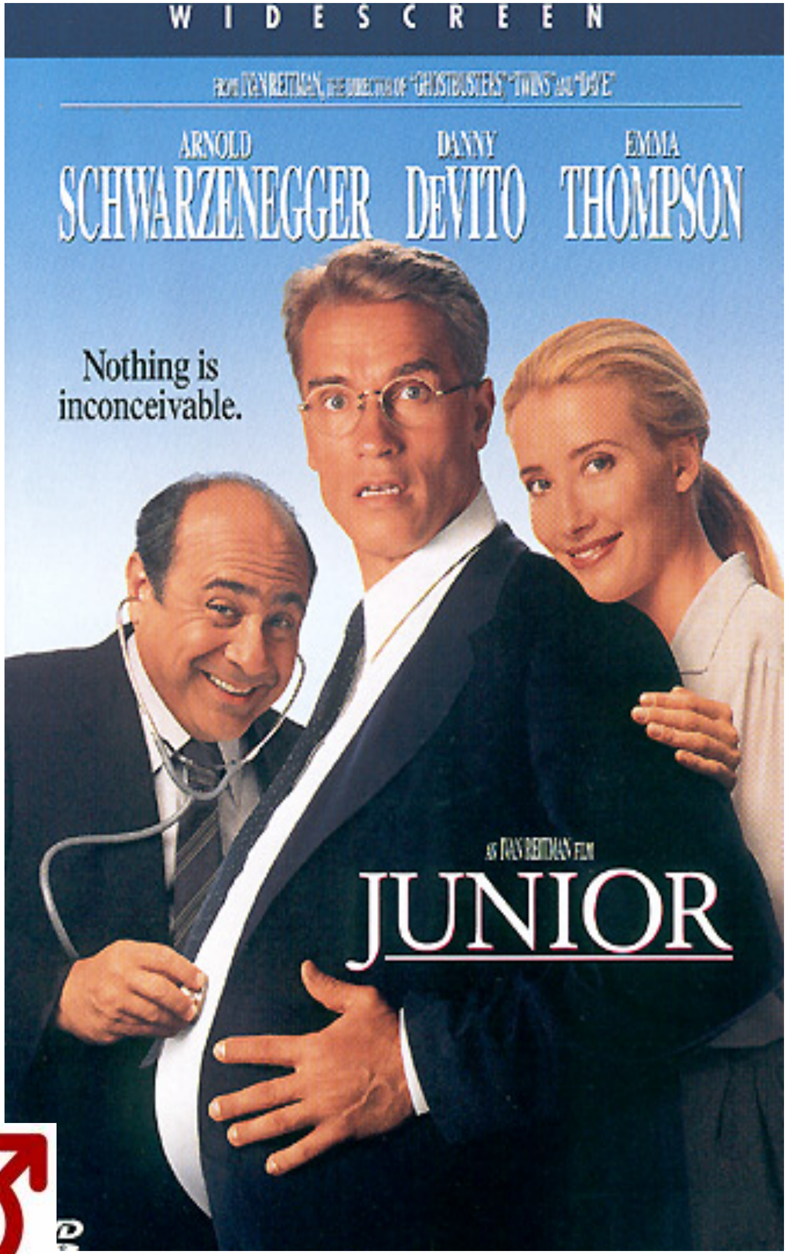
Hermaphrodites (XX/XY)

Brief Report

A True Hermaphrodite Chimera Resulting from Embryo Amalgamation after in Vitro Fertilization

Lisa Strain, Ph.D., John C.S. Dean, F.R.C.P.(Edin.),
Mark P.R. Hamilton, F.R.C.O.G.,
and David T. Bonthron, M.R.C.P.

Strain et al, New Engl J Med 338:166 (1998)



Medical breakthrough lets dad be a mom!

MAN GIVES BIRTH TO A HEALTHY BABY BOY!

FRANKFURT, Germany — A 31-year-old man has just given birth to a 4-pound, 7-ounce baby boy and the new mom/dad is sharing his remarkable experience exclusively with *Weekly World News* readers!

"I hardly know where to begin," Karl Holzer told *The NEWS*. "I've always wanted to have a baby but I didn't really expect to have

Filipino man lied about his pregnancy

TRANSSEXUELLER VATER

"Schwangerer Mann" bekommt zweites Kind

10. Juni 2009 08.52 Uhr, dpa

Der transsexuelle US-Amerikaner Thomas Beatie hat hat sein zweites Kind zur Welt gebracht.

picture-alliance/ dpa Bild 1 von 3

Thomas Beatie (35) hatte bis Anfang zwanzig als Frau gelebt

True Hermaphrodite With Bilateral Ovotestes, Bilateral Gonadoblastomas and Dysgerminomas, 46, XX/46, XY Karyotype, and a Successful Pregnancy

Aleksander Talerman, MD, FRCPath,*† Marion S. Verp, MD,†
Elizabeth Senekjian, MD,† Theresa Gilewski, MD,‡
and Nicholas Vogelzang, MD‡


Medical breakthrough lets dad be a mom!

MAN GIVES BIRTH TO A HEALTHY BABY BOY!

FRANKFURT, Germany — A 21-year-old man has just given birth to a 4-pound, 7-ounce baby boy, and the new mom/dad is sharing his remarkable experience exclusively with Weekly World News readers.

Filipino man lied about his pregnancy

The first case (to the authors' knowledge) is reported of a true hermaphrodite with bilateral ovotestes, bilateral gonadoblastomas and dysgerminomas, a 46, XX/46,XY karyotype, and a successful pregnancy. The true hermaphroditism was diagnosed during infancy. The patient was subsequently found to have a gonadoblastoma and a microscopic dysgerminoma in the gonad diagnosed as an ovotestis and excised during infancy. The successful pregnancy occurred when the patient was 29 years old. A year later a large gonadal tumor affecting the remaining gonad was excised. The gonad was found to be an ovotestis, and the tumor was a dysgerminoma arising from a gonadoblastoma. This case further emphasizes the malignant potential of the Y chromosome in patients with abnormal gonads. *Cancer* 66:2668–2672, 1990.

Talerman et al, Cancer 66:3668 (1990)

Chimerism in a fertile woman with 46,XY karyotype and female phenotype

R.Sudik[1], S.Jakubiczka[2], F.Nawroth[1], E.Gilberg[3] and P.F.Wieacker[2,4]

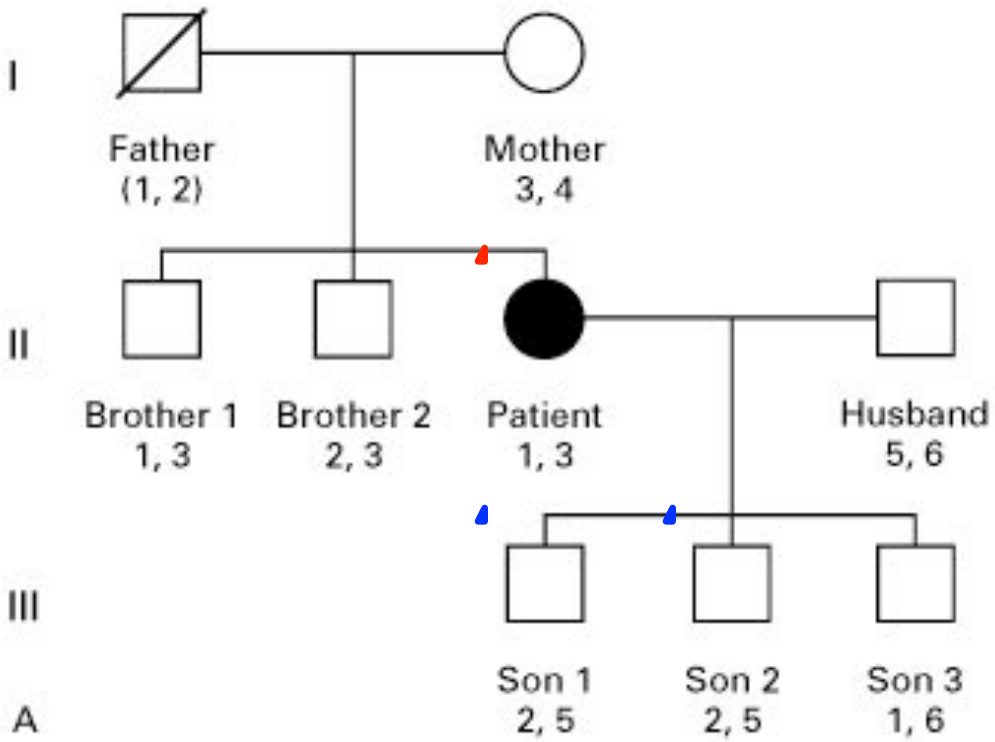
[1]Department of Obstetrics and Gynecology, Klinikum Neubrandenburg, [2]Institute of Human Genetics, Otto-von-Guericke University Magdeburg, and [3]Department of Pediatrics, Klinikum Neubrandenburg, Germany

