pass through a cell membrane without its dissolved salt (O'Donovan, 1960). This probably applies also to the entry of fluid into the eye. There is also good evidence that the ciliary body maintains an active transport of sodium (Cole, 1960), which must be of primary importance in determining the volume of intraocular fluid—that is, the intraocular pressure throughout the day.

In conclusion, I would like to record my appreciation of the honour of being invited to give this Lecture—and of the facilities provided by the Birmingham and Midland Eye Hospital which have made this research work possible.

I am indebted to the editors and publishers of the *Transactions of the Ophthalmological Society of the United Kingdom* and of the *British Journal of Ophthalmology*, respectively, for permission to reproduce Figs. 1 and 3, and 7 to 11.

REFERENCES

- Barraquer, J., and Escibano, J. (1957). *Rev. clin. esp.*, **64**, 310.
 Becker, B. (1955). *Amer. J. Ophthalm.*, **39**, No. 2, Suppl., p. 177.
 — (1957). *Arch. Ophthalm.* (Chicago), **58**, 862.
 Brown, J. A. (1943). *Brit. med. J.*, **2**, 201.
 Campbell, D. A. (1952). *Trans. ophthalm. Soc. U.K.*, **72**, 457.
 — (1960). *Brit. J. Ophthalm.*, **44**, 415.
 — Hay, K. M., and Tonks, E. L. (1951). *Brit. med. J.*, **2**, 1424.
 — Jones, M., Renner, N. E. A., and Tonks, E. L. (1957). *Brit. J. Ophthalm.*, **41**, 746.
 — Renner, N. E. A., and Tonks, E. L. (1958). *Ibid.*, **42**, 732.
 — Tonks, E. L., and Jones, M. (1956). *Ibid.*, **40**, 283.
 Cole, D. F. (1960). *Ibid.*, **44**, 225.
 Davies, D. W. (1959). *Brit. med. J.*, **1**, 214.
 Davson, H. (1956). *Physiology of the Ocular and Cerebrospinal Fluids*. Churchill, London.
 Duke-Elder, Sir W. S. (1957). *Trans. ophthalm. Soc. U.K.*, **77**, 205.
 Galin, M. A., Aizawa, F., and McLean, J. M. (1959a). *Arch. Ophthalm.* (Chicago), **62**, 347.
 — (1959b). *Ibid.*, **62**, 1099.
 Glushien, A. S., and Fisher, E. R. (1956). *J. Amer. med. Ass.*, **160**, 204.
 Hay, K. M. (1952). *Practitioner*, **168**, 271.
 Javid, M. (1958). *Surg. Clin. N. Amer.*, **38**, 907.
 Langham, M. E. (1955). *J. Physiol. (Lond.)*, **128**, 78P.
 — and Lee, P. M. (1957). *Brit. J. Ophthalm.*, **41**, 65.
 Lawrence, W. (1833). *Treatise on the Diseases of the Eye*. London.
 Leydhecker, W. (1950). *Brit. J. Ophthalm.*, **34**, 457.
 Mackenzie, Sir W. (1830). *Treatise on Diseases of the Eye*. Longman, London.
 Middlemore, R. (1835). *Treatise on the Diseases of the Eye*. Longman, London.
 O'Donovan, D. K. (1960). *J. Irish med. Ass.*, **46**, 64.
 Pitts, R. F. (1959). *The Physiological Basis of Diuretic Therapy*. Thomas, Illinois, U.S.A.
 Smith, Priestley (1879). *Glaucoma*. Churchill, London.
 Stubbs, J., and Pennybacker, J. (1960). *Lancet*, **1**, 1094.

