Premarital genetic investigations: effect of genetic counselling

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الاستقصاءات الوراثية قبل الزواج: تأثير التوعية الوراثية

نجوى عبد المجيد ومها سعد علي زكي وسيدة علي حماد

خلاصة: على مدى عامين، أحيل 86 زوجاً (172 حالة) إلى عيادة الوراثة بالمركز القومي للبحوث بهدف تزويدهم بالتوعية الوراثية قبل الزواج. وتبيَّن أن 73.25% منهم كانت لديهم اضطرابات وراثية مختلفة في عائلاتهم. وحدث زواج الأقارب في 86.04% من الحالات. وأظهرت الاستقصاءات الوراثية وجود شذوذات صبغية (خلل في الكروموسومات) في 26 حالة (15.11%). وكانت هناك نتائج أخرى غير طبيعية في 23 حالة (13.37%). وبعد تقديم التوعية الوراثية، تمت متابعة ثلاثين زوجاً بعد الإخصاب. واحتاج عشرة منهم إلى بزل السَّلَى الذي كشف عن أجنّة غير سوية لدى اثنتين من الأمهات. أما الأزواج الآخرون فقد أنجبوا نسلاً سويا. وخلاصة القول إن التوعية الوراثية قبل الزواج لها فائدة عظيمة في اكتشاف الاضطرابات الوراثية. وهي خطوة أساسية نحو تغيير المواقف تجاه اختبارات ما قبل الزواج والإقلال من زواج الأقارب.

ABSTRACT Over a period of 2 years, 86 couples (172 cases) were referred to the genetics clinic of the National Research Centre for premarital genetic counselling. About 73.25% had a family history of different genetic disorders. Consanguinity was found in 86.04%. Genetic investigations revealed chromosomal abnormalities in 26 cases (15.11%); 23 cases (13.37%) had other abnormal results. After genetic counselling, postconceptional follow-up was carried out for 30 couples; 10 of them required amniocentesis that showed abnormal fetuses in 2 mothers. Other couples had normal offspring. We conclude that premarital genetic counselling is of great use in the detection of genetic disorders and is an essential step in changing attitudes towards premarital testing and reducing consanguineous marriage.

Examens génétiques prénuptiaux : effet du conseil génétique

RESUME Sur une période de deux ans, 86 couples (172 cas) ont été adressés à la clinique de génétique du Centre national de recherche pour le conseil génétique prénuptial. Près de 73,25% avaient des antécédents familiaux de différents troubles génétiques. La consanguinité a été trouvée chez 86,04%. Les examens génétiques ont révélé des anomalies chromosomiques dans 26 cas (15,11%); 23 cas (13,37%) avaient d'autres résultats anormaux. Après le conseil génétique, on a effectué un suivi après procréation pour 30 couples; 10 d'entre eux ont eu besoin d'une amniocentèse qui a montré des fœtus anormaux chez deux mères. Les autres couples ont eu des nouveau-nés normaux. Nous concluons que le conseil génétique prénuptial est d'une grande utilité dans le dépistage des troubles génétiques et qu'il s'agit d'une étape essentielle pour changer les attitudes vis-à-vis des tests prénuptiaux et pour faire diminuer les mariages consanguins.

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Introduction

Genetics has an impact on the health of all individuals, their offspring and future generations. A number of surveys have indicated that globally at least 2 per 1000 neonates have autosomal recessive disorders, 2–10 per 1000 have autosomal dominant disorders, 1–2 per 1000 have X-linked recessive disorders, 6–7 per 1000 have chromosomal abnormalities and about 20 per 1000 have congenital malformations [*1*]. In Egypt, Mokhtar et al. estimated the frequency of autosomal recessive disorders to be 33.6%, autosomal dominant disorders to be 13.4%, X-linked disorders to be 6.7% and chromosomal abnormalities to be 3.4% among patients with genetic diseases [*2*]. Chromosomal abnormalities are present in approximately 50% of all spontaneous miscarriages. After birth, the incidence of chromosomal abnormalities is dramatically reduced to 0.5%–1% while it is 5% if stillborns are considered [*3*].