[4]To whom correspondence should be addressed at: Universitätsklinikum Magdeburg, Institut für Humangenetik, Leipziger Strasse 44, 39120 Magdeburg, Germany. E-mail: Peter.Wieacker@medizin.uni-magdeburg.de

We report on the unexpected finding of a 46,XY karyotype in a 30 year-old woman with normal ovarian function and a former pregnancy at 17 years of age. Chromosome analysis was performed prior to intracyoplasmic sperm injection (ICSI), due to infertility of her husband. Repeated chromosome analysis in lymphocytes of the female resulted in a normal male karyotype. Fluorescence in-situ hybridization (FISH) analysis of cultured lymphocyte interphase nuclei detected in 99% of the cells one X and one Y chromosome-specific signal respectively, whereas two X chromosome-specific signals were observed in only 1% of the nuclei. Chromosome analysis of fibroblasts of ovarian and muscular tissues as well as of skin revealed a normal female karyotype (46,XX). Chimerism could be proven by variable number of tandem repeats (VNTR) analysis. Since the case history of the patient revealed that her twin brother died shortly after birth, it can be assumed that chimerism is caused by feto–fetal transfusion during pregnancy and delivery of the proposita.

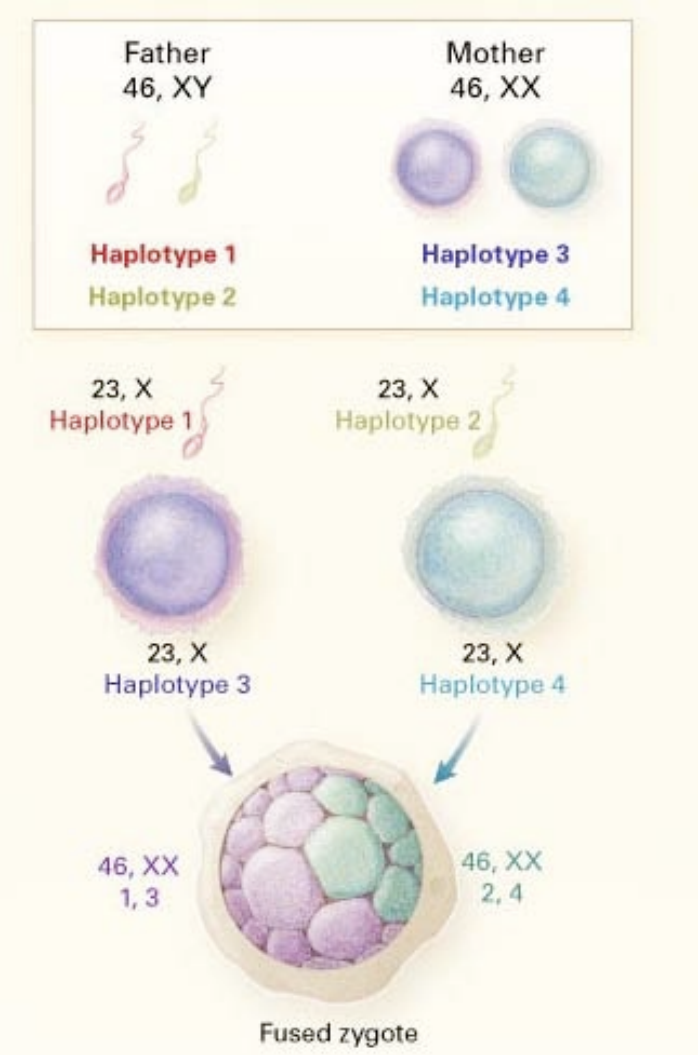
Sudik et al, Human Reprod 16:56 (2001)

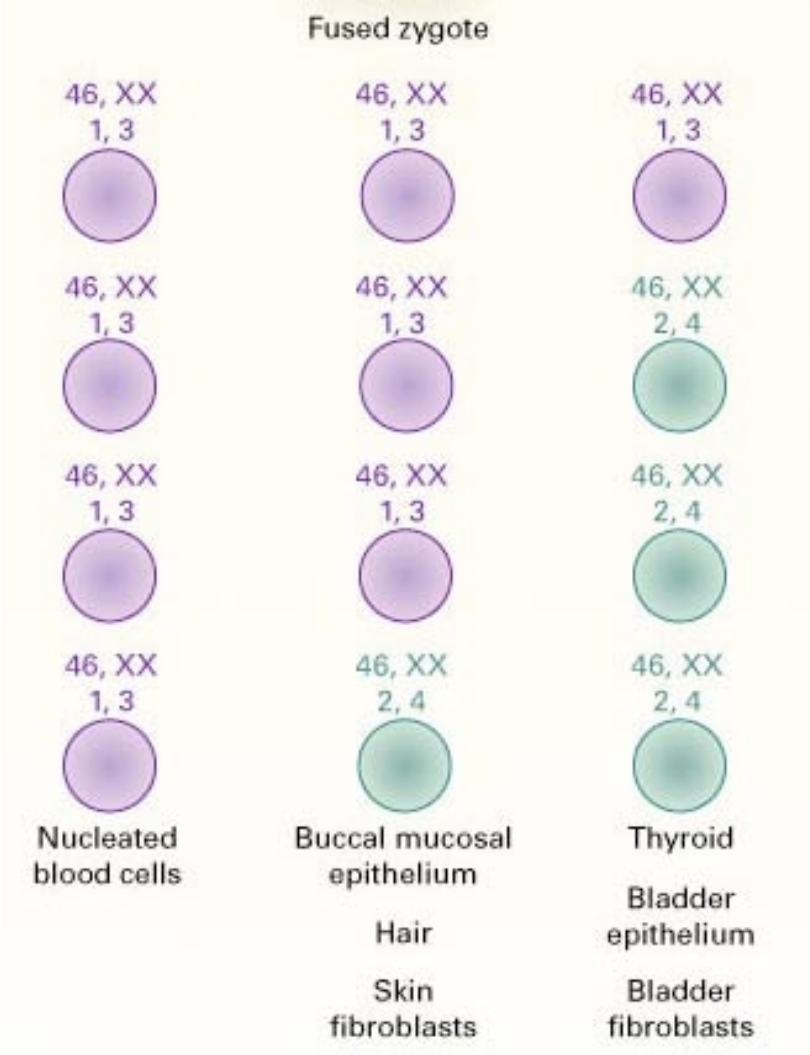
Tetragametic Chimerism



Yu et al, New Engl J Med 346:1454 (2002)

