

London *et al* (1964) recorded the case of a 28-year-old woman who had menstrual periods for 5 years and then became amenorrhoeic. He assumed that the XX cells had to be present for the ovaries to function regularly as indicated by normal menstruation. If there is a lack of these XX cells primary amenorrhoea will occur and if the XX cells are 'used up' then the amenorrhoea will be secondary.

### Summary

A case is reported of a 20-year-old woman with a 45,X complement, with dwarfism and numerous other signs of Turner's syndrome, who has been menstruating for the past five years.

The question remains whether a single X-chromosome is sufficient for fertility or whether a mosaic pattern has to be suspected in the ovaries of fertile females with Turner's syndrome.

We are indebted to John L. Hamerton DSc for expert advice and to Dr Immo Lawaczek who referred the patient. Cytogenetic studies were performed by Dr Heiner Cramer at the Institute of Humangenetics, University of Marburg.

LOTHAR HAUSMANN and KLAUS-M. GOEBEL

*Department of Medicine, University of Marburg, Germany*

### REFERENCES

- Arakaki, D. T. and Sparkes, R. S. (1963). Microtechnique for culturing leukocytes from whole blood. *Cytogenetics*, **2**, 57-60.
- Bahner, F., Schwarz, G., Hienz, H. A., and Walter, K. (1960a). Turner-Syndrom mit voll ausgebildeten sekundären Geschlechtsmerkmalen und Fertilität. *Acta Endocrinologica*, **35**, 397-404.
- Bahner, F., Schwarz, G., Harnden, D. G., Jacobs, P. A., Hienz, H. A., and Walter, K. (1960b). A fertile female with XO sex chromosome constitution. *Lancet*, **2**, 100-101.
- Campenhout, J. van, Lord, J., Vauclair, R., Lanthier, A., and Berard, M. (1969). The phenotype and gonadal histology in XO/XY mosaic individuals: Report of two personal cases. *Journal of Obstetrics and Gynaecology*, **76**, 631-639.
- Kaufman, R. L., Rimoin, L., Woolf, R. B., Warren, R. J., and Sly, W. S. (1971). Sex chromosome mosaicism (XO/XX/XXY/XY) in a phenotypic female. *Journal of the American Medical Association*, **215**, 1941-1944.
- London, D. R., Kemp, N. H., Ellis, J. R., and Mittwoch, U. (1964). Turner's Syndrome with secondary amenorrhoea and sex chromosome mosaicism. *Acta Endocrinologica*, **46**, 341-351.
- Ullrich, O. (1951). Der Status Bonnevie-Ullrich im Rahmen anderer 'Dyscranio-Dysphalangien'. *Ergebnis innere Medizin und Kinderheilkunde*, **2** (New Series), 412-466.
- Zárate, A., Garcia-Reyes, J. A., Castelazo-Ayala, C., Estevez, R., and Silva, J. (1969). Turner's phenotype with menstruation, XO karyotype and germ cells in the ovary. *Obstetrics and Gynecology*, **33**, 818-821.

## Deletion of the Long Arms of Chromosome 18 (46,XX,18q-) Associated with Absence of IgA and Hypothyroidism in an Adult

### Case Report

The patient (Fig. 1) is a female aged 21. No details of her birth are known beyond the fact that her mother was aged 35 years and died 8 years later of lung cancer. There is no information about the father.

The patient was admitted to a mental deficiency hospital at age 8 years. She was thought to suffer from atypical Down's syndrome.

On examination at the age of 21 years her height was 142 cm with a sole to pubis measurement of 69 cm and a span of 137 cm; head circumference was 51 cm. She weighed 62.14 kg. Her face showed midfacial hypoplasia and a carp mouth. There were bilateral epicanthic folds and an internal, alternating strabismus. Her hair, which was fair in colour, had normal female distribution although her head hair was receding slightly at the temples. Her fingers were short and all had ulnar loops. She had generalized muscular hypotonia. Specialist investigations showed the eyes to have normal refraction. She had 50% perceptive deafness. The external meati and petrous bones were normal. The patient was hypotensive (BP 100/50). A soft systolic murmur was present following exercise and was best heard at the apex. The heart was enlarged on x-ray and an ECG showed probable right ventricular hypertrophy. There were no physical signs of heart failure, and no goitre.

