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# SEX CHROMOSOME ABERRATIONS IN SCHIZOPHRENIA

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SUMMARY

Research on sex chromosome aberrations has made considerable progress. There are evidences that possession of an extra X chromosome may affect the mental health of an individual. All the male schizophrenia patients registered during the period of study, who were not under treatment, constituted the patient sample. They numbered two hundered eighty seven. A properly matched control sample of two hundred thirty three healthy persons was also examined. Nuclear sexing and Karyotype was done for (*a*) all the chromatin positive cases in patient as well as control sample (*b*) ten per cent cases of normal XY individual's of patient sample(28) and control sample (23) Photography was done for the positive slides. The patients who showed chromation positive XXY pattern were studied further clinically along with Rorschach test and Bhatia battery. The schizophrenics showed more prevalence of chromatin positive than the control sample.

Research on the implications of sex chromosome aberrations has made considerable progress. Of the two chromosomes, X and Y, more work has been done on the X chromosome because it is comparatively easier to screen large series, consequent on the discovery of sex chromatin by Barr. Screening for the Y chromosomes is rather difficult because of the tissue culture involved. Thus many works are reported on males possessing an extra X chromosome in different clinical conditions. Preponderance of such chromosomal aberration, i.e. an additional X chromosome in cases of mental retardation, compared to general population is an accepted fact today. It has also been postulated (Frosman 1970) that an abnormal sex chromosome complement may have an unfavourable effect on mental health in several ways. It may contribute to the development of functional psychoses and may also influence behaviour. A number of workers have also reported a higher prevalence of sex chromatin in male patients in mental hospitals than in the general population (Carr *et al.*, 1961, Raphel and Shaw 1963, Nielsen 1964a, Hambert 1966, Olanders 1967 and Maclean *et al.* 1968). In view of the fact that schizophrenics constitute the vast majority of mental hospital populations, this higher prevalence rate of sex chromatin in males is likely to have been contributed by them but so far only two surveys of schizophrenics alone have been reported in the literature (Jagielo 1961, Tedeschi and Freeman 1962). Their findings were quite significant. Prevalence rate was found to be 0.94 and 1.21 per cent respectively against an expectation of 0.17 per cent in general population.

Diagnosis of schizophrenia is still a debatable issue and subject to transcultural bias. A diagnosis of schizophrenia by one institution may not be supported by another and even two psychiatrists from the same hospital may not agree on such a diagnosis. Hence more research is necessary to confirm the findings of these two workers. The present project was planned with two aims, firstly to add to the list of earlier works and secondly to report figures from a country where no such work has been reported so far.

## MATERIAL AND METHOD

The present study was carried out at the Armed Forces Medical College between 1975 and 1978. All schizophrenic patients

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admitted to command Hospital, Pune during this period were included. Two patients had to be excluded since they were on a long term drug regime which could have had some effect on the chromosomes. Diagnosis was established clinically along the lines of Chatterjee and Golecha (1974) A total of two hundred eighty seven patients were screened. Chromosomal study was carried out before any drug treatment was started. A control sample of two hundred thirty three healthy volunteer students and staff of the college and hospital was also screened for comparison. Mean age of the test sample was 31.63 years while in the control it was 27.78 years. Mean duration of illness was 170 days. Fresh cases numbered 230 while there were 57 cases admitted on relapse. Table I gives the patient particulars. Clinical presentation of the patients were typed according to the predominant symptom pattern. Clinical typings are presented in Table 2.

TABLE I—(*Patient Particulars*)
(N=287)

| | |
|---|---|
| Mean Age | 31.63 Yrs. s.d.=11.80 |
| Mean Duration of illness | 170 days. s.d.=24.00 |
| Fresh cases | 230.(80%) |
| Relapse cases | 57.(20%) |

TABLE 2—(*Clinical Types*)
N=287

| | | |
|---|---|---|
| Hebephrenic | 63 | 21.95% |
| Catatonic | 102 | 35.54% |
| Paranoid | 87 | 30.31% |
| Simple | 0 | 0 |
| Undifferentiated | 35 | 12.19% |

## METHOD

Chromosomal investigations were carried out at the improvised cytogenetic cell in the ultracentrifuge room of the pathology department of the college. Nuclear sexing and Karyotype of the chromosomal spread both from control and the test sample were strictly done in accordance with the international standardisation of human cytogenetics, as proposed at the Denver Convention (1960). The details were as below :

