This could be due to some central effects of the medication or to misinterpretation of the peripheral side-effects and possible autonomic instability. The latter seemed to be a factor in case (f).

Conclusion

These cases provide further evidence for the occurrence of panic attacks outside of pure panic disorder, with or without agoraphobia. Their relationship to the patients' other, schizophrenic, symptoms varied from running a closely parallel course to being apparently independent. It is suggested that antipsychotics may increase panic attacks in some cases.

References

AMERICAN PSYCHIATRIC ASSOCIATION (1980) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn) (DSM-III). Washington, DC: APA.

—— (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III-R). Washington, DC: APA.

ARGYLE, N. (1988) The nature of cognitions in panic disorder. *Behaviour Research and Therapy*, **26**, 261–264.

—— & ROTH, M. (1989) A phenomenological study of 90 patients with panic disorder. Part II. *Psychiatric Developments*, **3**, 187–209.

ASHTON, C. H. (1987) Caffeine and health. *British Medical Journal*, **295**, 1293–1294.

BOYD, J. H. (1986) Use of mental health services for the treatment of panic disorder. *American Journal of Psychiatry*, **143**, 1569–1574.

DONALDSON, S. R., GELENBERG, A. J. & BALDESSARINI, R. J. (1978) The pharmacologic treatment of schizophrenia. *Schizophrenia Bulletin*, **9**, 504–527.

GRUZELIER, J. H. & VENABLES, P. H. (1972) Skin conductance orienting activity in a heterogenous sample of schizophrenics; possible evidence of limbic dysfunction. *Journal of Nervous and Mental Disease*, **155**, 277–287.

KAHN, J. P., DRUSIN, R. E., KLEIN, D. F., *et al* (1987) Schizophrenia, panic anxiety and Alprazolam (letter). *American Journal of Psychiatry*, **144**, 527–528.

——, ——, ——, *et al* (1988) Adjunctive alprazolam for schizophrenia with panic anxiety: clinical observation and pathogenetic implications. *American Journal of Psychiatry*, **145**, 742–744.

KLEIN, D. F. (1980) Anxiety reconceptualised. *Comprehensive Psychiatry*, **21**, 411–427.

LADER, M. H. & MATHEWS, A. M. (1968) A physiological model of phobic anxiety and desensitisation. *Behaviour Research and Therapy*, **6**, 411–421.

SANDBEG, L. & SIRIS, S. (1987) Panic disorder in schizophrenia. *Journal of Nervous and Mental Disease*, **175**, 627–628.

SPITZER, R. L. & WILLIAMS, J. B. W. (1983) *Structured Clinical Interview for DSM-III-R, Upjohn version. 10/15/83*. New York: New York State Psychiatric Institute.

WORLD HEALTH ORGANIZATION (1978) *Mental Disorders: Glossary and Guide to their Classification in Accordance with the Ninth Revision of the International Classification of Diseases* (ICD-9). Geneva: WHO.

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Schizophrenia and Marfan Syndrome

PINKHAS SIROTA, MOSHE FRYDMAN and LEA SIROTA

Five index patients and three of their first-degree relatives were affected both by schizophrenia and Marfan syndrome. Since the association appears statistically significant, the possibility of linkage disequilibrium between adjacent genes or a cytogenetic abnormality causing both disorders is suggested. These hypotheses are testable and hold promise in attempting to map the 'schizophrenia susceptibility gene' by the candidate-gene approach.

Marfan syndrome (MS) is a dominantly inherited disorder of connective tissue. Typically, the patients are tall and have an asthenic body build. Stretching of the zonula with dislocation of the lenses, dilatation of the aortic root, prolapse of the mitral valve, and often fatal dissection of the aorta are the most

characteristic and serious findings. Many additional features have been reported, but in the absence of a biochemical test or marker, the presence of at least one major musculoskeletal, cardiac or ocular feature, in addition to the typical phenotype, is necessary for unequivocal diagnosis (Pyeritz & McKusick, 1979).

A patient with MS and schizophrenia has been reported by Romano & Linares (1987). We report five unrelated patients and three of their first-degree relatives, who had both conditions.

Case reports

Patients 1–4 were in-patients of Gehah Psychiatric Hospital and were referred and admitted for schizophrenia. In patients 2 and 3, MS was suspected clinically by one of us (PS) and the diagnosis confirmed as indicated in Table I. Cases 1 and 4 were ascertained by systematically studying patient records, looking for MS. Patient 5 was referred from a genetic clinic in another hospital because of suspected schizophrenia. Information regarding three additional cases was obtained through family studies of the index patients. The family pedigrees are shown in Fig. 1.

The diagnosis of MS in our patients complied with the stringent criteria of Pyeritz & McKusick (1979). Similarly, the diagnosis of schizophrenia was based on the DSM-III-R classification (American Psychiatric Association, 1987).