Her intelligence fell into the group of mild mental retardation (International Classification of Diseases).

### Protein Studies

Serum total protein was 7.9 g/100 ml. Electrophoresis on cellulose acetate was normal with the exception of a moderately increased  $\gamma$ -globulin level (2.0 g/100 ml).

The serum immunoglobulins were examined on 4 occasions. At no time was IgA detectable by immunoelectrophoresis (Grabar and Burtin, 1964) on agar gel against specific antisera (Behringwerke AG, Marburg-Lahn, Germany). The IgG and IgM arcs appeared qualitatively normal. The serum concentrations of immunoglobulins were measured by single radial immunodiffusion (Mancini, Carbonara, and Heremans, 1965) in agar gel containing specific rabbit antisera against human immunoglobulins (Wellcome Reagents Ltd, Beckenham, England). The Wellcome antiserum to IgA appeared to be specific as it gave, on immunoelectrophoresis, a single arc with normal human serum.

The results of the immunodiffusion measurements are shown in the Table. The IgA concentration (measured

on undiluted serum) was very low or undetectable. The concentration of IgG was raised. This increase in IgG was noted in one of the IgA-deficient patients of Hobbs (1968) and might represent an antibody response to infections to which the IgA deficiency made the patient more susceptible. Indeed, during the period in which our patient's immunoglobulins were being estimated she had superficial or middle ear infections on several oc-

casions and in October 1970 had an appendectomy for acute appendicitis. This may also be relevant to the observed rise in IgM concentration although this remained within normal limits.

TABLE  
IMMUNOGLOBULIN CONCENTRATION IN  
THE SERUM ( $\mu\text{g}/100\text{ ml}$ )

Date	IgG	IgA	IgM
5/70	2540	< 2	40
6/70	2530	< 2	90
12/70	3000	10	130
5/71	2720	5	200
Normal	800-1800	90-450	60-250

### Thyroid Studies

The serum protein-bound iodine (Riley and Gochman, 1964) was reduced at  $2.5\ \mu\text{g}/100\text{ ml}$ , on 2 occasions. This low result was not the consequence of a deficiency of a thyroxine binding globulin because a  $T_3$  resin uptake (Gimlette, 1967) was in the hypothyroid range at 0.028. There was no evidence of auto-antibodies to the thyroid from the complement fixation test (Roitt and Doniach, 1958) or from the tanned red-cell haemagglutination test (Fulthorpe *et al*, 1961).

### Chromosome Studies

Cells were examined from a culture of the peripheral blood and from a fibroblast culture from the skin. All cells were found to have an abnormal chromosome replacing a member of the E group. Pairing of the chromosomes from photographs after staining with quinacrine hydrochloride (Atebrin) revealed no abnormality of any other chromosome. It is also clear that it is chromosome 18 which is affected because chromosome 17 is strongly fluorescent only on the distal portion of the long arms but normally both proximal and distal portions of the long arms of chromosome 18 are bright. In this patient the distal fluorescent region is deleted from chromosome 18 (Fig. 2).

The abnormality was not found in any of the relatives examined but no first degree relatives were available.

### Discussion

Low intelligence, small stature, poor muscular tone, carp mouth, midfacial hypoplasia, and internal strabismus are all features of this patient which have been reported in other cases of the Eq - syndrome (de Grouchy *et al*, 1964; Lejeune *et al*, 1966; Wertelecki, Schindler, and Gerald, 1966; Insley, 1967; Nance *et al*, 1968). Her fingers, however, are short rather than long and tapered, and show a complete absence of whorl patterns (*cf*, Wertelecki *et al*, 1966). Hypothyroidism is not a characteristic of the syndrome but absence of IgA has been reported