*Nuclear Sexing*

The method pioneered by Sanderson and Stewart (1961) was adopted, as we found it quite satisfactory and we also had some experience of this method from one of our earlier research projects (Basu and Dutt, 1976). Buccal scrapings obtained by a spatula were deposited on a glass slide. A drop of lacto-aceto orcein was placed on it. Scrapings were mixed with the stain drop by the corner of a slide. Then a cover slip was placed over it. Excess stain was removed from the inverted slide by applying uniform pressure with filter paper. Under an ordinary microscope using 100 objective lens, search was made for any Barr body. Five hundred cells were counted and the presence of Barr body positive cell was expressed as per cent of total cells counted. Fig. I shows a Barr body positive cell.

*Karyotype*

Total chromosomal analysis and karyotype were performed for (*a*) all the Barr body positive cases in the patient sample as well as the control (*b*) ten per cent (28) Barr negative cases and (*c*) ten per cent of the control sample (23). Lymphocyte culture system was adopted along the lines of Moorehead *et al.* (1960) as modified by Basu and Dutt (1976). After treating each culture tube with 0.5 ml colchicine and centrifuging the cell pellets were treated with 0.075 M KCl, incubated and further centrifuged. Pellets were fixed by gradually adding a mixture of methanol and glacial acetic acid (3 : 1) and then centrifuged. The process was repeated thrice till a faint cloudy suspension was obtained. Slides were made, fixed and stained by

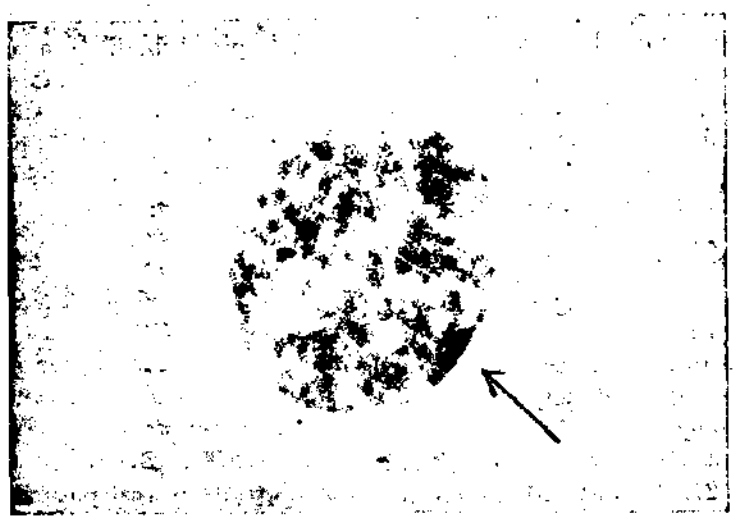

Fig. 1. Arrow points to the Barr body.

acetorcin. Scanning was done under higher objective lens and a number of ideal spreads were selected. Photography was done using an oil immersion lens. Finally Karyotype was done from selected print-out copies of the photograph in the Karyotype card.

*Clinical Evaluation of Positive Cases :*

Detailed clinical study of the symptoms, of premorbid personality and also psychological testing—Rorschach and Intelligence testing (Bhatia's Battery) were done for the positive cases.

OBSERVATIONS

Nuclear sexing pattern of the schizophrenics and the control are presented in Table 3.

TABLE 3—*Nuclear Sexing*

| Sample | No. of Bar positive | Rate per cent |
|---|---|---|
| Schizophrenics (N=287) | 5 | 1.74 |
| Control (N=233) | 1 | 0.42 |

The difference in two samples is statistically significant. ($p<0.01$)

Chromosomal analysis results are tabulated in Table 4.