"Drugs cost £10,500 more in 1959–60 and medical and surgical equipment £19,000 more. A good deal of the increase for 1959–60 was deliberate, since whatever spare resources were available towards the end of the year were devoted mainly to clearing requests for such items outstanding from previous years because of lack of funds. The results for the third financial year of the new method of hospital costing confirmed earlier impressions that the B'ward's hospitals are economical in comparison with other like hospitals. At the Royal Hospital in 1959–60, for instance, it cost £25 10s. 1d. to treat an in-patient for one week, which is the lowest cost of all acute teaching hospitals operating the main costing scheme and compares very favourably with an average cost of £30 14s. 11d. per week for acute teaching hospitals in the provinces and £36 6s. 8d. for those in the London area. It is even slightly lower than the average weekly cost of £25 12s. for all acute non-teaching hospitals in England and Wales. Similarly, the cost of an out-patient attendance at the Royal Hospital in 1959–60 was, at 4s. 9d., lower than at any other acute teaching hospital, and also lower than the average for any non-teaching hospital Region in England and Wales." (*United Sheffield Hospitals Twelfth Report*, 1960.)

A NEW VARIANT OF HUMAN INTERSEX WITH DISCUSSION ON THE DEVELOPMENTAL ASPECTS*

BY

PRABHAKER N. SHAH, M.D., F.C.P.S.(Vet.)

S. N. NAIK, B.Sc., M.Sc.

D. K. MAHAJAN, M.Sc.

M. J. DAVE, M.Sc.

AND

J. C. PAYMASTER, F.R.C.S.Ed.

Indian Cancer Research Centre and Tata Memorial Hospital,
Parel, Bombay 12, India

The recent chromosome studies on the various intersex states in man suggest that the Y chromosome is strongly male-determining (Jacobs and Strong, 1959; Ford *et al.*, 1959). There is, however, some evidence to suggest that the presence of the Y chromosome is not sufficient to ensure normal development of male gonads and genitalia. In testicular feminization (Jacobs *et al.*, 1959; Grumbach, 1960) and in "pure" gonadal dysgenesis (Harnden and Stewart, 1959) a nearly normal female phenotype develops in the presence of a Y chromosome. Moreover, the development of testicular tissue, and masculinization, in the absence of a Y chromosome in some cases of true hermaphroditism (Harnden and Armstrong, 1959; Hungerford *et al.*, 1959; Ferguson-Smith *et al.*, 1960; Marques de Assis *et al.*, 1960; Shah *et al.*, 1961), suggests that other factors play an important part in influencing the course of sex development. This hypothesis is strongly supported by the present case, in which bilateral testes were found in a patient with apparently an XX sex-chromosome constitution. This patient, but for the cytological studies, would undoubtedly have been classified as a male pseudo-hermaphrodite. We feel that the detailed clinical, endocrinological, and cytological studies on this case provide valuable new information on the spectrum of intersexuality in man.

Case History

The patient was referred to the endocrine clinic at this institution on June 30, 1959, when he was 20 years of age, with ambiguous external genitalia. According to his father, the patient was a full-term spontaneously delivered baby. For the first two weeks after birth the patient's grandmother, however, doubted the correctness of the assignment of sex in view of the size of the phallus, and therefore a doctor was consulted. The family physician confirmed the male sex of the patient and thereafter he was reared as a boy. The father was advised to have the child operated on for hypospadias when he reached the age of 10 years. It was when he was presented for this operation in June, 1959, that he came to our notice.

The father was 35 and the mother 19 years old when the patient was born. The mother had no illness, nor was she given any hormone treatment during the first trimester of pregnancy. Inquiry into the history of the sibs of the father and mother and their children revealed nothing pertinent. The patient is the oldest in a sibship of nine (five males and four females). He has had no serious illness

*Based on the paper presented at the First International Congress of Endocrinology, Copenhagen, 1960.

except cerebral malaria at the age of 2 years and typhoid at the age of 3 years. On the whole he has enjoyed good health, though his physical growth and mental development have always been below normal. His I.Q. is less than 50.

Physical Examination.—At the time of admission the patient was a slightly built, poorly nourished individual with a pigeon-shaped chest. He had no facial or axillary hair. The suprapubic hair was sparse and of feminine distribution (Fig. 1). In the left inguinal canal a reducible round mass 3 cm. in diameter was seen to bulge out (Fig. 2 A). His voice was slightly broken. He weighed 75 lb. (34 kg.) and measured 60 in. (152.5 cm.) in height. He had eunuchoid skeletal proportions; the span was 64 in. (162.5 cm.); pubic symphysis to vertex measured 28 in. (71 cm.), and the sole to pubic symphysis 32 in. (81 cm.). Blood-pressure was 108/70 mm. Hg.