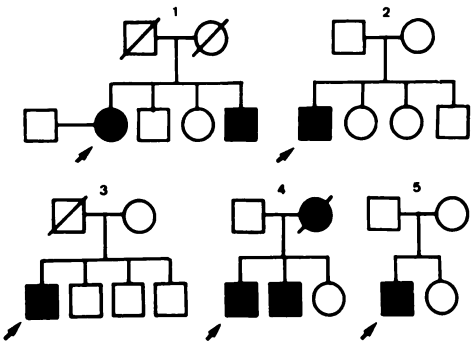

FIG. 1. Family pedigrees 1–5, indicated by arrows (□ male, ○ female, filled shapes indicate sufferers and bars indicate deceased family members).

Case 1

The patient was evaluated at the age of 51 years. She has a brother with schizophrenia and MS, a sister with hyperglycosuria who is otherwise normal, and an unaffected brother. The patient is of Ashkenazi Jewish origin. Her

TABLE I
Characteristics of five patients with the Marfan syndrome and schizophrenia

	1	*2*	*3*	*4*	*5*
Sex	F	M	M	M	M
Age: years	51	19	26	23	19
Height: m (percentile)	1.78 (>97)	1.98 (>97)	1.97 (>97)	2.01 (>97)	1.86 (90)
Clinical features					
Ocular					
ectopia lentis	+	–	–	+	–
myopia	–	+	+	–	+
other	+	–	–	–	–
Cardiovascular					
clinical evidence for mitral-valve prolapse	+	+	+	+	+
echo evidence for mitral-valve prolapse	not done	+	+	–	+
clinical evidence for aortic regurgitation	+	+	+	–	+
echo evidence for aortic regurgitation	not done	+	+	–	+
Musculoskeletal					
arachnodactyly	+	+	+	+	+
pectus deformity	+	+	+	+	+
high narrow palate	+	+	+	+	+
joint hypermobility	+	+	+	+	+
vertebral column deformity	+	+	+	+	+
inguinal hernia	–	+	–	+	–
Positive family history	MS/S[1]	–	–	MS/S[1]	–
Age at onset of schizophrenia: years	19	14	19	20	17
Type of schizophrenia	Paranoid	Disorganised	Disorganised	Paranoid	Paranoid

1. Marfan syndrome and schizophrenia.

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parents and the rest of her family perished in the Holocaust and no other data are available. The diagnosis of MS was based on the findings reported in Table I, including cataract and adhesions of the lens to the cornea.

She was admitted several times for long periods in different psychiatric hospitals because of thought disorders with persecutory delusions, ideas of reference, blunted affect, and auditory hallucinations, with constant deterioration in her personality and narrowing of her ability to form interpersonal relationships.

Case 2

A 19-year-old male of Sephardic Jewish origin had multiple admissions to different mental hospitals because of schizophrenia since the age of 14. The diagnosis of MS was based on skeletal, ocular and cardiovascular findings (Table I). In addition, the metacarpal index of the second and third metacarpals in both hands was 9.4 and 9.2 respectively (normal up to 8.7).

His parents and three siblings are normal.

Case 3

A 26-year-old male of Ashkenazi Jewish origin had, since 14 years of age, presented disturbed emotional and social behaviour, and at 19 years of age he had an acute psychotic episode which led to admission and to his premature discharge from military service. He was diagnosed as suffering from hebephrenic schizophrenia (disorganised type).

The diagnosis of MS was established at 26 years of age and was based on the typical musculoskeletal, ocular and cardiac findings (Table I).

His parents and three siblings are normal.

Case 4

A 23-year-old male of Sephardic Jewish origin was found to have schizophrenia of the paranoid type. The diagnosis of MS was based on the typical musculoskeletal ocular and cardiac features (Table I).

His mother, a schizophrenic, died of heart disease associated with MS and an affected brother had cardiac surgery and is reported to suffer from schizophrenia. The father and another sibling are normal.

Case 5

A 19-year-old male of Sephardic Jewish origin was admitted to a psychiatric hospital at age 17 because of a paranoid hallucinatory episode. Subsequently, he had multiple psychiatric admissions and was diagnosed as having schizophrenia, paranoid type.

The patient had the typical musculoskeletal, ocular and cardiac findings of MS (Table I).

The parents and his sister are normal.

Laboratory studies

Urinary excretion of amino acids was normal in all patients and homocystinuria and cystinuria were excluded by the cyanide nitroprusside test.

Discussion

Although the basic defect in MS is yet unknown, many lines of evidence indicate that abnormal collagen is being produced (Pyeritz & McKusick, 1981). In fact, a 38-base-pair insertion in the gene encoding the alpha-2 chain of type I collagen on chromosome 7q was reported in one case by Henke *et al* (1985). However, other workers did not find linkage between MS and the four major fibrillar collagen genes on chromosomes 17q, 7q, 12q, and 2q (Ogilvie, *et al*, 1987). These data support the notion that MS is genetically heterogeneous, and raise the possibility that a mutation in a gene responsible for post-transcriptional modification of collagen is the cause of MS (Pyeritz & McKusick, 1981; Ogilvie *et al*, 1987).

Sherrington *et al* (1988) studied five Icelandic and two British families and found strong evidence localising a schizophrenia-susceptibility locus to proximal 5q ($z = 6.49$). However, another group of investigators studying the same markers and several other loci on the long arm of chromosome 5 found no suggestion of linkage with any of the markers studied. Furthermore, they were able to exclude linkage across 40 map units (cM) of this region (Kennedy *et al*, 1988). Since schizophrenia is probably genetically hetereogeneous, these results are not necessarily contradictory (Lander, 1988).