TABLE 4—*Chromosomal analysis (Karyotype)*

| Sample | Chromatin | Karyotype |
|---|---|---|
| Schizophrenics | 5 | XXY=4<br>XXY/XY=1 |
| Control | 1 | XY=1 |
| Schizophrenics (N=28). | 0 | aXY=28 |
| Control (N=23) | 0 | XY=23 |

It will be seen that sex chromosome abnormalities were found only in the schizophrenics while in all others the XY pattern was present. The single chromatin positive case in the control did not show any chromosome anomaly ; it could have been an artefact. Out of the five abnormal chromosome constitutions in test sample, four had shown XXY pattern while one was a mosaic, with XXY/XY. Fig. 2 shows a typical 47 XXY chromosome pattern, one of the four cases found. Fig. 3A and 3B depict the mosaic, 3A giving the 46 XY pattern and 3B showing the XXY pattern

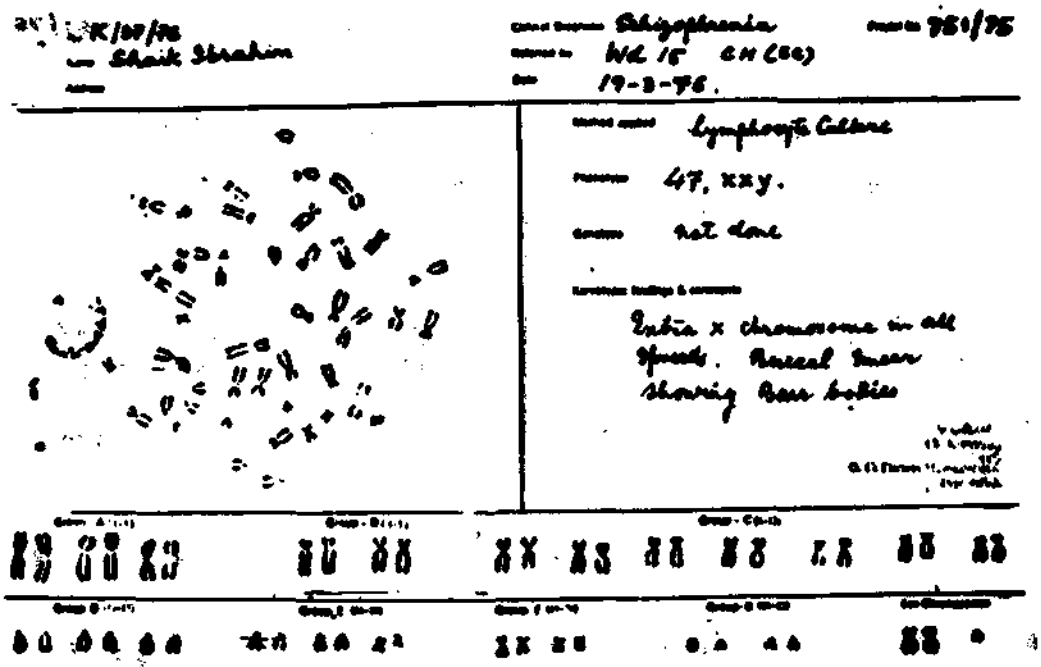


Fig. 2. Typical 47 XXY pattern in one of the positive cases.