The external genitalia were hermaphroditic in appearance. The phallus was 4.5 cm. in length and 6.5 cm. in girth. There were two skin folds with scrotal rugae and pigmentation, but no gonads could be palpated in these. Separation of these folds revealed a vestibulum in which separate urethral and vaginal openings were present (Fig. 2 B). The vaginal canal measured 7.5 cm. in length. On rectal examination no midline structure—for example, prostate or uterus—was palpable. The rest of the clinical examination revealed nothing of note.

FIG. 1

Laboratory Findings.—The routine urine and blood analyses (including the haemoglobin pattern) showed no unusual feature. Fluoroscopic examination of the chest disclosed no abnormality. X-ray photographs of the limbs revealed no structural abnormality, but the bone age was 14 years. The skull was normal. Radio-opaque material was injected into the vagina under pressure. Fig. 3 shows an x-ray photograph of the pelvis in which can be seen a vaginal canal with a thin tract extending into the right pelvic cavity suggesting a fistulous tract—remnant of the Müllerian duct.

The urinary excretion of 17-ketosteroids was 5.5 mg./24 hours (average of three estimations); and the 17-ketogenic steroids excretion was 6.1 mg./24 hours (average of three estimations). The plasma corticosteroids were 20–21 µg./

100 ml. of plasma. The urinary gonadotrophins were raised at 100 m.u. per 24 hours.*

The findings on laparotomy are shown in Fig. 4. On each side a gonad macroscopically resembling a testis was present. Similarly, structures resembling epididymis and vas deferens

FIG. 3.—X-ray photograph of the pelvis after injection of a radio-opaque material, revealing a vaginal canal and a thin tract on the right side representing the remnant of the right Müllerian duct.

FIG. 4.—Artist's sketch of the findings seen on exploration of the abdomen.

were present on each side. A broad ligament was present but no uterine mass was seen or palpable. The structures shown in the areas demarcated within the dark circle were removed and subjected to histological examination.

Each gonad measured 2 cm. in length, 1 cm. in breadth, and 0.8 cm. in thickness. Histological examination of the gonad stained with haematoxylin and eosin revealed immature seminiferous tubules lined by a single layer of undifferentiated cells. Fields showing six or seven hyalinized tubules were occasionally seen in some of the sections. The Leydig cells were seen in well-defined large clumps localized near the tubules; these cells have vesicular nuclei with well-defined granular cytoplasm (Fig. 5). Sections of the testis stained with Mallory's connective-tissue stain showed a mild degree of tubular fibrosis, and those stained with Weigert's stain revealed a total absence of elastic fibres in the tubular wall of the testes.

Microscopical examination of sections of the organs resembling epididymis and vas deferens on both sides

FIG. 2.—Close-up of the external genitalia. A: showing the bulging of a round mass 3 cm. in diameter in the left inguinal region. B: the hermaphroditic appearance of external genitalia.

*At our laboratory the normal hormonal values in women of active reproductive ages are as follows: urinary 17-ketosteroids, 4–13 mg./24 hours; urinary 17-ketogenic steroids, 4–10 mg./24 hours; plasma corticosteroids, 5–22.5 µg./100 ml. of plasma; urinary gonadotrophins, 6–50 m.u./24 hours.

revealed the typical structure of these tissues (Fig. 6 A and B).

The nuclei of the Leydig cells of the testes and also of cells from the skin, the buccal mucosa, and the vaginal epithelium showed a normal female proportion of sex

FIG. 5.—Histological section from the right testis. (H. and E. $\times 140$.) The sections from the left gonad were identical in appearance.

chromatin bodies. The sex chromatin bodies were typical and were stained by the modified Feulgen technique (Lillie, 1954).