In order to estimate the possible significance of the concomitant occurrence of schizophrenia and MS in our patients, we assumed that the number of individuals with both disorders follows a binominal distribution. Since the sample size was very large (Jewish population 3.436×10^6), we used a normal approximation. Classic MS is relatively rare, with a prevalence of 4–6/100 000 (Pyeritz & McKusick, 1979). Schizophrenia is more common, with a lifetime prevalence 2–4/1000 (Kaplan & Sadock, 1985). The joint probability of independently acquiring both conditions is 8×10^{-8} to 24×10^{-8}. Our observation of five index patients gives a population frequency of 6.872×10^{-5}, which exceeds the 95th percentile (9.957×10^{-7}), under the assumption of independence of the two conditions.

Although it can be argued that the prevalence of MS, schizophrenia, or both is greater in Israel than in other parts of the world, there is no evidence to support such a view. Admittedly, ascertainment bias could account for the observation of MS among

schizophrenic patients; however, since four of the cases were found among the patient population of a single mental hospital, and since we did not include the three additional familial cases in the calculations, we feel that our estimate may be conservative.

It is possible that a factor related to MS, such as social isolation, the constant threat of the potentially fatal disease, and the emotional turmoil that accompanies the diagnosis, reveal disease symptoms which otherwise would not have been expressed. Nevertheless, the fact that schizophrenia was already established when MS was diagnosed in patients 2 and 3 does not favour this hypothesis.

In the two families (1, 4) in which MS occurred more than once, the affected relatives also had schizophrenia, while non-affected relatives had neither. This observation and the seemingly non-random association between MS and schizophrenia may result from linkage disequilibrium between the MS gene and the heritable component of schizophrenia. A minute chromosomal aberration (deletion, trisomy or translocation) involving two adjacent genes may be responsible for such a phenomenon. This possibility may explain the presumed *de novo* occurrence of schizophrenia and MS in patients 2, 3 and 5. It is interesting to note in this respect that Bassett *et al* (1988) reported an uncle and nephew with schizophrenia and partial trisomy of chromosomal band 5q11.2–5q13.3. Once the assignment of the MS gene is established, this possibility may become testable by looking for linkage between schizophrenia and polymorphic genetic markers located close to the MS locus.

Finally, as argued above, both schizophrenia and MS are probably genetically heterogeneous, and so several conditions with a similar phenotype may each be determined by a mutation in a different gene, with a different chromosomal location. It is conceivable that a schizophrenic condition may be part of the phenotype of a Marfan-like syndrome, in which case the association reflects a pleitropic effect of the mutant gene itself (i.e. one gene with multiple effects). Such a possibility may explain on ethnic grounds both the rarity of this association and its peculiar occurrence in Israel.

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References

AMERICAN PSYCHIATRIC ASSOCIATION (1987) *Diagnostic and Statistical Manual of Mental Disorders* (3rd edn, revised) (DSM-III – R). Washington, DC: APA.

BASSETT, A. S., MCGILLIVRAY, B. C., JONES, B. D., *et al* (1988) Partial trisomy chromosome 5 cosegregrating with schizophrenia. *Lancet*, *i*, 799–801.

HENKE, E., LEADER, M., TAJIMA, S., *et al* (1985) A 38 base pair insertion in the pro alpha 2 (1) collagen gene of a patient with Marfan syndrome. *Journal of Cellular Biochemistry*, **27**, 168–174.

KAPLAN, H. I. & SADOCK, B. J. (eds) (1985) *Comprehensive Textbook of Psychiatry* (4th edn), p. 644. Baltimore: Williams and Wilkins.

KENNEDY, J. L., GIUFFRA, L. A., MOISES, H. W., *et al* (1988) Evidence against linkage of schizophrenia to markers on chromosome 5 in a northern Swedish pedigree. *Nature*, **336**, 167–170.

LANDER, E. S. (1988) Splitting schizophrenia. *Nature*, **336**, 105–106.

OGILVIE, D. J., WORDSWORTH, B. P., PRIESTLEY, L. M., *et al* (1987) Segregation of all four major fibrillar collagen genes in the Marfan syndrome. *American Journal of Human Genetics*, **41**, 1071–1082.

PYERITZ, R. E. & MCKUSICK, V. A. (1979) The Marfan syndrome: diagnosis and management. *New England Journal of Medicine*, **300**, 772–777.

—— & —— (1981) Basic defects in the Marfan syndrome. *New England Journal of Medicine*, **305**, 1011–1012.

ROMANO, J. & LINARES, R. L. (1987) Marfan syndrome and schizophrenia: a case report (letter). *Archives of General Psychiatry*, **44**, 190–192.

SHERRINGTON, R., BRYNJOLFSSON, J., PETURSSON, H., *et al* (1988) Localisation of a susceptibility locus for schizophrenia on chromosome 5. *Nature*, **336**, 164–167.

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