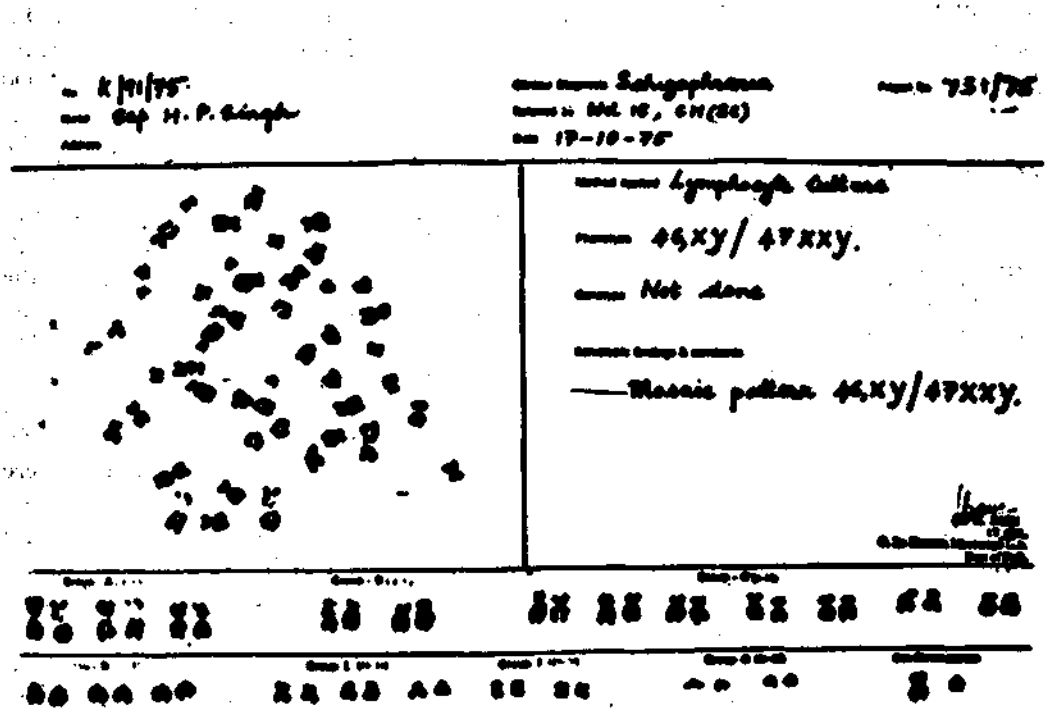


Fig. 3A. Showing 46 XY in the mosaic.

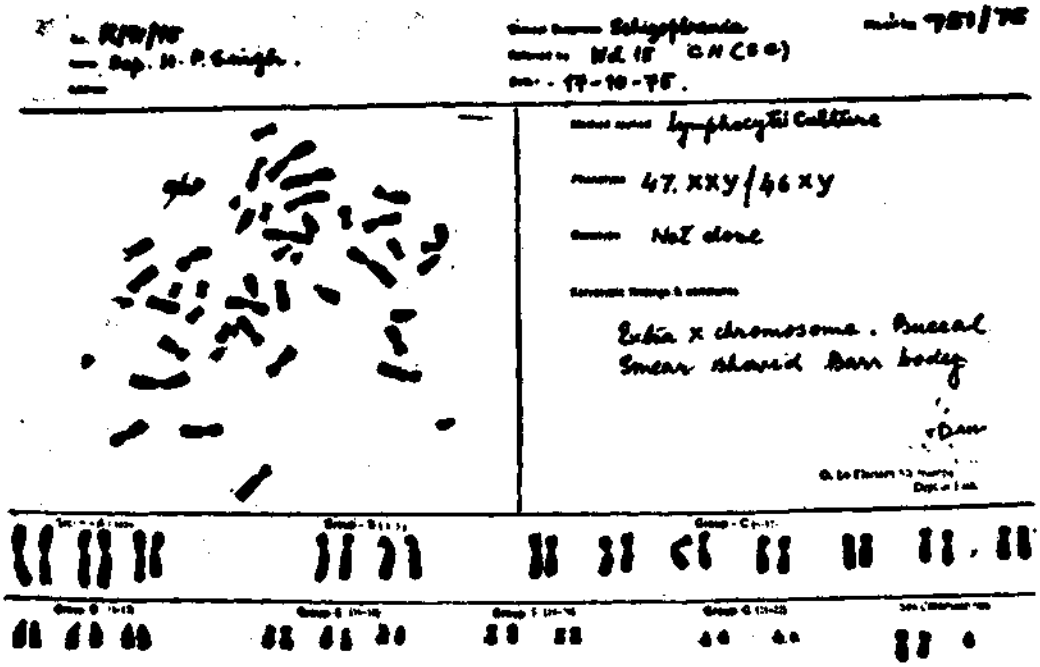


Fig. 3B. Showing 47XXY of the same mosaic.

in two different metaphase Spreads of the same patient.

*Clinical Details of Barr Positive Cases*

Findings of these cases were :

(*a*) Premorbid history was insufficient. Symptom pattern was of paranoid schizophrenia in majority of cases.

(*b*) All of them showed paranoid features in Rorschach test.

(*c*) None had any evidence of testicular atrophy or hypogonadism clinically.

(*d*) Intelligence Quotient of these cases were rather below normal. Mean IQ of the five cases was 83.

Appreciation of the extent of sex chromosome aberration in schizophrenia will be evident if we look at different populations. Let us look first at the extent of positive population at birth. To be relevant to our survey only male births should be taken into account. A number of surveys have been made on the new born male babies in different countries, which are presented in Table 5. Frosman in his Blake Marsh Lecture of 1970 gave a figure of 0.17 per cent from a world pool of 42000 new born boys surveyed and considered the figure as a prototype. The figure in the Table (0.16%) also runs very close to this. But the question remains whether this figure is comparable with that of adult population, to be comparable in turn to the adult schizophrenics? Possibly not, because the figures are higher for still born males, and secondly the chromatin positive boys run the risk of premature deaths too often. Unfortunately not many studies are available in healthy adult males though there are many for the hospital population. Only two such works are available in literature which are given in Table 6 below.

