Major birth defects among infants with Down syndrome in Alexandria, Egypt (1995–2000): trends and risk factors

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التشوهات الولادية الكبرى بين الأطفال المصابين بمتلازمة داون في الإسكندرية، مصر

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خلاصة: قام الباحثون بتقييم النظرية التي تقول بأن المَجين المثلّث الصبغي 21 يتفاعل مع العوامل البيئية خلال مرحلة باكرة من الحمل، ليزيد من احتمال خطر الإصابة بالتشوهات الولادية لدى المرضى المصابين بمتلازمة داون في الإسكندرية، مصر. وقد تم تنفيذ دراسة للحالات والشواهد شملت 514 طفلاً ممن تأكد لديهم تشخيص الإصابة بمتلازمة داون وذلك في الفترة من 1 تموز/يوليو 1995 وحتى 31 حزيران/يونيو 2000. وتم تحليل العوامل الوراثية والبيولوجية والبيئية والإنجابية. وقد أظهر تحليل التحوُّف اللوجستي المتعدّد أن العوامل التالية تترافق مع ازدياد خطر الإصابة بمرض القلب الخلقي بين المصابين بمتلازمة داون: القرابة بين الوالديس، والقرابة بين أبوي الوالدة، وتناول الأم للمضادات الحيوية أثناء الحمل، واستخدام أقراص منع الحمل، وإصابة الأم بالسكري. كما أن الحمى لدى الأم أثناء الحمل ترافقت بازدياد خطورة التشوهات الهضمية.

ABSTRACT We evaluated the hypothesis that the trisomy 21 genome interacts with environmental factors during early pregnancy to increase the risk for birth anomalies in Down syndrome infants in Alexandria, Egypt. A case–control study on 514 infants with confirmed Down syndrome was carried out from 1 July 1995 to 30 June 2000. Genetic, biological, environmental and reproductive factors were analysed. Multiple logistic regression analysis showed the following factors to be independently associated with increased risk of congenital heart diseases among Down syndrome patients: parental consanguinity, maternal parents' consanguinity, mother's antibiotics use in pregnancy, oral contraceptive use and diabetes in the mother. Fever in the mother during pregnancy was associated with increased risk of gastrointestinal anomalies.

Les principales malformations congénitales chez des nouveau-nés atteints du syndrome de Down à Alexandrie (Egypte), 1995–2000 : tendances et facteurs de risque

RESUME Nous avons évalué l'hypothèse selon laquelle le génome de la trisomie 21 et des facteurs environnementaux ont une influence réciproque au début de la grossesse pour augmenter le risque d'anomalies congénitales chez des nouveau-nés atteints du syndrome de Down à Alexandrie (Egypte). Une étude cas-témoin a été réalisée du 1er juillet 1995 au 30 juin 2000 sur 514 nouveau-nés chez lesquels le syndrome de Down a été confirmé. Des facteurs génétiques, biologiques, environnementaux et reproductifs ont été analysés. L'analyse de régression logistique multiple a montré une association indépendante des facteurs suivants avec un risque accru de cardiopathies congénitales chez les patients atteints du syndrome de Down : consanguinité des parents, consanguinité des parents de la mère, utilisation d'antibiotiques par la mère durant la grossesse, utilisation de contraceptifs oraux et diabète chez la mère. La fièvre de la mère durant la grossesse était associée à un risque accru d'anomalies gastro-intestinales.

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Introduction

Chromosome 21 is the smallest human autosome. It contains 225 genes and 59 pseudogenes. An extra copy of chromosome 21 usually causes Down syndrome (DS) [*1*]. In some cases, however, it is caused by the presence of only the distal half of chromosome 21, band q22 [*2*]. Infants with DS, or trisomy 21, are at much higher risk than others for specific additional congenital anomalies that are not always part of the DS phenotype. These include gastrointestinal and severe cardiac defects [*3–7*].

The basis of the association between chromosome 21 triplication and these specific birth defects is still obscure. Nevertheless, it seems likely that some disorders are attributable to dosage imbalance at one or a few loci, as well as environmental factors that could interact with an already susceptible genotype [*8*]. Feingold et al. have proposed that some of the abnormalities of DS are attributable to overexpression at specific loci, resulting from the presence of two identical copies of a susceptibility allele inherited from the parent of origin of trisomy [*9*].

Shapiro has suggested that most disorders associated with DS result from the reduced ability of embryos with chromosomal imbalance to neutralize environmental insults [*10*]. Proponents of the dosage effect acknowledge that environmental factors could influence the expression of associated defects.

The aim of this study was to evaluate the hypothesis that the trisomy 21 genome interacts with environmental factors during early pregnancy to increase risk for specific associated defects of DS in Alexandria, Egypt.

Methods

A case–control strategy was implemented. The study population included all infants with DS attending the Human Genetics Clinic, Medical Research Institute, University of Alexandria during the period 1 July 1995 to 30 June 2000. This clinic receives the great majority of cases with genetic disorders from different urban and rural areas of Alexandria. The DS patients in our study were referred from paediatric hospitals and private clinics. The clinical diagnosis of DS was made at birth or shortly thereafter and cytogenetic analysis was carried out. Cases were defined as those with any DS-associated defects (cardiac, gastrointestinal and others), while controls were defined as otherwise healthy at delivery. The diagnosis of congenital heart diseases was based on echocardiography, while the diagnosis of gastrointestinal anomalies was confirmed by imaging studies or surgery.