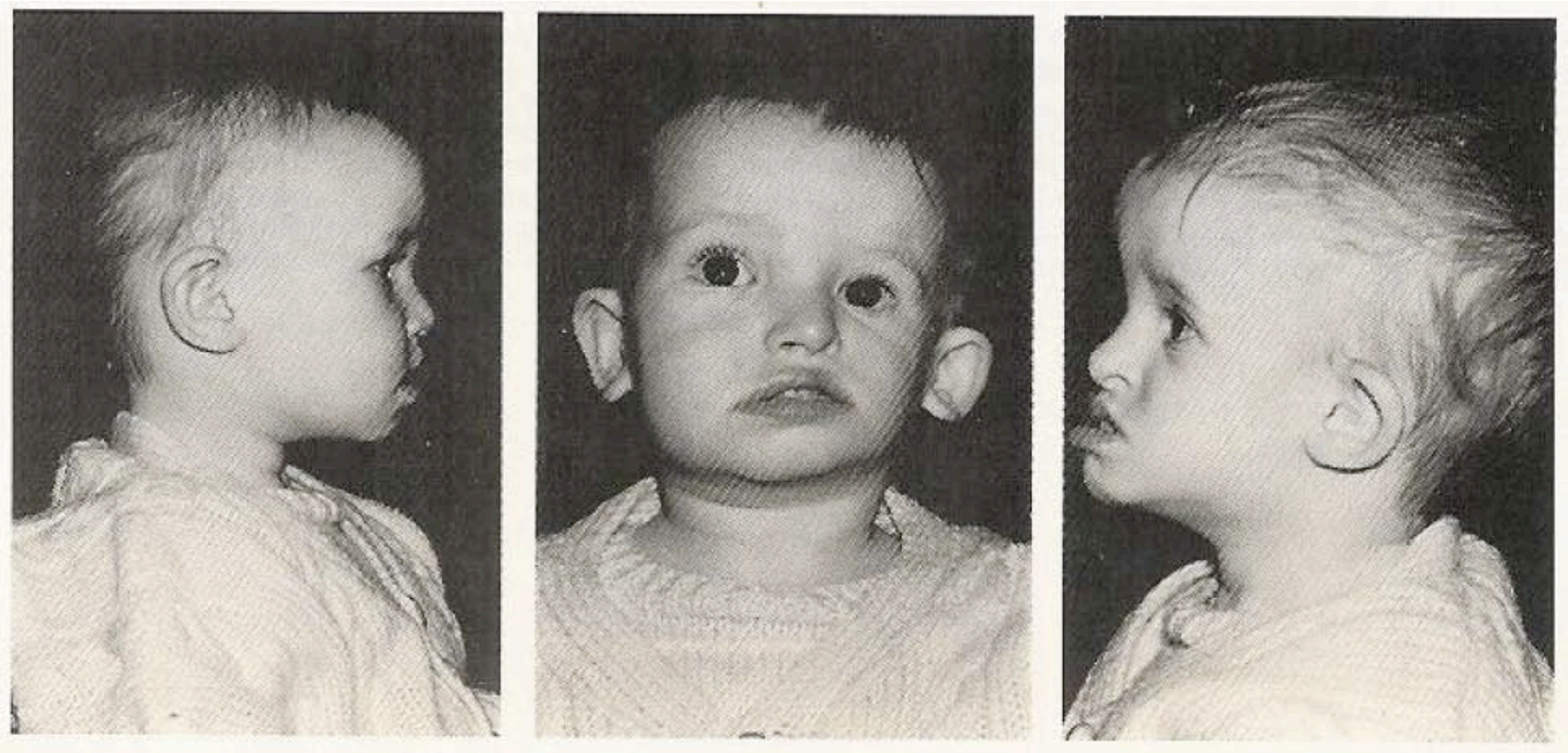
Tetragametic Chimerism





Yu et al, New Engl J Med 346:1454 (2002)

A human parthenogenetic mosaic/chimera



Phenotypic male
Peripheral blood female
(maternal parthenogenetic)

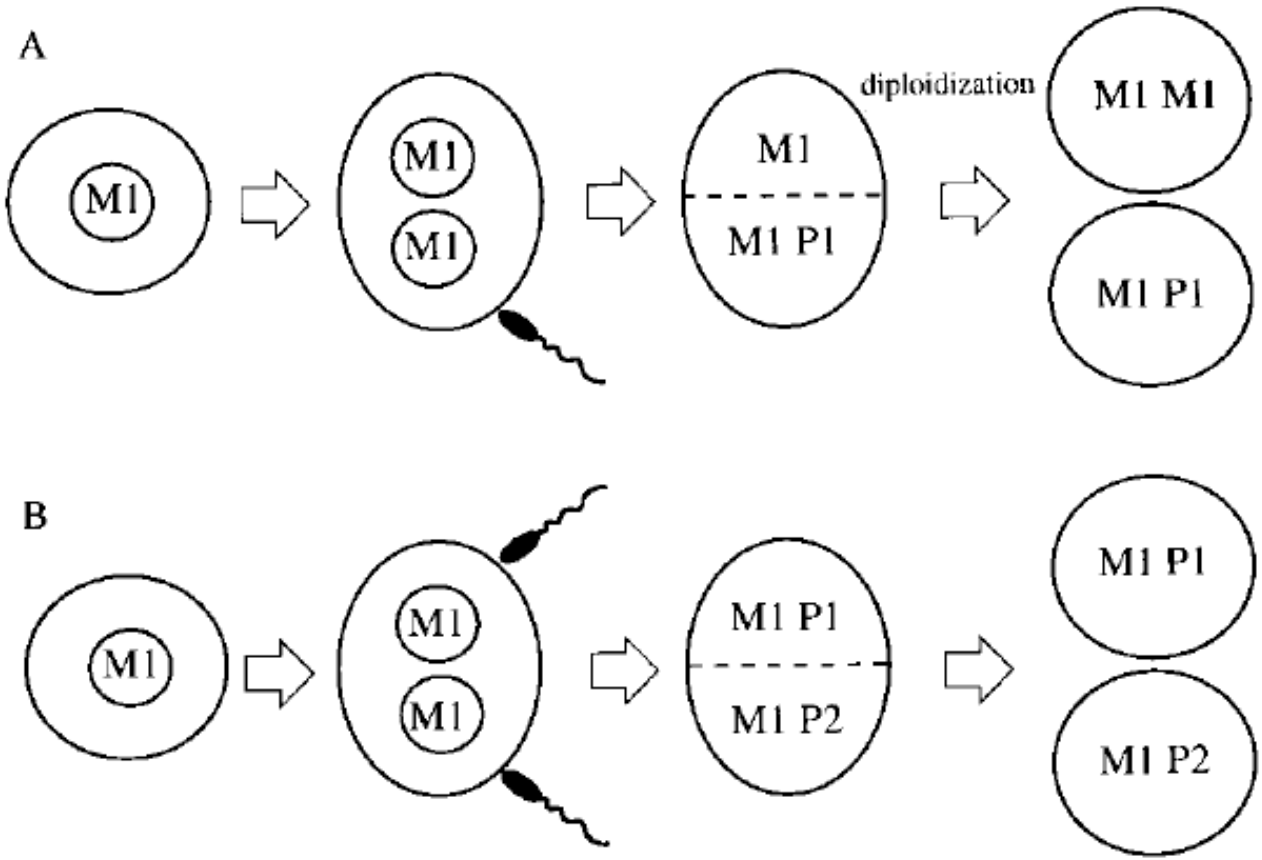
Strain et al, Nature Genetics 11:164 (1995)