It will be seen that there is not much difference between the figures of adult males and that of new born boys. Now let us see the position in the hospital population. The different surveys have been summarised in Table 7.

After reviewing the surveys in different populations let us concentrate on schizophrenia. As has already been said only two such studies are available; their findings alongwith the present work are presented in Table 8.

TABLE 5—*Nuclear sexing of new born male babies*

| Worker | Country | No. surveyed | No. positive | Per cent |
|---|---|---|---|---|
| Court Brown (1969) .. .. | U. K. .. | 14,000 | 27 | 0.19 |
| Lubo & Ruddle (1969) .. .. | U.S.A. .. | 2,222 | 4 | 0.18 |
| Ratcliffe *et al.* (1970) .. .. | U.K. .. .. | 3,496 | 4 | 0.11 |
| Robinson & Puck (1965 & 1970) .. | U.S.A. .. | 5,000 | 7 | 0.14 |
| Sergovich (1969) .. .. | Canada .. | 1,066 | 1 | 0.093 |
| Walzer *et al.* (1969) .. .. | U.S.A. .. | 1,931 | 4 | 0.20 |
| Total .. .. .. | .. | 27,715 | 47 | 0.16 |

TABLE 6—*Nuclear sexing of adult healthy males*

| Worker | Country | No. examined | No. positive | Per cent |
|---|---|---|---|---|
| Kaplan and Norfleet (1961) .. | U.S.A. .. | 1,000 | 2 | 0.20 |
| Hambert (1965) .. .. | Sweden .. | 2,752 | 6 | 0.22 |
| Total .. .. | .. | 3,752 | 8 | 0.21 |

TABLE 7—*Nuclear sexing of mental hospital population*

| Worker | Country | No. examined | No. positive | Per cent |
|---|---|---|---|---|
| Carr *et al.* (1961) .. .. | Canada .. | 254 | 1 | 0.39 |
| Raphel and Shaw (1968) .. | U.S.A. .. | 105 | 1 | 0.95 |
| Nielsen (1964a) .. .. | Denmark .. | 450 | 5 | 1.11 |
| Hambert (1966) .. .. | Sweden .. | 6,265 | 30 | 0.48 |
| Maclean *et al.* (1968) .. .. | U. K. .. | 6,000 | 30 | 0.50 |
| Total .. .. | .. | 13,074 | 67 | 0.51 |

TABLE 8—*Nuclear sexing of schizophrenic males*

| Workers | Country | No. examined | No. positive | Per cent |
|---|---|---|---|---|
| Jagiello (1961) .. .. | U.K. .. | 530 | 5 | 0.94 |
| Todeschi and Freeman (1962) .. | U.S.A. .. | 248 | 3 | 1.21 |
| Present Study Chatterjee and Basu (1979) | India .. | 287 | 5 | 1.74 |
| Total .. .. | .. | 1,065 | 13 | 1.22 |

TABLE 9—*Chromatin positive cases in mental retardation*

| Workes | Country | No. examined | No. positive | Per cent. |
|---|---|---|---|---|
| Mosier *et al.* (1960) .. | .. U.S.A. .. | 1,252 | 10 | 0.80 |
| Barr *et al.* (1960) .. | .. Canada .. | 1,506 | 13 | 0.86 |
| Maclean *et al.* (1962) .. | .. U.K. .. | 2,607 | 28 | 1.07 |
| de la Chapelle (1963) .. | .. Finland .. | 1,581 | 6 | 0.32 |
| Anderson *et al.* (1964) .. | .. South Africa .. | 763 | 5 | 0.66 |
| Hambert (1966) .. | .. Sewden .. | 958 | 19 | 1.98 |
| Prader *et al.* (1958) .. | .. Switzerland .. | 336 | 8 | 2.38 |
| Total | .. .. | 9,003 | 89 | 0.98 |