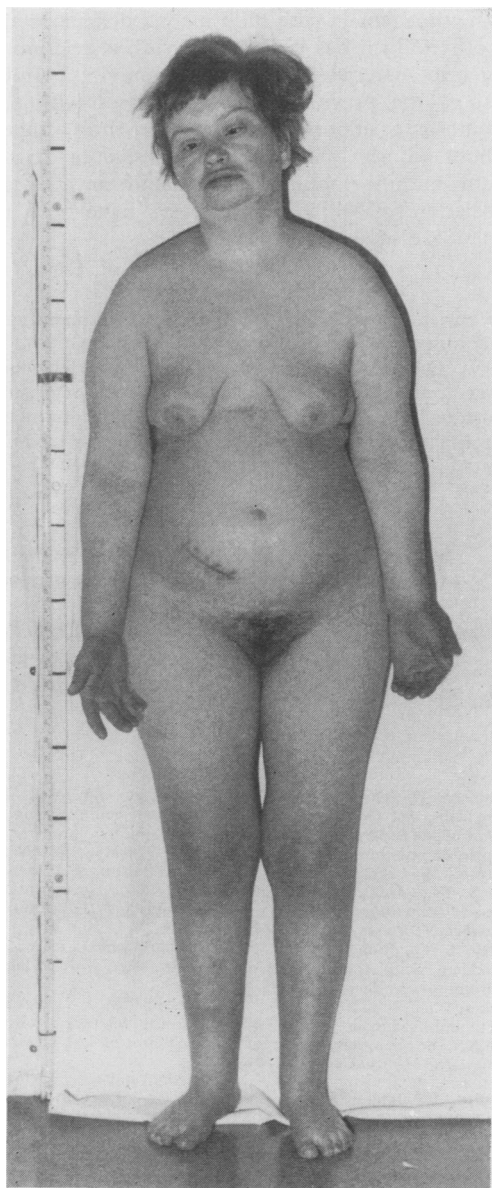


FIG. 1. The proposita.

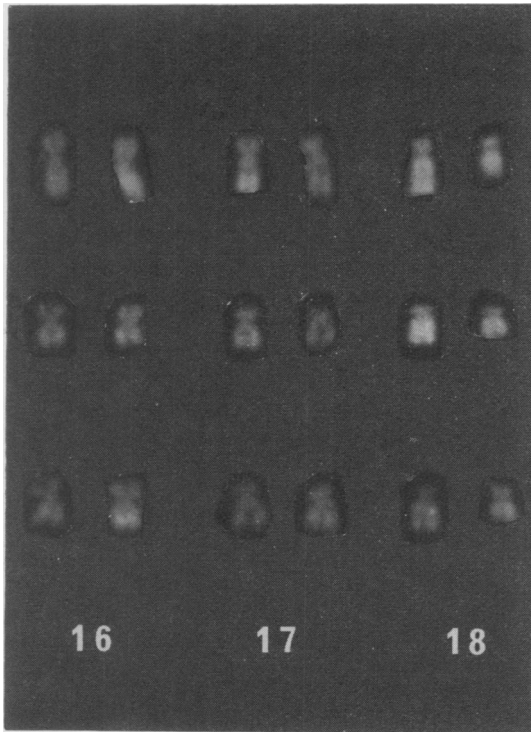


FIG. 2. Partial karyotypes from 3 cells to show extent of deletion from chromosome 18. The chromosomes were stained with quinacrine hydrochloride and observed by incident fluorescence.

previously (Stewart *et al*, 1968; Feingold *et al*, 1969). It has also been found in cases with a ring E chromosome (Finley *et al*, 1968) and even in patients with a deletion from the *short* arm of the chromosome (Daentle and Smith, 1968; Fischer *et al*, 1970). These cases were all children and values for IgA levels in normal children are lower than in adults (Hobbs, 1970). Our patient is now aged 21 years so failure of development of this immunoglobulin can be considered virtually certain.