Am. J. Hum. Genet. 62:937–940, 1998

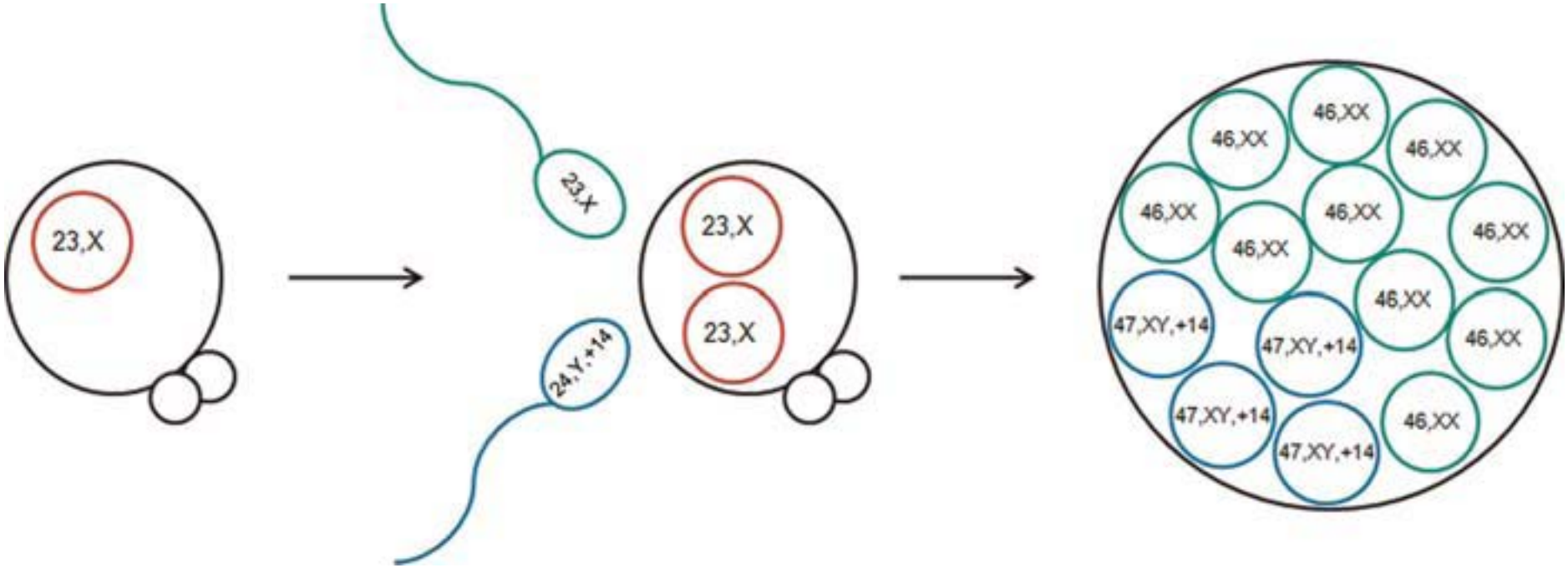
Polymorphic Detection of a Parthenogenetic Maternal and Double Paternal Contribution to a 46,XX/46,XY Hermaphrodite

Jacques C. Giltay,[1,2] Tibor Brunt,[1] Frits A. Beemer,[1,2] Jan-Maarten Wit,[3,*]
Hans Kristian Ploos van Amstel,[1,2] Peter L. Pearson,[1] and Cisca Wijmenga[1]

[1]Department of Human Genetics, Utrecht University, [2]Clinical Genetics Center Utrecht, and [3]Wilhelmina Children's Hospital, Utrecht, The Netherlands

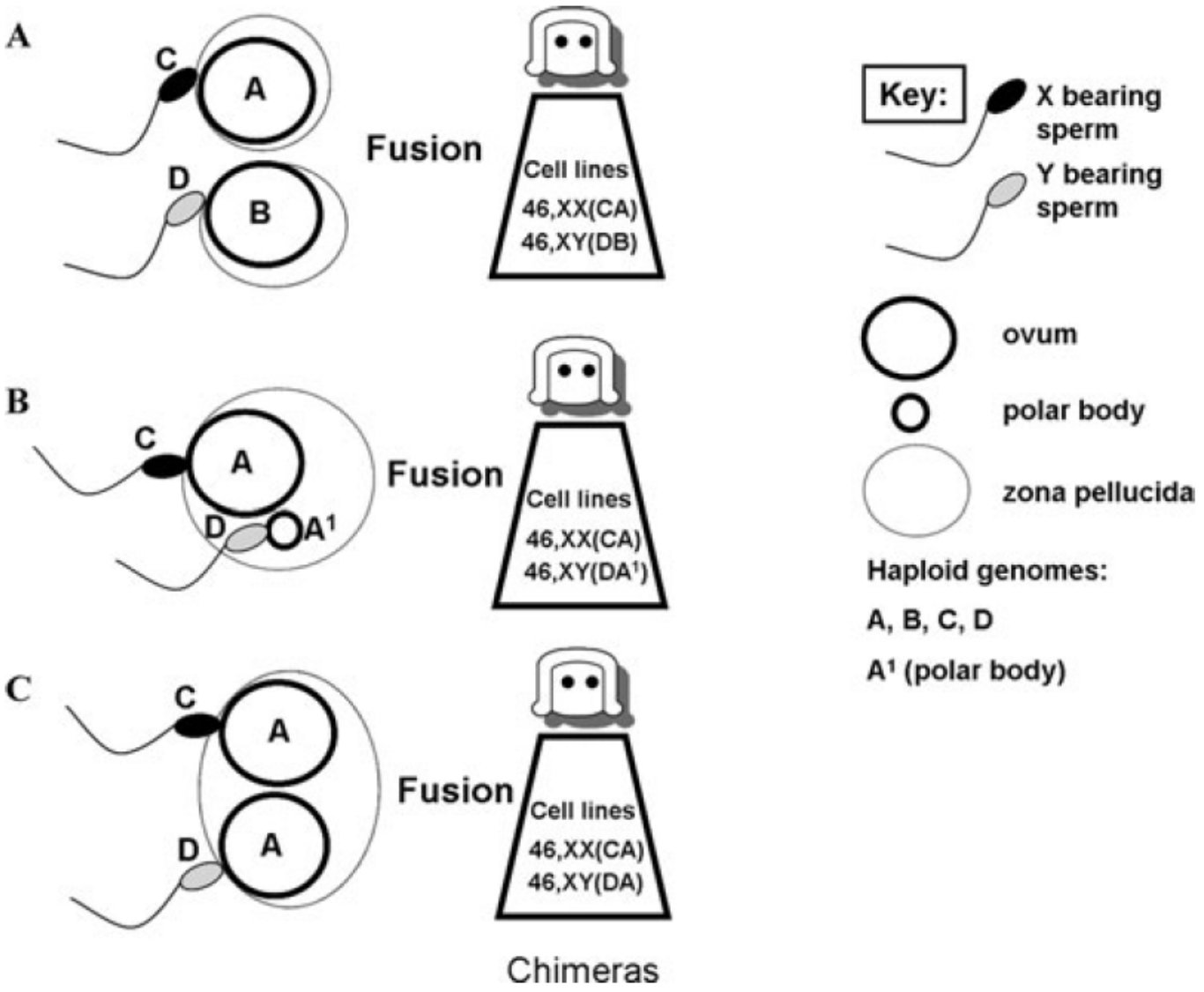


Parthenogenetic activation and dispermic fertilization: 46,XX/47XY,+14



Winberg et al, Am J Med Genet 152A:2277:68 (2010)

46,XX/47XY,+21 and 46,XX/46,XY



Ramsay et al, Ann NY Acad Sci 1151:68 (2009)

Gynadromorph birds are mixed sex-chimaeras

Somatic sex identity is cell autonomous in the chicken

Zhao et al, Nature 464:237 (2010)