We can also take into account the findings of Hambert (1966) (vide Table 7). Out of his 30 chromatin positive caess, 21 had features of undisputable psychosis, paranoid states being the commonest making 0.33 per cent positive which is significantly higher than the expectation. Polani (1969) also surveyed 4306 chronic psychotics of whom 95% were schizophrenic. In his survey 0.6 per cent were chromatin positive. None had any evidence of senile or organic psychoses. There are at least two works in female patients. One is of Maclean *et al.* (1968) and the other of Olanders (1968) in Scotland; together they make 0.28 per cent. prevalence compared to 0.1 per cent in that of the new born girls in the same country. These findings point to the fact that the possession of an extra X chromosome irrespective of sex, is definitely a handicap which increases one's susceptibility to schizophrenia. After all schizophrenia is only a unique way, the central nervous system reacts to injuries ; and this uniqueness is determined possibly by multitude of factors, one of them being an extra chromosome. Schizophrenic reaction could be due to cerebral dysfunction/minimal brain damage, which may in turn may be due to gonosomal aberration. Findings of abnormal EEG pattern in the sex chromatin positive cases of Hambert and Frey (1964, 1966) lead support to this idea. It is certainly not the only cause but one of them surely. Chromosomal aberrations are being increasingly implicated in social maladjustment as well as in criminal conduct. Whether this affects the schizophrenic or not, is anybody's guess.

Since an increased prevalence of chromatin positive cases in Mental retardation is more or less established let us look at this area and try to find out any relation between the two conditions. Some of the important findings of a number of workers are presented for ready reference in Table 9.

For the sake of comparison of all the populations surveyed vis a vis the schizophrenics, a Table is presented below, (Table 10).

TABLE 10—*Chromatin positive prevalence in different categories*

| Category | Total No. examined | Chromatin positive (%) |
|---|---|---|
| A. New born boys | 27,715 | 0.16 |
| B. Adult healthy males | 3,752 | 0.21 |
| 3. Mental hospital adult male patients | 13,074 | 0.51 |
| O. Adult male schizophrenics .. | 1,065 | 1.22 |
| E. Mental retardation adult cases .. | 9,003 | 0.98 |

The differences between D vs A, D vs B, D vs C are significant at 0.001 level while for D vs E it is at 0.02 level.

Cytogenetically all the five chromatin positive cases were Klinefelter's syndrome. (A mosaic pattern is also known in this disease). They were all either normal or slightly below normal in their intelligence. This brings us to the question of whether there is a relation between schizophrenia and mild mental retardation. It appears that there is a positive relation. Today we do not believe that the mental features of Klinefelter's disease are secondary to the hypogonadic state but rather that most of the symptoms are psychogenic. In fact many patients are not hypogonadic; in our series none had any evidence of this. Possession of one extra X chromosome is probably responsible for withdrawal, asocial and antisocial features. If the number of extra chromosome is more than one, e.g. XXXY or XXXXY, then retardation is very profound (Polani 1969). In some of the surveys where nuclear sexing has been done on the antisocial group of mentally retarded only, the prevalence of XXY pattern is much higher than the mentally retarded in general. Frosman and Hambert (1963) found as many as 2 per cent sex chromatin positive in antisocial slightly retarded men. Hambert also showed that this rate was ten times the rate in the normal population and significantly higher than the mentally retarded in general, who were not antisocial. Prader (1958) also says that this syndrome is five to ten times more common in subnormals. Nielsen (1964b), Casey *et al.* (1966) and Court Brown *et al.* (1968) confirmed these findings. Money and Hirsch (1963) found five sex chromatin positive in 1700 mental defectives and of the five, two were schizophrenics. On the other hand in the report of Tedeschi and Freeman (1962) of the three chromatin positive cases among 248 schizophrenics, only one was a mental defective. On the basis of these observations one is tempted to postulate that possession of a XXY constitution either in the normal population or in the retarded, is a handicap which makes one vulnerable to schizophrenia.

Preponderance of chromatin positive cases in schizophrenia brings a few more considerations. In classical psycho-analysis, conflict and confusion in bisexual identification are well known dynamics of the schizophrenics . Will these XXY cases account for the curable cases of Kemft (1949)? It may also account for at least some of the latent schizophrenics manifesting in homosexuality. Paranoid symptoms appearing so commonly in these cases might be their self-defence. Rorschach studies have demonstrated the defence (Zucker 1952), and it is worhtwhile to do the nuclear sexing in these cases, when most of these cases fall into the paranoid types. Low androgen excretion some times reported in the male schizophrenics as by Hoskins and Pincus (1949) could also be due to these XXY cases.

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