Premarital genetic investigations play a very important role in the detection of many genetic disorders. Premarital counselling is useful in order to explain the underlying nature of these genetic diseases; when there is a lack of understanding, a variety of genetic diseases tend to surface.

Subjects and methods

Among 2139 cases referred to the clinic of the Department of Human Genetics, National Research Centre over a period of 2 successive years, 86 couples (172 cases) were referred for premarital genetic counselling.

For all cases, the following were carried out: complete genetic and family history, pedigree construction and clinical genetic examination; chromosomal analysis by Giemsa-trypsin banding technique [*4*]; metabolic screening tests [*5*], especially for consanguineous couples. Induction of fragility test was carried out using methotrexate [*6*] for suspected cases with a family history of mental retardation. Other investigations were carried out depending on the individual case and family history, such as the glucose tolerance test, haemoglobin electrophoresis, factor VIII level, creatine phosphokinase, electromyography, electroencephalography, hearing tests, eye evaluation and intelligence quotient.

Results

This study included 172 cases (86 couples); only 7 couples (8.13%) were referred by physicians, while 79 (91.86%) were self-referred. Reasons for referral of the 86 couples are shown in Table 1. Consanguinity was positive in 74 couples (86.04%). The mean age of male partners was 29.32 years (range: 24–37 years), while the mean age of female partners was 25.26 years (range: 18–31 years). A family history of genetic diseases was present in 73.25% of the couples. The frequencies of these genetic disorders are shown in Table 2.

Table 1 **Reason for referral of the couples**

Reason	No. (n = 86)	%
Consanguineous marriage	74	86.04
Affected siblings	21	24.42
Other affected family members	42	48.84
More than one genetic disorder in the family	19	22.09
Non-specific	2	2.33

Table 2 **Frequency of different genetic disorders among couples with a positive family history**

Disorder	Frequency (%)
Down syndrome	7.8
Multiple congenital anomalies	3.9
Idiopathic mental retardation	23.4
Neurological disorders	18.7
Neuromuscular disorders	4.8
Psychological problems	7.8
Sensorineural hearing loss	3.9
Eye abnormalities	6.3
Skin diseases	2.3
Haematological diseases	4.7
Congenital heart diseases	3.1
Bone disorders	1.6
Endocrinal disorders	10.9
Abnormal sexual differentiation	0.8

Chromosomal studies were conducted for all cases (172 cases), out of which 26 cases (15.11%) had chromosomal aberrations. Karyotypes of couples with coincidentally affected male and female partners are presented in Table 3; those with a single partner affected are given in Table 4. The percentage of structural aberrations in male partners was 53.84% (14 cases) and that in female partners was 34.62% (9 cases) (Figures 1 and 2). The percentage of numerical aberrations in male partners was 7.69% (2 cases) and that in female partners was

Table 4 **Karyotypes of couples in whom only one of the partners was affected**

Couple no.	Karyotype
1	46,XX/46,XX,i(1)(q22qter), Sa(14,22,21,22)
2	46,XY, +15mar
3	46,XY ,+15 p/47,XY,+5
4	46,XX/46,XX,Sa(21,22,14)/46,XX, isochromatid break 2q35/47,XX,+mar
5	46,XX/46,XX, break in 8q22
6	46,XY/46,XY,del(16)(q23qter)
7	46,XX/46XX,inv(X)(pter→ p11.1::q13.3→p11.1::q13.3→qter)
8	46,XX/46,XX,inv(5)(q11q13.1)
9	46,XX,15 p+
10	46,XY/ 46,XY,cent.br(9)
11	46,XY/46,XY,inv(17)(p11.2q11.2)
12	46,XY/46,XY,g(5)(q31.1)46,XY,g(4)(q32)
13	46,XX/45,X–21
14	46,XY/47,XY,+3
15	46,XX/46,XX,t(7;14)(7qter→ 7p15.1::14q32.2→14qter,14pter→ 14q32.2::7p15.1→7pter)
16	46,XY/46,XY,inv(14)(q13q21)
17	46,XY/46,XY,t(1;2) (q11.2q22.2)
18	46,XY,+der(?)t(15;?)(q22;?)