Natural Chimera

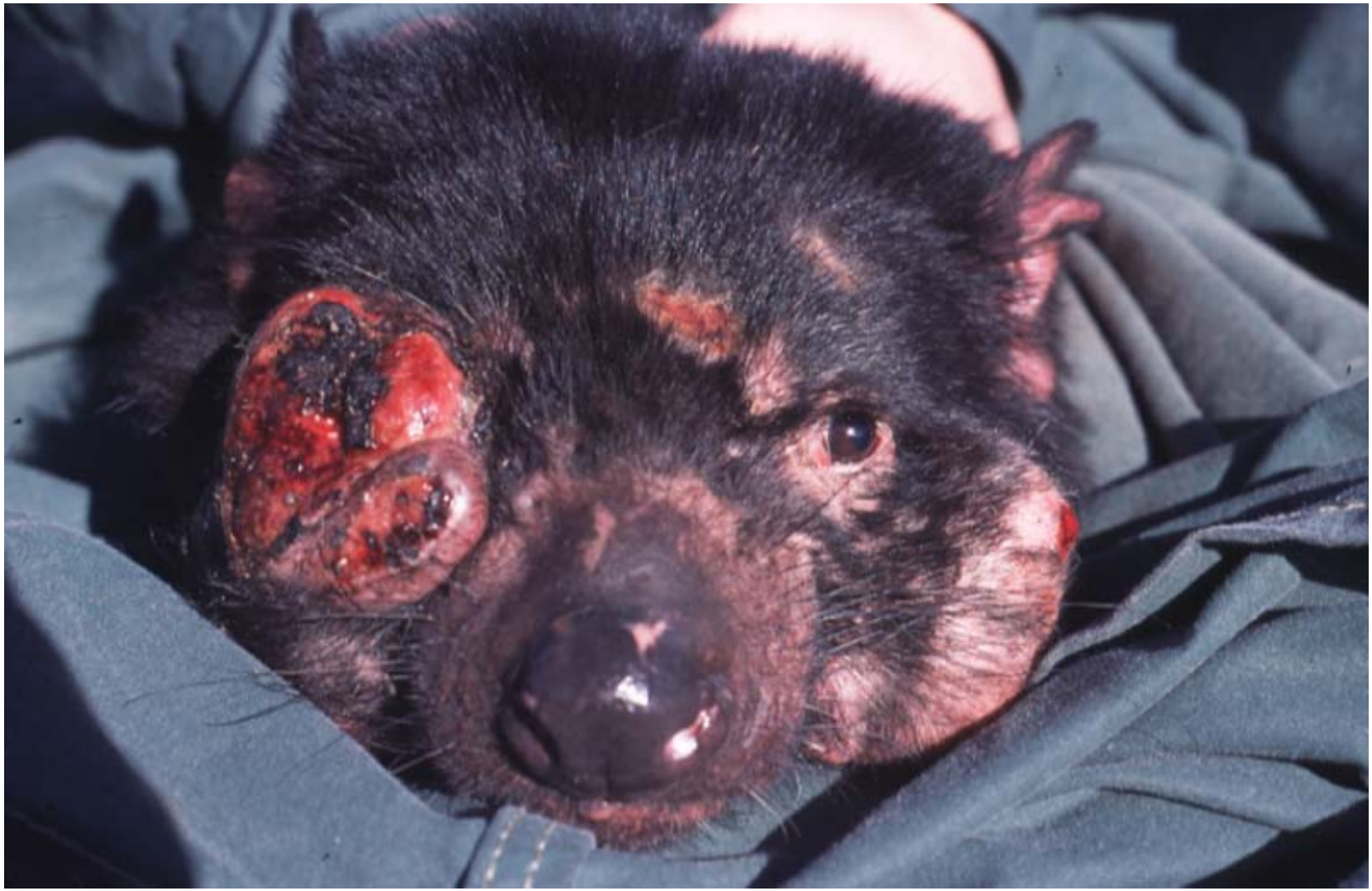
- Fetal-maternal chimera
- Blood sharing and twin chimera
- Whole body or dispermic chimera
- **Tumor chimera**
- Germ cell chimera

Rinkevich, Human Immunol 62:651 (2001)

Tasmanian Devil

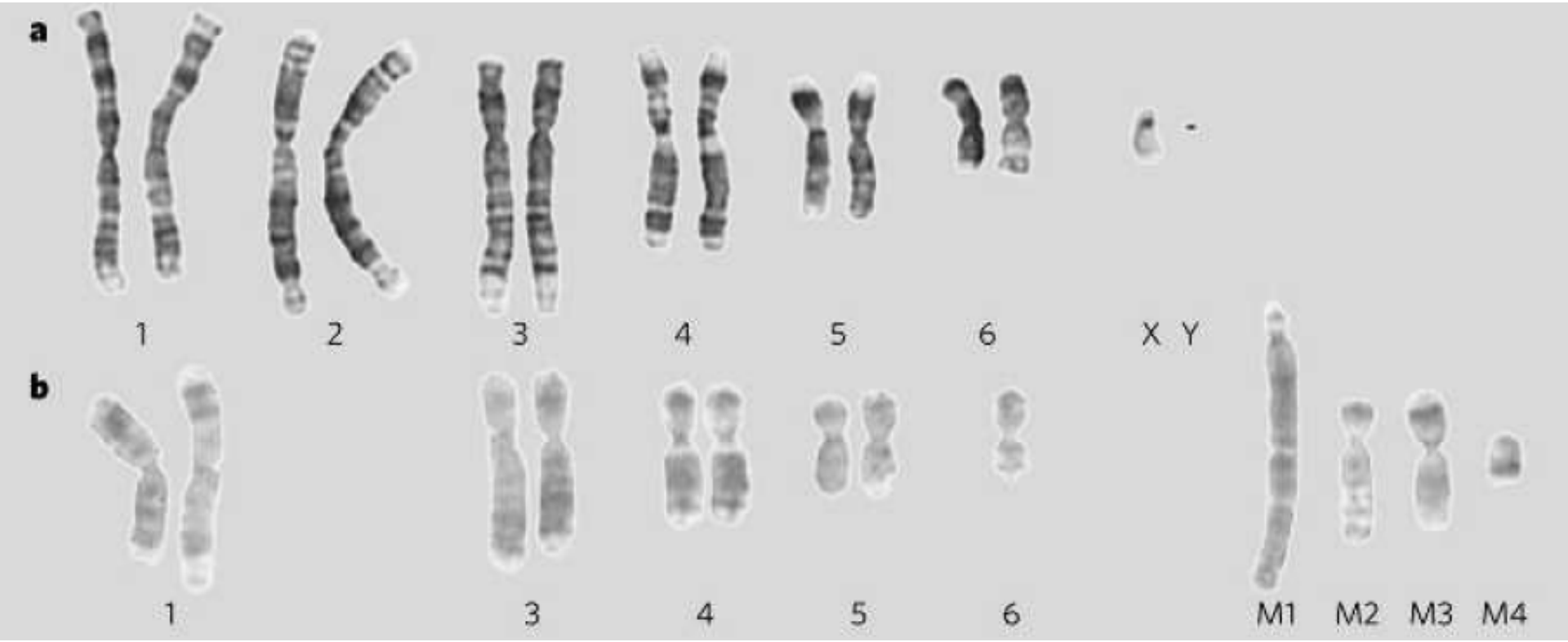
Pearse & Swift, Nature 439:549 (2006)