The incidence of individuals in the population with absence of IgA is reported to be as high as 1 in 500 (Bachmann, 1965; Hobbs, 1968). If this represents the frequency of the homozygote for a recessive gene about 8% of the population will carry the gene on one chromosome and thus 4% of individuals with a loss of one of the IgA genes through chromosome deletion would be expected to show absence of IgA. The association of absence of IgA with deletions from either end of the chromosome may be connected with the observation that in any one cell only one allele for immunoglobulin

production appears to be active (Giblett, 1969). There is no information on how this gene repression operates but it is possible that, as in X chromosome anomalies, it is the deleted chromosome which is inactivated. If this is true the region of the chromosome deleted is unimportant; only the gene on the complete chromosome will be active.

### Summary

An adult female with mild mental deficiency and hypothyroidism has been found with a deletion of long arm material from chromosome 18. Unlike most of the previously reported cases with this chromosome abnormality she has short fingers without whorls. She has gross reduction in the serum immunoglobulin A; the significance of this association, of which several cases have been reported, is discussed.

We wish to thank Dr J. P. Mellon for allowing us to study his patient and Professor I. R. C. Batchelor and Dr W. W. Park for encouragement and helpful criticism. We are grateful to Dr T. E. Isles for  $T_3$  uptake measurements, to Dr D. M. Green for confirming the absence of thyroid antibodies, and to Miss June Sim for technical assistance.

M. J. W. FAED, R. WHYTE, C. R. PATERSON,  
MARGARET McCATHIE, and JANET ROBERTSON

*Cytogenetics Laboratory, Department of Pathology  
and the Departments of Psychiatry and Clinical  
Chemistry, University of Dundee, Dundee, UK*

### REFERENCES

- Bachmann, R. (1965). Studies on serum  $\gamma$ A globulin level. III. Frequency of A- $\gamma$  A-globulinemia. *Scandinavian Journal of Clinical and Laboratory Investigation*, **17**, 316-320.
- Daentle, D. and Smith, D. (1968). Quoted by Stewart *et al* (1968).
- Feingold, M., Schwartz, R. S., Atkins, L., Anderson, R., Bartsocas, C. S., Page, D. L., and Littlefield, J. W. (1969). IgA deficiency associated with partial deletion of chromosome 18. *American Journal of Diseases of Children*, **117**, 129-136.
- Finley, S. C., Finley, W. H., Noto, T. A., Uchida, I. A., and Roddam, R. F. (1968). IgA absence associated with a ring-18 chromosome. *Lancet*, **1**, 1095-1096.
- Fischer, P., Golob, E., Friedrich, F., Kunze-Mühl, E., Doleschel, W., and Aichmair, H. (1970). Autosomal deletion syndrome 46,XX,18p-: a new case report with absence of IgA in serum. *Journal of Medical Genetics*, **7**, 91-98.
- Fulthorpe, A. J., Roitt, I. M., Doniach, D., and Couchman, K. (1961). A stable sheep red cell preparation for detecting thyroglobulin auto-antibodies, and its clinical applications. *Journal of Clinical Pathology*, **14**, 654-660.
- Giblett, E. R. (1969). *Genetic Markers in Human Blood*, p. 8. Blackwell Scientific Publications, Oxford and Edinburgh.
- Gimlette, T. M. D. (1967). Use of sephadex column chromatography in the assessment of thyroid status. *Journal of Clinical Pathology*, **20**, 170-174.

