Chromosomal abnormalities and mental disorders

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THE almost constant concomitance of severe intellectual impairment with autosomal chromosome imbalance is well known. Mental defect is a more variable manifestation in the presence of sex chromosome anomalies. In both categories, however, the impairment of cognitive function has been the centre of much attention. The initial reason for this was, no doubt, the discovery of mongolism as the first condition in man to be associated with a chromosomal disorder (Lejeune, Gautier & Turpin, 1959). Subsequently, many cytogenetic investigations have been based on populations of the mentally subnormal with the possible effect that attention has been focused so sharply on cognitive capacity that other aspects of mental function have been relatively neglected, in the early years at least.

It is, however, not true to say that psychiatric changes, especially in the field of personality, had not been observed until recently. Psychological observations on patients with Klinefelter's syndrome were made as early as 1953 by Züblin. New interest was aroused when Court Brown (1962) drew attention to the possibility of a relationship between sex chromosome aberrations and antisocial behaviour. From a study of the histories of males with an abnormal sex chromosome complement in institutions for the mentally subnormal, he found that a high proportion were admitted to such institutions following antisocial acts such as larceny, arson and indecent exposure. Interest in this concept was greatly enhanced by the later findings of Jacobs *et al.* (1965) of men with a XYY sex chromosome complement who had criminal records and were detained at a State mental hospital under conditions of maximum security.

This paper will be confined to psychiatric effects other than cognitive defect found in association with chromosomal disorders. Such effects if present in individuals with autosomal chromosome defects are overshadowed by gross mental subnormality. Therefore, the discussion will be confined to psychiatric effects seen in the most well-defined syndromes associated with abnormalities of the sex chromosomes.

Klinefelter's syndrome (XXY karyotype)

Züblin (1953) made the first psychological

observations of patients with Klinefelter's syndrome before it was technically possible to ascertain the sex-chromatin status of the subjects. He described six patients, of less than average intelligence, as showing some degree of emotional childishness, and being querulous, apathetic and lacking drive. They tended to be withdrawn, and to have difficulty in making relationships with others. They were lacking in sexual drive, and were sensitive about the physical features of their condition including sparse hair, small testes and gynaecomastia.

This picture fits in well with that drawn by Pasqualini, Vidal & Bur (1957) who observed thirty-one Klinefelter subjects. These were described as having been timid and hypokinetic from an early age; as being usually idle, sleeping too much and lacking vital interests. They had few friends, and were shy and restrained.

Nielsen *et al.* (1969) listed the following features as characteristic of individuals with Klinefelter's syndrome: immaturity, insecurity, boastful and self-assertive behaviour, little energy and initiative, none or few spare time interests, poor relations with parents or siblings, few or no friends, school performance below average, a high tendency to word-blindness, mainly doing unexact work as unskilled labourers, a high risk of mental illness, weak sexual libido and potency.

In connection with a high risk of mental illness among patients with Klinefelter's syndrome postulated by Nielsen (1969) one is struck by the comment in the monograph of Nielsen *et al.* (1969) that 'patients with Klinefelter's syndrome are extremely open and confident with very weak and ineffective defence mechanisms, and the frequency of neurosis is most probably much lower than expected in the general population'. It was suggested that a comparatively high percentage of Klinefelter patients showing the symptoms listed above might be diagnosed as suffering from character disorder.

An earlier work, by Forssman & Hambert (1963) throws some light on the kind of psychiatric breakdown that is seen in Klinefelter syndrome patients who have found their way into mental hospitals. They screened the sex chromatin of 1625 men in three mental hospitals and found ten with positive sex chromatin (an incidence of 1:163, which is

greatly in excess of the frequency suggested by Polani (1966) for the XXY karyotype of about one in 600 live-born males at birth). These ten men had a wide variety of psychiatric disorders including episodic confusion, schizophreniform and paranoid states, manic depressive psychosis, obsessional disorders and epilepsy. The majority had abnormal electroencephalograms.

In one of Nielsen's earlier studies (1964) he found five chromatin-positive subjects in a buccal smear survey of 450 male Danish mental hospital patients (giving a proportion of 11.1/1000). Forty-four percent of the group surveyed were schizophrenic patients, and an especially interesting finding was the absence of Klinefelter's syndrome amongst these. This brought the prevalence rate for Klinefelter's syndrome among the non-schizophrenic patients to 20.8/1000, leaving the prevalence rate among the schizophrenics at zero. The idea that the Klinefelter condition may serve as a genetically-based protection against schizophrenia is an attractive one, but schizophrenia coincident with Klinefelter's syndrome has, in fact, been found in other studies. Out of 210 schizophrenic patients Raphael & Shaw (1963) found one patient with Klinefelter's syndrome. Severe psychiatric disorders including schizophrenia in two patients, occurred in one third of the series of fifty patients between the ages of 17 and 66 with Klinefelter's syndrome whose records were studied by Becker *et al* (1966). These patients had been seen at the Mayo Clinic from 1956 to 1962. It should be pointed out that the criteria for psychiatric diagnosis was not made clear in this report.