Facial-tumour in Tasmanian Devil



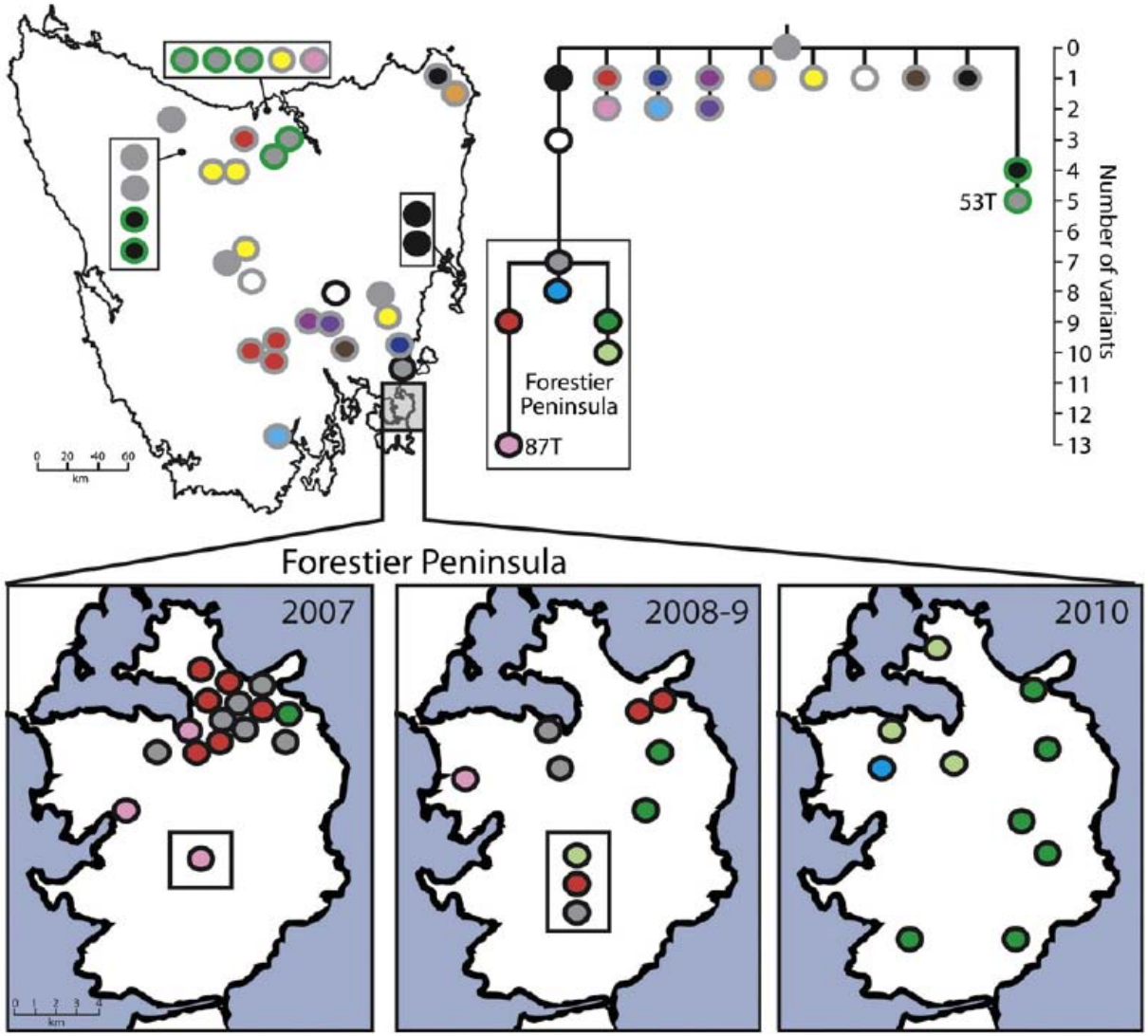
Pearse & Swift, Nature 439:549 (2006)

Transmission of Devil Facial-tumour Disease



Pearse & Swift, Nature 439:549 (2006)

Phylogenetic tree of genetic variations in 104 DFTD tumors from 69 Tasmanian devils



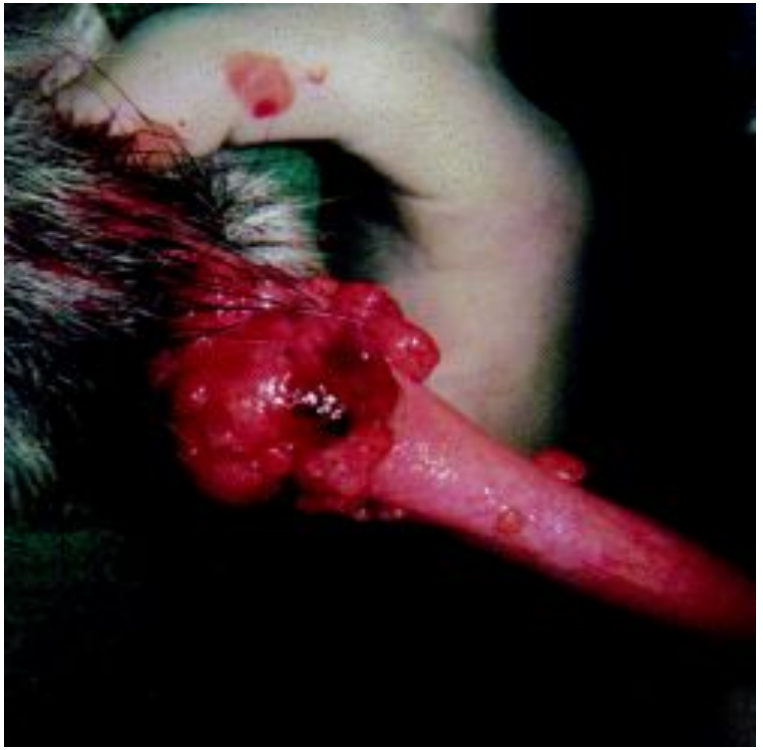
Murchison et al, Cell 148:780 (2012)

Canine Transmissible Veneral Tumor

Table 1. Sources of CTVT Samples

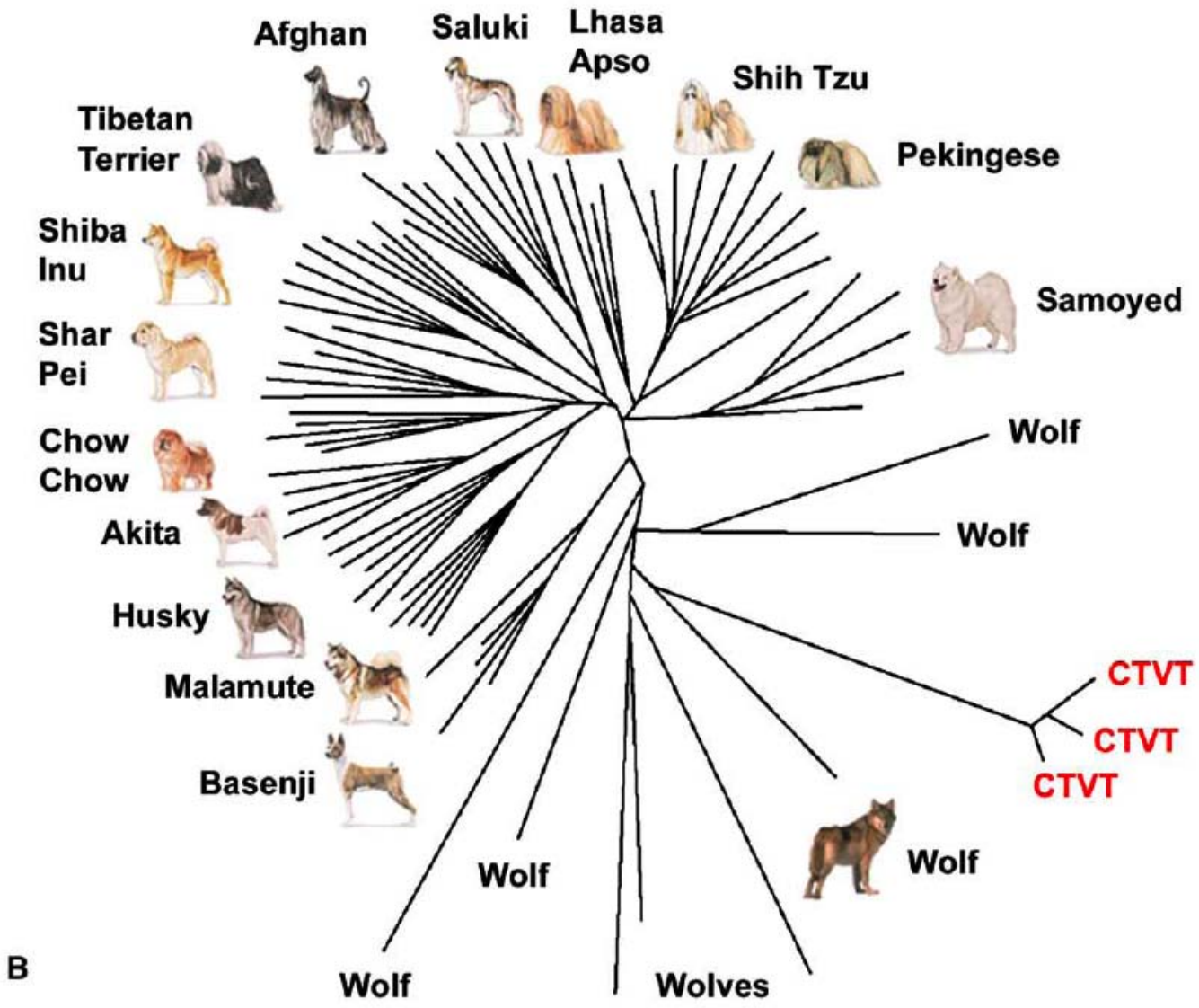
Fresh Tumors with Matching Blood Sample	
Place	Number
Catania, Italy	5
Messina, Italy	5
Kolkata, India	4
Nairobi, Kenya	2
Paraffin-Embedded Archival Tumors	
Country	Number
Brazil	4
Italy	5
Spain	4
Turkey	9
USA	2
Total	40

Details of age, sex, breed of dog, and site of tumor are in Table S1.