A skin biopsy specimen was sent from Bombay to Edinburgh, and a culture was established from this tissue by the method of Harnden (1960). The chromosomes were found to be 46 in number and indistinguishable from those of a normal female—that is, they had an apparently XX sex chromosome constitution. The few cells with other than 46 chromosomes are thought to be due to technical errors, and the cell with a count of 47 chromosomes could not have been interpreted as having an XXY sex chromosome constitution (see Table I and Fig. 7). A second biopsy specimen sent later failed to grow.

Discussion

Recent data indicate that Klinefelter's syndrome, which was thought at one time to be an example of complete sex reversal in the chromatin-positive individual, is associated with an abnormal complement of sex chromosomes (Jacobs and Strong, 1959). The only apparent exception is the case reported by Ford *et al.* (1958) to have 46 chromosomes and an XX sex chromosome constitution. This finding was based on

Chromosome Counts From Skin

Chromosome Count					Total Cells	
<45	45	46	47	>48	Counted	Analysed
2	2	26	1	—	31	3

FIG. 7.—Mitotic metaphase of a cell from skin culture. This shows 46 chromosomes and XX constitution.

the examination of only five cells and is therefore not thought to be conclusive. All the other reported cases of chromatin-positive Klinefelter's syndrome appear to have an XXY sex chromosome constitution or are XX/XXY sex chromosome mosaics (Ford *et al.*, 1959).

FIG. 6.—Histological section from the right epididymis (A) and vas deferens (B). (H. and E. $\times 44$.) The sections from the similar structures on the left side revealed identical microscopical pictures.

The present patient, therefore, is the first chromatin-positive individual in whom both gonads, on detailed sectioning, proved to be testes and whose sex chromosome constitution is apparently that of a normal female.

This observation in itself suggests that an abnormal complement of chromosomes is not the only mechanism through which abnormal sex development is brought about and that several causal factors may be involved. The fact that all the cases of chromatin-positive true hermaphroditism so far studied have a normal female chromosome constitution also supports this contention (Harnden and Armstrong, 1959; Hungerford *et al.*, 1959; Ferguson-Smith *et al.*, 1960; Marques de Assis *et al.*, 1960; Shah *et al.*, 1961). The finding that there is a female sex chromatin pattern in various tissues of this patient and that the cells of a small skin biopsy specimen have normal female chromosomes does not rule out the possibility that the patient may be an XX/XXY mosaic. This could probably be resolved by examination of the chromosomes from the peripheral blood or bone-marrow, but this is not at present possible.

If by further study we exclude this possibility, two interpretations can be offered for the altered gonadogenesis which would be consistent with the finding of an XX sex chromosome complement. First the sex reversal could have been effected by an autosomal recessive gene mutation such as the one described in *Drosophila* by Sturtevant (1945). An alternative explanation would be that deleterious environmental factors had destroyed the cortex at the time when cortico-medullary competition is occurring. If either of these explanations is correct the present case may be only a partial expression of the phenomenon, and it may be that an individual clinically indistinguishable from a case of chromatin-positive Klinefelter's syndrome may eventually be found to have a normal female chromosome complement.

Whatever the various aetiological factors may be in this particular case, they appear to act either through their influence on the production of foetal testicular morphogenetic secretion or by altering the responsiveness of the tissues to these hormones. The evidence is not at present sufficient to enable one to choose between these two alternatives.

As we pointed out at the beginning, it is wise to think of human intersexuality as a spectrum of cases, or perhaps several such spectra, rather than as a number of clearly defined categories into which individual cases can be neatly fitted. One can postulate a spectrum of individuals with an XX sex chromosome constitution ranging from the normal female on the one hand to the hypothetical Klinefelter's type male with an XX sex chromosome constitution on the other. The present case would fit well into this spectrum. In the normal female only the cortex of the gonad is developed. One half of the spectrum would be composed of individuals with a decreasing amount of cortical development and no medullary development. At the midpoint would be cases of pure gonadal dysgenesis where both cortex and medulla fail to develop (Hoffenberg and Jackson, 1957). The other half of the spectrum would be composed of individuals in whom the cortex failed to develop and in whom there is an increasing amount of medullary development. The case of Greenblatt *et al.* (1956) which is now designated "ovarian dysgenesis with vestigial medullary development," where the cortex fails to develop but where a slight development of the medulla

gives a phallic enlargement in an otherwise female phenotype, would be one of the first cases in this progression. The present case where the extensive development of the medulla combined with absence of the cortex leads to a considerable degree of masculinization, would be a link between Greenblatt's case and the hypothetical XX case of Klinefelter's syndrome.