Table 3 **Karyotypes of couples in whom both the male and female partner were affected**

Couple no.	Karyotype	
	Male	Female
1	46,XY,t(3;9)(p23p24.2)	46,XX/46,XX,17p+
2	46,XY/46,XY,inv(9)(pter q13::q22?q13::q22?qter)	46,XX/46,XX,dup(12)(pter q15::q13.1 qter)
3	46,XY/46,XY,del(6)(q26)/46,XY,del(4)(q35.1)	46,XX/45,XO
4	46,XY,t(9,4)(9pter?q31::q34?4qter,4pter?4q35:: 9q31 ?9qter)	46,XX,t(9,4)(9pter?q31::q34?4qter, 4pter?4q35::9q31?9qter)

11.53% (3 cases). Two cases (7.69%) had both structural and numerical aberrations. The percentage with sex chromosome abnormality was 7.69% (2 cases).

After meticulous and thorough pedigree analysis, specific investigations were recommended for suspected cases. Abnormal results other than chromosomal aberrations were detected in 23 cases (13.37%). These were abnormal metabolic screening in 8 cases (4.65%), abnormal glucose tolerance test in 4 cases (2.32%), haematological disorders in 3 cases (1.74%) (sickle-cell trait, β-thalassaemia trait and haemophilia carrier female), myotonia in 1 case (0.58%), epileptogenic focus in 1 case (0.58%), sensorineural deafness in 2 cases (1.16%), mild mental retardation in 1 case (0.58%) and progressive high myopia in 3 cases (1.74%).

Postconceptional follow-up was carried out for 30 couples. Amniocentesis was recommended to couples with proven chromosomal abnormalities or with suspected history of non-disjunction in the family. Out of 10 cases who underwent amniocentesis, abnormal chromosomal results were found in 2 (20%) fetuses. The first fetus had 46,XX,t(3;9) and intrauterine growth retardation revealed by ultrasound; the pregnancy was terminated. Both mother and father of this fetus were first cousins, and they had a history of abnormal chromosomal studies proven on premarital investigations and counselling (couple no. 1, Table 3). Amniocentesis for the second fetus showed trisomy 21 in all metaphases. Parental chromosomal analysis was normal but the mother had a sister with 47,XX+21 (Down syndrome) detected through the premarital counselling. The parents preferred to continue with the pregnancy. The other 8 couples had normal offspring.

Discussion

In a study conducted by Eshra et al. in 1989 [7] on knowledge and attitudes towards premarital counselling and examination in Egypt, their results showed a great lack of knowledge, even among educated respondents, about the actual term "premarital counselling". In recent years, however, premarital counselling has gained acceptance. In our study, the number of couples who sought genetic investigations increased during the 2 years, 36 couples in the first year and 50 couples in the second. Furthermore, 91.86% of them were self-referred which indicates the increased awareness of the public.

In our study, the rate of consanguinity was 86.04%; the consanguinity rate among the general population in Egypt is 36.8% [8]. Jaber et al. reported that the rate of congenital malformation among the offspring of related parents was 2.5 times higher than that among the offspring of unrelated parents, mainly due to the expression of autosomal recessives disorders [9]. They stated that consanguineous marriage had declined considerably and, in recent years, had ceased in the United States and Western Europe. However, in parts of Africa, Asia and the Indian subcontinent, especially among Muslims and Hindus, such marriages continue to take place on a large scale and show only a slight indication of a decline. This observation indicates the need for studies such as ours to raise awareness about premarital genetic counselling in order to reduce consanguineous marriage.