Murgia et al, Cell 126:477 (2006)

Canine Transmissible Veneral Tumor



Murgia et al, Cell 126:477 (2006)

FATAL HOMOTRANSPLANTED MELANOMA

A Case Report

PRESENTED HERE IS A SINGLE CASE OF FATAL homotransplanted melanoma, which we believe is the first of its kind to be reported. We feel that this merits particular attention. The relationship of fatal homotransplanted mela-

Scanlon et al, Cancer 18:782 (1965)

TRANSMISSION OF CANCER IN MAN

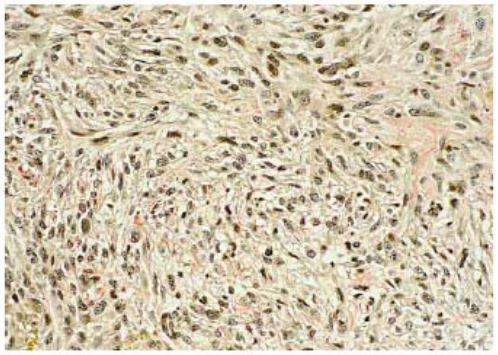
Tentative Guidelines Referring to the Possible Effects of Inoculation of Homologous Cancer Extracts in Man

LUDWIK GROSS, MD

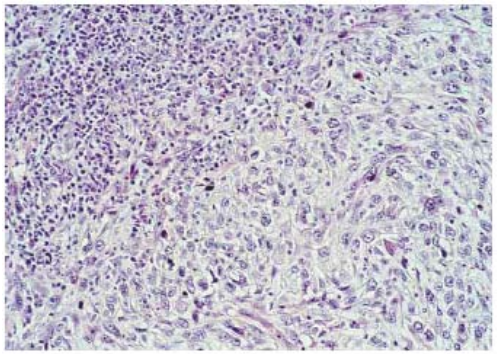
Inoculation of humans with live human cancer extracts may lead to the establishment of progressively growing tumors in the recipients and cause dissemination of a fatal disease. Close relatives are particularly susceptible to the inoculation of tumors from genetically related donors. The results of inoculation of cancer extracts from human patients to unrelated human recipients are unpredictable. In rare instances, the implanted tumors may "take," grow progressively, and lead to a generalization of the disease. Administration of immunosuppressive drugs, such as azathioprine or prednisone, lowers natural resistance of the host to heterologous tumors; patients receiving such treatment are particularly susceptible to transmission of human cancer.

Gross, Cancer 28:785 (1971)

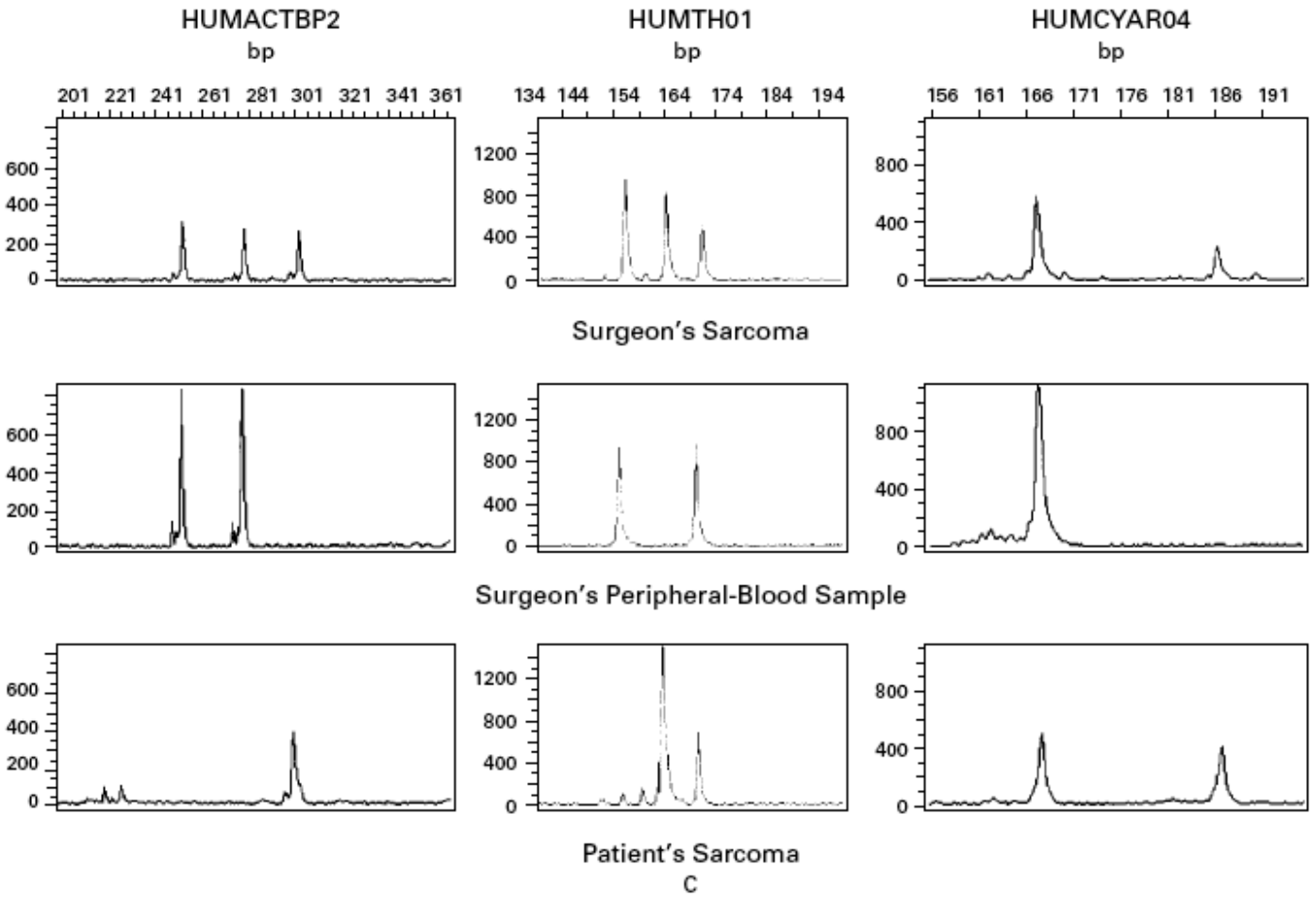
Genetic Analysis of a Sarcoma Acidentally Transplanted from a Patient to a Surgeon



A



B



Gärtner et al, New Engl J Med 335:1495 (1996)

Immunologically silent cancer clone transmission from mother to offspring

Takeshi Isoda[a,1], Anthony M. Ford[b,1], Daisuke Tomizawa[a], Frederik W. van Delft[b], David Gonzalez De Castro[b], Norkio Mitsuiki[a], Joannah Score[c], Tomohiko Taki[d], Tomohiro Morio[a], Masatoshi Takagi[a], Hiroh Saji[e], Mel Greaves[b,2,3], and Shuki Mizutani[a,2,3]

Rare cases of possible materno-fetal transmission of cancer have been recorded over the past 100 years but evidence for a shared cancer clone has been very limited. We provide genetic evidence for mother to offspring transmission, in utero, of a leukemic cell clone. Maternal and infant cancer clones shared the same unique *BCR-ABL1* genomic fusion sequence, indicating a shared, single-cell origin. Microsatellite markers in the infant cancer were all of maternal origin. Additionally, the infant, maternally-derived cancer cells had a major deletion on one copy of chromosome 6p that included deletion of HLA alleles that were not inherited by the infant (i.e., foreign to the infant), suggesting a possible mechanism for immune evasion.