Summary

A case of male pseudohermaphroditism having female sex chromatin pattern in several tissues and normal female chromosome constitution from the skin culture is presented. These findings are discussed in the light of the present knowledge on the developmental aspects of intersexuality.

We are grateful to Dr. V. R. Khanolkar, Director, Indian Cancer Research Centre, for the interest he has shown in this investigation and for his encouragement. We are deeply indebted to Dr. D. G. Harnden, of the Western General Hospital, for carrying out the chromosomal study of this patient. We thank Dr. Warren O. Nelson, Medical Director, Population Council Inc., New York, for reviewing the sections of the testes, epididymis, and vas deferens, and Miss Perin Master for carrying out the I.Q. test of the patient.

REFERENCES

- Ferguson-Smith, M. A., Johnston, A. W., and Weinberg, A. N. (1960). *Lancet*, **2**, 126.
 Ford, C. E., Jacobs, P. A., and Lajtha, L. G. (1958). *Nature (Lond.)*, **181**, 1565.
 — Polani, P. E., Briggs, J. H., and Bishop, P. M. F. (1959). *Ibid.*, **183**, 1030.
 Greenblatt, R. B., Carmona, N., and Higdon, L. (1956). *J. clin. Endocr.*, **16**, 235.
 Grumbach, M. M. (1960). In *Clinical Endocrinology I*, edited by E. B. Astwood, p. 407. New York.
 Harnden, D. G. (1960). *Brit. J. exp. Path.*, **41**, 31.
 — and Armstrong, C. N. (1959). *Brit. med. J.*, **2**, 1287.
 — and Stewart, J. S. S. (1959). *Ibid.*, **2**, 1285.
 Hoffenberg, R., and Jackson, W. P. U. (1957). *Ibid.*, **1**, 1281.
 Hungerford, D. A., Donnelly, A. J., Nowell, P. C., and Beck, S. (1959). *Amer. J. hum. Genet.*, **11**, 215.
 Jacobs, P. A., Baikie, A. G., Court Brown, W. M., Forrest, H., Roy, J. R., Stewart, J. S. S., and Lennox, B. (1959). *Lancet*, **2**, 591.
 — and Strong, J. A. (1959). *Nature (Lond.)*, **183**, 302.
 Lillie, R. D. (1954). *Histopathologic Technic and Practical Histochemistry*, p. 132. Blakiston, New York.
 Marques de Assis, L., Epps, D. R., Bottura, C., and Ferrari, I. (1960). *Lancet*, **2**, 129.
 Shah, P. N., Mahajan, D. K., and Paymaster, J. C. (1961). Unpublished data.
 Sturtevant, A. H. (1945). *Genetics*, **30**, 297.

The *Annual Report of the National Assistance Board 1960* (Cmd.1410, H.M.S.O.) records a total net expenditure during the year of about £187½m., of which more than £166m. was for allowances under the National Assistance Act, 1948, and nearly £11m. for non-contributory old age pensions. Weekly national assistance allowances increased in number during the year to 1,857,000. A majority (70%) of the 1,857,000 allowances were being paid to old people. Sick people and others unable to work—for example, women with family ties—accounted for about 23%; less than 7% were unemployed and registering for work. Most recipients—two out of every three—were women; most of these were widows, mainly elderly widows receiving retirement pensions by right of their husbands' national insurance. This year's *Report* also deals specially with three small "problem" groups: men in doubtful health who have a long record of unemployment, men who seem unwilling to work, and the "unsettled" men who frequent reception centres.