Chromosomal analysis of our cases revealed 26 cases (15.11%) with chromosomal abnormalities, either structural aberrations or numerical aberrations or both. Both male and female partners were carriers in 4 couples. These results indicate the importance of chromosomal analysis as part of

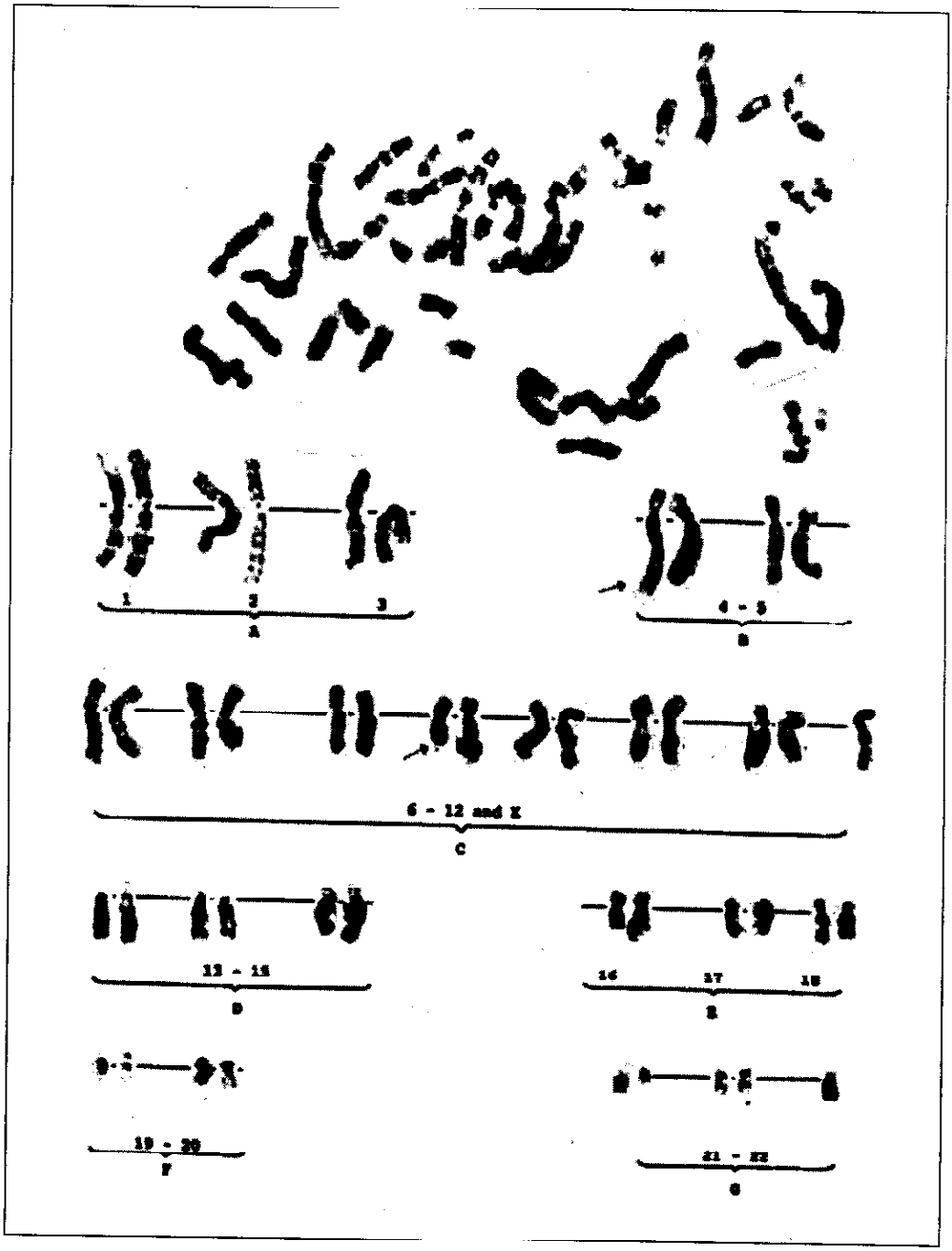

Figure 1 G-banded karyotype of male partner of couple no. 4 (Table 3) showing 46,XY,t(9;4)(q31q35)