- Grabar, P. and Burtin, P. (eds.) (1964). *Immuno-electrophoretic Analysis*. Elsevier, Amsterdam, London, and New York.
- Grouchy, J. de, Royer, P., Salmon, C., and Lamy, M. (1964). Délétion partielle des bras long du chromosome 18. *Pathologie et Biologie*, **12**, 579-582.
- Hobbs, J. R. (1968). Immune imbalance in dysgammaglobulinaemia type IV. *Lancet*, **1**, 110-114.
- Hobbs, J. R. (1970). Simplified radial immunodiffusion. *Association of Clinical Pathologists Broadsheet*, **68**.
- Insley, J. (1967). Syndrome associated with a deficiency of part of the long arm of chromosome No. 18. *Archives of Disease in Childhood*, **42**, 140-146.
- Lejeune, J., Berger, R., Lafourcade, J., and Réthoré, M.-O. (1966). La délétion partielle du bras long du chromosome 18. Individualisation d'un nouvel état morbide. *Annales de Génétique*, **9**, 32-38.
- Mancini, G., Carbonara, A. O., and Heremans, J. F. (1965). Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry*, **2**, 235-254.
- Nance, W. E., Higdon, S. H., Chown, B., and Engel, E. (1968). Partial E-18 long-arm deletion. *Lancet*, **1**, 303.
- Riley, M. and Gochman, N. (1964). Cited in *Technicon Method Sheet*, No. 56. Technicon Corporation, Terrytown, New York.
- Roitt, I. M. and Doniach, D. (1958). Human auto-immune thyroiditis: serological studies. *Lancet*, **2**, 1027-1033.
- Stewart, J., Go, S., Ellis, E., and Robinson, A. (1968). IgA and partial deletions of chromosome 18. *Lancet*, **2**, 779.
- Wertelecki, W., Schindler, A. M., and Gerald, P. S. (1966). Partial deletion of chromosome 18. *Lancet*, **2**, 641.

mother. The father was 27 years old and there were two older sibs. The mother, father, brother, and sister are all phenotypically normal. There was no family history of mental retardation or congenital malformations. The parents are of Italian ancestry and non-consanguineous.

## Inherited Pericentric Inversion of a Group D (13-15) Chromosome

Pericentric inversions of autosomes have been reported infrequently in human subjects, and have been reviewed by Jacobs *et al* (1967), Weitkamp *et al* (1969), Crandal and Sparkes (1970), and Wilson *et al* (1970).

We report a family showing both a pericentric inversion and an unbalanced crossover segregation product from the inversion. The present family shows inheritance through two generations of a structurally abnormal D chromosome interpreted as a pericentric inversion. The carriers of inversion are phenotypically normal and show no increased frequency of congenital malformation or fetal loss. The propositus described below is the only known individual with an unbalanced crossover segregation product from the inversion.

### Case Report

The pedigree of the family is shown in Fig. 1. The propositus, a male infant (III.3), was the product of a full term pregnancy born to a gravida 3, para 2 25-year-old

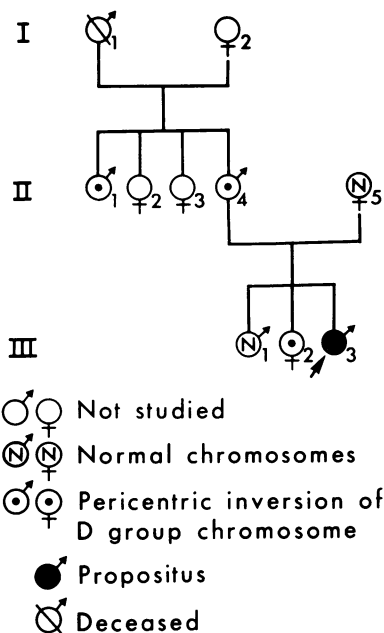


FIG. 1. Pedigree of the family.

The propositus weighed 2890 g at birth. He had some respiratory distress on the second day of life and radiographs revealed an over-inflated, hyperlucent left lung. Repeat radiological examination on the 7th day revealed equal expansion and aeration of both lungs.

The patient was first admitted to The Hospital for Sick Children at 5 weeks of age because of difficulty in breathing and diarrhoea. He weighed 4.2 kg, was 56 cm long, and lay in an opisthotonic position. He had an unusual looking round face with slight micrognathia and somewhat low set ears (Fig. 2). There was pitting oedema of both feet. The heart, lungs, and abdomen appeared normal except for a small umbilical hernia. External genitalia were normal male and both testes were descended (Fig. 3).

The infant was treated for gastroenteritis and discharged after 20 days of hospitalization. Since then he has been hospitalized on 4 separate occasions for repeated attacks of pneumonia and respiratory distress.

He was last admitted in June 1969 at 9 months of age because of cardiac failure and severe respiratory distress. He weighed 7.5 kg (<3rd centile). A loud pansystolic murmur was heard best in the 4th left intercostal space