Turner's syndrome

Turner's syndrome which is characterized by the XO sex chromosome complement may be regarded as the extreme end of the spectrum of ovarian dysgenesis. Patients with Turner's syndrome show dwarfing of stature and a number of marked physical abnormalities which vary from case to case. These include a low growth of hair over the forehead and the nape of the neck, webbing of the neck, a wide carrying angle of the arms, a broad flat shield-shaped chest with widely spaced nipples, absence of secondary sexual development, and amenorrhoea. The last two features are directly related to the basic pathological feature of the syndrome which is ovarian dysgenesis. The ovary is non-functioning and may be represented merely by a streak of fibrous tissue with a few non-functioning graafian follicles.

It is possible that many of the psychological features in Turner's syndrome are secondary, arising from sensitivity due to oddness of appearance or physiological function. In a study by Sabbath *et al*. (1961) of seven adolescent girls with ovarian dysgenesis, the degree of dwarfing of stature seemed to

influence considerably their attitudes and behaviour. Four of these girls were under 55 in. tall, so that they had the appearance of midgets. Their voices were high and thin, and their features were doll-like. Their manner is described as ranging from tom-boyishness to exaggerated prissiness. They tended to be shy in interview and to speak with an air of un-involvement and vagueness. The taller girls in the group looked more like early adolescents; they spoke more freely and spontaneously and showed a broader range of interests. A major concern amongst the group as a whole was their shortness of stature. Some were concerned about their absence of menses and of the normal female bodily characteristics, others denied that they felt a difference in these respects, which may have been a pretence that they did not care. It was felt that the attitude of vagueness and blandness in the group was a result of the powerful sweeping denial used to handle the many conflicts that these girls' congenital abnormality had produced.

Lack of involvement, vagueness, and passivity of personality were also observed in a series of patients with Turner's syndrome studied by Hampson, Hampson & Money (1955). Although none of these girls was considered neurotic or psychotic, lack of mastery, aggressiveness and initiative were seen to be marked characteristics of their personality make-up. In a later study from the Johns Hopkins University School of Medicine (Ehrhardt, Greenberg & Money, 1970) data were in agreement with earlier studies from the Research Unit headed by Dr John Money. These showed that girls and women with Turner's syndrome are unequivocally feminine in their gender role and gender identity based on interest in toys, athletic pursuits, clothing and cosmetics, infant care, boy friends, romance and marriage. The patients and controls were also tested in this study with the Draw-a-Person test and the Lynn Structured Doll Play Test. The results suggested that girls with Turner's syndrome were no less feminine than girls in a control group. Differences which occurred pointed rather in the other direction. The results of this study support very strongly the acceptance of the feminine role by patients with Turner's syndrome.

The XYY syndrome

The first account of a patient with the XYY syndrome was made in 1962 by Hauschka *et al*. Their patient was a 44-year-old man, 6 ft tall, of average intelligence and without conspicuous physical defects. His karyotype was examined on account of abnormality amongst his offspring including a mongol with autosomal trisomy G. No psychiatric abnormalities were noted in his case. His only failing recorded in the report was an

inability to keep employers satisfied with his performance as a manual worker. This single case did not arouse very much attention.

Three years later, however, great interest was aroused in the XYY syndrome following the report by Jacobs *et al.* (1965). They described seven men out of a series of 197 patients with criminal records who were detained at a State mental hospital in Scotland under conditions of maximum security. The clinical observations in these seven patients and in two others subsequently identified in another series of patients at the same hospital were described by Price *et al.* (1966). The XYY males were tall, six of the nine being 6 ft or more in height. Eight of them were classified as being high-grade mental defectives or as being below average in intelligence. The ninth patient was described as being of average intelligence; however, he had a mental illness with schizophrenic features. Most of the series had frequently absconded from other mental hospitals. They had often shown aggressive or violent behaviour. All nine suffered from a severe degree of personality disorder (Price & Whatmore, 1967). This, however, could not be accounted for by any known history of brain damage, epilepsy or psychosis. The outstanding personality features of these men were extreme instability and irresponsibility, and in their criminal behaviour they did not appear to have considered any but the most immediate consequences of their actions. They showed very little depth of feeling in their emotional responses or in relationships with others. Their emotional instability combined with an incapacity to tolerate the mildest frustration seemed to have been their main stumbling block in social adjustment.