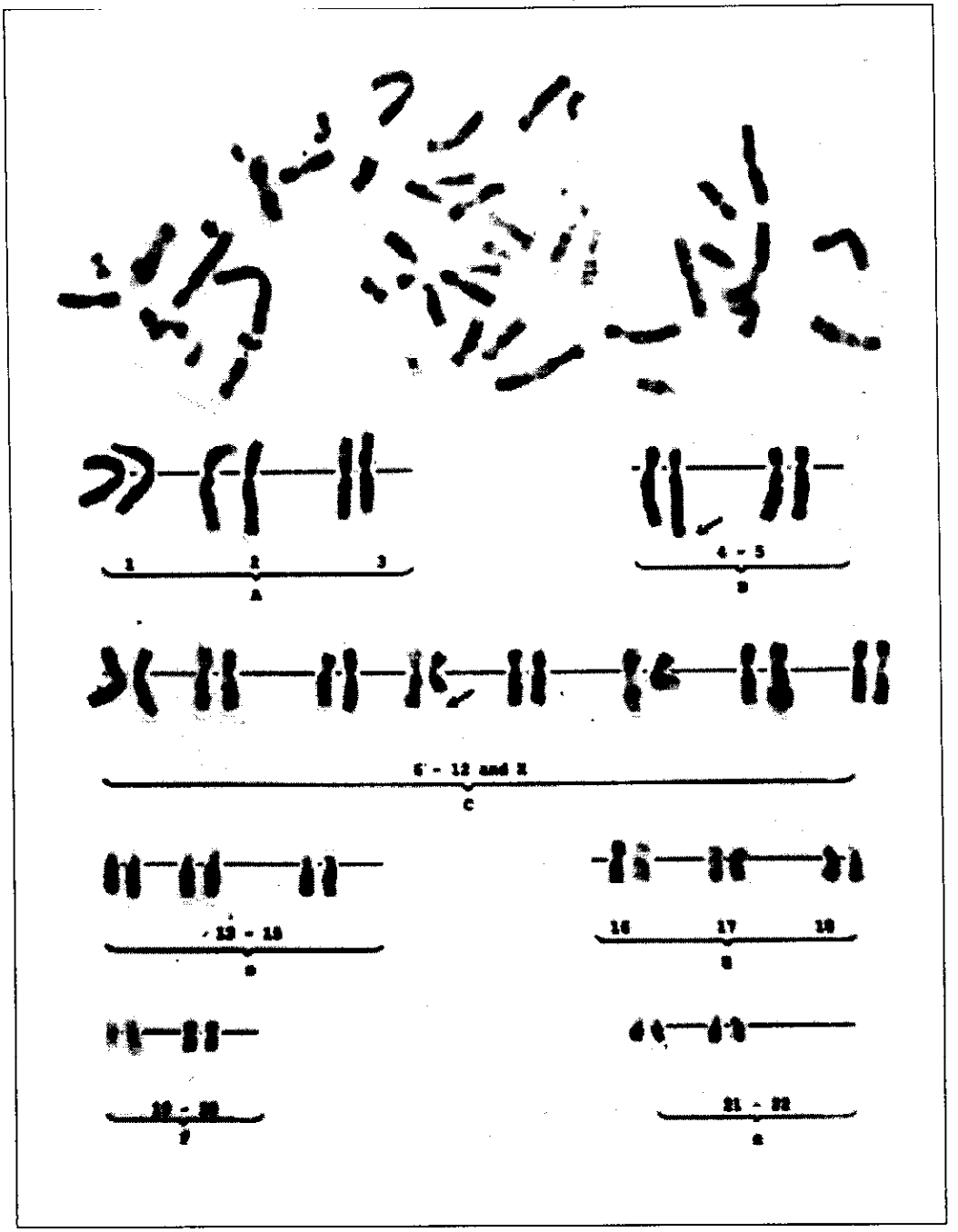

Figure 2 G-banded karyotype of female partner of couple no. 4 (Table 3) showing 46,XX,t(9;4)(q31q35)