Isoda et al, PNAS 106:17882 (2009)

Complete Hydatidiform Moles (CHM)

Diploid (46,XX) benign tumors that arise from the fertilization of an empty ovum by a single 23,X sperm

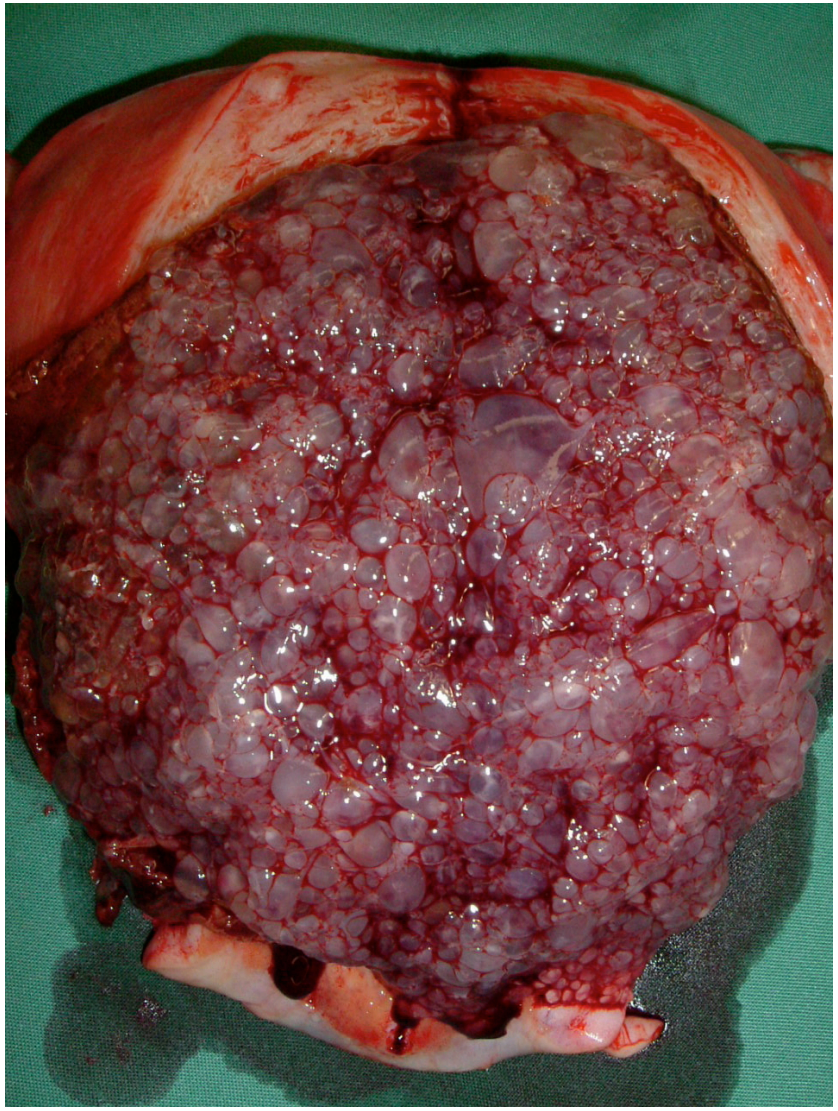


TABLE 1: HuSNP genotyping results

Case	Sample	Pass rate (%)	Heterozygous SNPs (%)
1	4-mother	85.9	28.6
	4-CHM	88.9	0.3
2	11-mother	81.6	27.8
	11-CHM	82.7	0.1
3	13-mother	81.9	27.1
	13-CHM	84.7	0.4
4	18-mother	82.4	25.4
	18-CHM	81.3	0.1
5	22-mother	81.3	26.6
	22-CHM	82.7	0.75
	Average mother	82.6	27.1
	Average CHM	84.1	0.33

Fan et al, Genomics 79:8 (2002)

Natural Chimera

- Fetal-maternal chimera
- Blood sharing and twin chimera
- Whole body or dispermic chimera
- Tumor chimera
- **Germ cell chimera**

Rinkevich, Human Immunol 62:651 (2001)

Germ-line Chimerism and Paternal Care in Marmosets

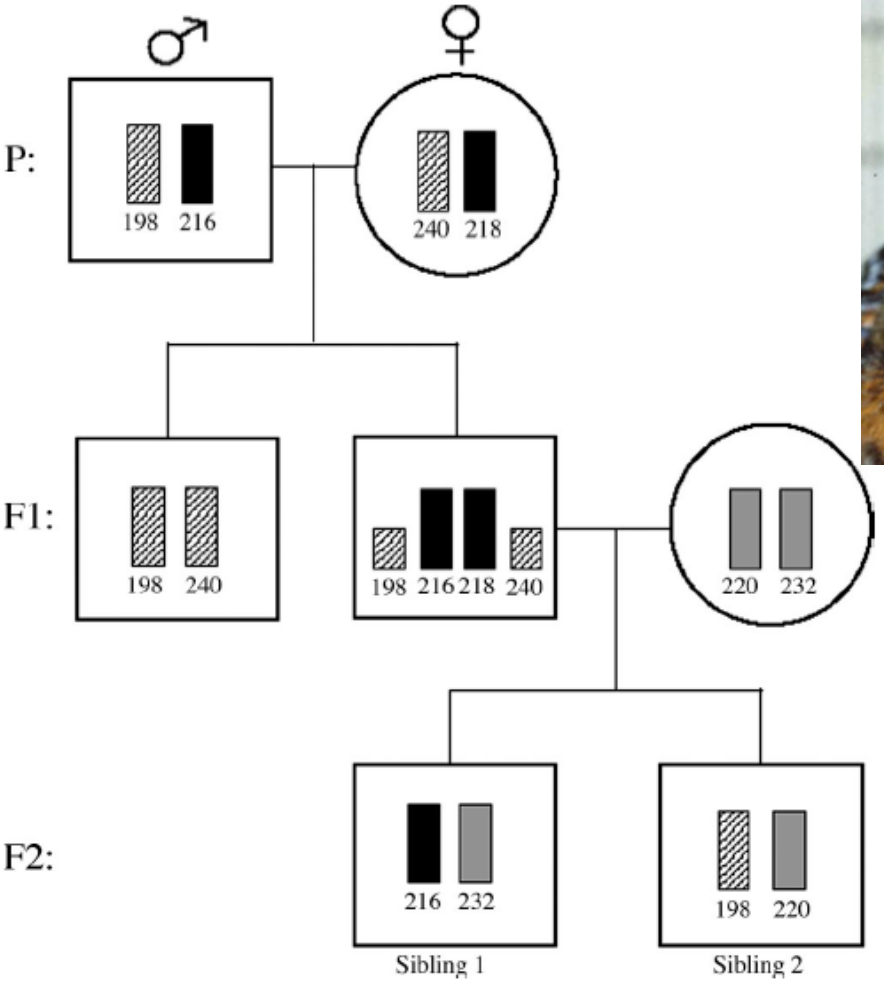
Table 1. The number of *Callithrix kuhlii* individuals chimeric for each tissue type

Tissue	Tissue type	Genotyped, no.	Chimeric, no.	Chimeric, %
Samples from deceased animals				
Placenta	H	7	7	100.0
Blood	H	2	2	100.0
Spleen	H	28	14	50.0
Liver	H	39	15	38.5
Heart	S	30	7	23.3
Hair	S	35	6	17.1
Lung	S	30	4	13.3
Kidney	S	33	4	12.1
Gonad	G	21	2	9.5
Skin	S	36	2	5.6
Brain	S	31	1	3.2
Muscle	S	34	1	2.9
Samples from living animals				
Sperm	G	7	4	57.1
Saliva	S	31	16	51.6
Blood	H	45	22	48.9
Hair	S	50	13	26.0
Fecal	S	22	2	9.09

H, hematopoietic; S, other somatic; G, germ line.

Ross et al, PNAS 104:6278 (2007)

Germ-line Chimerism and Paternal Care in Marmosets



Ross et al, PNAS 104:6278 (2007)

"Brainteaser" Pedigree