It seems that psychiatric manifestation in the form of behaviour disorder can appear at a very early age in the XYY syndrome. Three of the nine XYY males in the series just described had been convicted before the age of 10 years, and at least five of them had been in trouble before this with the Education Authorities or the Police. Evidence of very early psychiatric disturbance in a boy with the XYY syndrome is reported by Cowie & Kahn (1968). This boy's history indicated that he was aggressive and violent from an early age, being seen by a psychiatrist for these reasons initially at 4½ years of age. He would set fire to the room, destroy furniture, and attack other children. He began wandering from home at this age and would travel quite long distances. At school later his truancy and wandering became severe problems, and his vicious attacks on other children and complete lack of response to ordinary discipline called for special schooling at the age of 8½. He had an EEG record with borderline non-specific abnormalities. At the age of 8½ he was above the ninety-seventh percentile for height and

weight and from a baby had always been regarded as being large for his age. This reports suggests that the increased height which is a feature of the XYY syndrome appears before puberty.

The observation of a correlation between the XYY karyotype and violent antisocial behaviour carries with it ethical problems which may be connected with criminal responsibility. The question is not yet answered as to the strength of this correlation. Some XYY individuals have been found to be psychiatrically normal. It is possible that a concatenation of factors may be necessary in the case of a subject with the XYY karyotype to spark off violent and antisocial behaviour. These factors may well include environmental factors. It is very likely that our view of the correlation between criminality, violence and the XYY karyotype is at the moment a biased one. The picture could be made more clear by prospective studies of XYY individuals identified in new-born surveys. A crucial question is put by MacLachlan (1969). He asks, 'If the incidence of XYYs in the population is 1.5/1000 and only about 70 XYYs have been found in the United Kingdom—one expects 1500 among every million males—where are these other XYYs?'

Discussion

There are a number of pointers to suggest organic changes in the brain as a basis for the psychiatric effects seen in individuals with sex chromosome abnormalities. These include the EEG changes that have been observed in a number of studies, three of which are that of Hambert & Frey (1964) on Klinefelter syndrome subjects (age range 9 to over 70 years) and a control series; Mellbin's small but careful study of patients with Turner's syndrome (Mellbin, 1966); and the study of Poole (1969) which included a series of XYY males in a security prison for psychiatric treatment of offenders. Another indicator of organic change, which complements the abnormal EEG findings, is the suggestion of a connection between epilepsy and patients with sex chromosome abnormalities. Hambert (1964) found an increased incidence of chromatin-positive males in Swedish institutions for the epileptic; Nielsen (1969) found an increased frequency of previous and present epilepsy in a series of Klinefelter subjects though the difference was not statistically significant from the prevalence of epilepsy in the mental hospital from which some of the samples were drawn.

Quite a different line of approach has suggested the possibility of organic brain changes in Turner's syndrome. In psychometric studies of patients with this condition, Schaffer (1962) in using the WAIS or WISC tests and the Benton Visual Retention Test found a consistent pattern of cognitive strengths and weaknesses similar to that observed in cases of brain

damage. He suggested that the pattern of cognitive deficit was characteristic of Turner's syndrome, and might stem from an organic defect related to the chromosome anomaly.

It is tempting to speculate on the nature of a causal connection between a sex chromosome abnormality and possible organic changes in the brain. The concepts of Hambert (1964) as to how the Klinefelter syndrome and epilepsy might be connected could be extended to other sex chromosome syndromes and the possible concomitant organic brain changes that may underlie the psychiatric effects that are seen to accompany them. He suggested that possibly the chromosomal aberration leads to abnormality in the tissue of the central nervous system or makes it more vulnerable than otherwise. Possibly a hormonal imbalance (testosterone deficiency in the case of Klinefelter's syndrome) is damaging to the cerebrum during development. Thirdly, aneuploidy like other forms of embryopathy may lead to premature birth, predisposing to brain damage.

At a less fundamental level than the basic aetiology, much is still to be learned about the psychiatric phenomenology of the sex chromosome disorders. The range of psychiatric manifestations (which may extend to within limits of normal) in the different syndromes needs further study. Such work is vital if a scientific basis is to be provided for a solution to the ethical problem of the legal attitude towards criminal offenders who are known to have an abnormal sex chromosome complement.

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