genetic investigations in premarital counselling to identify couples who may require postconceptional amniocentesis. Uehara et al. evaluated the relation between parental chromosomal translocation and the outcome of pregnancy in 50 couples [*10*]. They found that the presence of a translocation was closely related to reproductive failure because of the chromosomal imbalance. However, prenatal chromosomal examination after the 15th gestational week showed that almost half of the fetuses had normal karyotypes and only 12.8% of the fetuses had a chromosomal imbalance because many chromosomally imbalanced fetuses are spontaneously aborted before amniocentesis. Tabor and Philip [*11*] found that the incidence of fetal chromosomal abnormalities was 1% in low-risk couples, while Bocian et al. [*12*] found that the incidence of chromosomal aberrations was 3.4% in families with a genetic risk. Cooper et al. concluded that translocations could be responsible for pregnancy losses not only as a result of aneuploid segregants, but also by causing other types of chromosome abnormality [*13*]. Also, satellite association is considered one of the factors predisposing to non-disjunction of the chromosomes [*14*]. In our study, we reported a couple with the same balanced translocation in both partners involving chromosomes 9 and 4 (couple no. 4, Table 3). The male partner had 46,XY,t(9;4)(q31q35) and the female partner had 46,XX,t(9;4)(q31q35) (Figures 1 and 2). They were first cousins as were their grandparents. A high risk of abnormalities involving chromosome 4 and 9 was suspected in their offspring.

Ten couples underwent postconceptional amniocentesis. Abnormal chromosomal results were found in only 2 fetuses (20%). The first had unbalanced translocation involving chromosomes 3 and 9. His parents had abnormal chromosomal analysis, the father had reciprocal translocation involving chromosomes 3 and 9 and the mother had 17p+ (couple no. 1, Table 3). The second fetus had trisomy 21 although parental chromosomes were normal and the mother was young (28 years old), but there was a history of non-disjunction in the family. This concurs with the study conducted by Al-Awadi et al. about the recurrence risk of Down syndrome in families with non-disjunction trisomy 21 [*15*]. They concluded that non-disjunction could be attributed to genetic, environmental or combined factors. The couple of the first fetus decided to terminate the pregnancy, while the second couple continued with their pregnancy. Saleem et al. [*16*] stated that parental attitude to prenatal diagnosis and pregnancy termination is a consequence of a balance between two vectors: parental understanding of the disease, its mode of inheritance and the prenatal diagnostic options available on the one hand, and traditional belief in fate, religious "punishment", social values, and economic and environmental factors on the other. Ekwo et al. reported that women with fewer living children perceived congenital malformations as more burdensome than those with more living children, and thus were more agreeable to amniocentesis [*17*].

Abnormal investigations other than chromosomal aberrations were found in 13.37% of our cases. Abnormal metabolic screening was found in 4.65% (8 cases). Metabolic disorders are individually rare but collectively numerous with wide variations in their frequencies in cases with mental retardation in different surveys [*2*]. Tayel et al. reported a frequency of 22% for metabolic defects among mentally retarded children in Egypt [*18*].

In our study, carriers of blood diseases were detected in 3 cases (1.74%); β-thalassaemia trait, sickle-cell trait and a haemophilic carrier female. Alwan and Modell

noted that thalassaemia, sickle-cell anaemia and glucose-6-phosphate dehydrogenase deficiency were the commonest single-gene disorders found in the Eastern Mediterranean Region [*19*].

Family history of genetic diseases was present in 63 couples (73.25%). Thus couples with a high incidence of genetic disorders tended to be the ones who attended premarital genetic counselling. As the number of known genetic disorders has grown into thousands, new technology has given us a catalogue of human chromosome disorders, an understanding of biochemical disorders and new techniques for prenatal diagnosis. Yet these concepts are difficult to understand, so we recommend comprehensive care with health care providers acting as information sources for genetic awareness.

In conclusion, premarital genetic counselling is an extremely important tool in the detection of genetic disorders and in the reduction of their incidence among offspring. In addition, family history and constructive analysis of pedigree are very informative as a guide to premarital genetic investigations.

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Note from the Editor

We would like to inform our readers that the next issue of the EMHJ will be a combined issue, Volume 6 Nos 5 & 6, and will include the EMHJ reviewers' panel for the year 2000.