A standardized form was used to collect data from the mothers of the patients. Information was collected on maternal age, paternal age, detailed pregnancy history particularly for maternal exposure during the first trimester to diseases (diabetes, hypertension), drugs (aspirin, antibiotics, hormones, contraceptive pills, insulin, corticosteroids), fever (over 38 °C), upper respiratory tract infection and irradiation. The time, frequency, dose and duration of exposure were determined as accurately as possible. Pedigrees were conducted to include sibs, abortions, still births, family history, maternal parents, paternal parents and parental consanguinity. We did not report minor defects or other major defects that were present in a few infants.

Statistical analysis was carried out with *SPSS*, version 9.0. A linear trend was applied to search for evidence of change in

Table 1 **Distribution of associated birth defects among 514 infants with Down syndrome, Alexandria, Egypt (1995–2000)**

Diagnostic category	No.	%
Otherwise healthy	206	40.1
Congenital heart diseases	198	38.5
Atrioventricular septal defect (AVSD)	91	17.7
Atrial septal defect	56	10.9
AVSD and atrial septal defect	21	4.1
Patent ductus arteriosus	13	2.5
Coarctation of aorta	11	2.1
Tetralogy of Fallot	6	1.2
Gastrointestinal anomalies	33	6.4
Duodenal atresia	22	4.3
Anal defects	7	1.4
Hirschsprung disease	4	0.8
Combinations[a]	28	5.4
Other malformations	49	9.5

[a]*Congenital heart diseases and gastrointestinal anomalies.*

the incidence rate of DS-associated defects (cardiac and gastrointestinal) over time.

Sex, maternal and paternal ages, exposure to X-ray or infections, attempted abortion, diabetes mellitus, hypertension, consanguinity (parental, maternal parents and paternal parents), birth order, drug intake (antibiotics, aspirin, hormones, pills and insulin) were treated as categorical variables. The crude measure of association between single putative risk factors and major birth defects was expressed as the odds ratio (OR) with 95% confidence interval (95% CI). Multiple associations were evaluated in multiple logistic regression models based on the backward stepwise selection. This procedure allowed the estimation of the strength of the association between each independent variable and the dependent variable taking into account the potential confounding effects of the other independent variables. The covariates were removed from the model if the likelihood ratio statistic based on the maximum likelihood estimates had a probability > 0.10. Each category of the predictor variables was contrasted with the initial category (reference category). An adjusted OR with 95% CI that did not include 1.0 was considered significant.

A separate model was created for each of the congenital heart diseases (CHD) and gastrointestinal anomalies (GIA).

Results

General characteristics of DS patients

Of the 514 cases, 93% (478/514) of the DS diagnoses were confirmed by a cytogenetic analysis; of these, 98.1% had standard trisomy 21. The few children with the DS phenotype who were mosaic (n = 3, 0.6%) or had a translocation (n = 6, 1.3%) were not considered separately in the statistical analysis.

Of the 514 DS infants, 206 (40.1%) had no major visceral anomalies and 308 (59.9%) had at least one major visceral malformation (Table1). The more common types of associated birth defects were cardiac anomalies (38.5%). The most common CHD were atrioventricular septal defect (AVSD) (17.7%), followed by atrial septal defect (10.9%): 21 patients (4.1%) had both AVSD and atrial septal defect. Among 33 (6.4%) patients with GIA, 22 (4.3%) had duodenal atresia, 7 (1.4%) had anal defects and 4 (0.8%) had Hirschsprung disease. An overlap between cardiac and gastrointestinal anomalies was detected in 28 (5.4%) patients and 49 (9.5%) patients had other anomalies.

Trends of major birth defects among DS patients

Figure 1 and Table 2 show temporal trends in the incidence rate of total DS-associated CHD. The rate of ascertained CHD rose dramatically from 29.76% in 1995 to 48.15% in 2000. This trend was highly significant in linear regression analysis ($P < 0.001$). The mean incidence rate of DS infants with GIA was about 6.4% over the study period and had remained stable with time ($P = 0.62$).

Table 2 **Distribution of patients with Down syndrome according to the presence of congenital heart diseases (CHD), Alexandria, Egypt (1995–2000)**

Year	Infants with Down syndrome No.	Infants with Down syndrome and CHD No.	%
1995	84	25	29.76
1996	80	28	35.00
1997	92	34	36.96
1998	86	33	38.37
1999	91	39	42.86
2000	81	39	48.15

Risk factors for major birth defects among DS patients

Tables 3 and 4 show the results of a univariate analysis of selected variables among the DS patients with major birth defects and their controls. Parental consanguinity (OR = 10.7, 95% CI: 6.4–17.7), maternal parents' consanguinity (OR = 2.4, 95% CI: 1.6–3.6), paternal parents' consanguinity (OR = 2.8, 95% CI: 1.4–5.4) and a history of fewer than three abortions (OR – 1.5, 95% CI: 1.0–2.3) were found to increase the risk of CHD. Environmental factors, namely maternal exposure to aspirin, antibiotics, female sex hormone and oral contraceptive pills, were significantly associated with increased risk of CHD (OR = 2.6, 95% CI: 1.4–4.6, OR = 2.4, 95% CI: 1.2–4.6, OR = 4.3, 95% CI: 1.6–11.7 and OR = 3.4, 95% CI: 1.8–6.4 respectively).

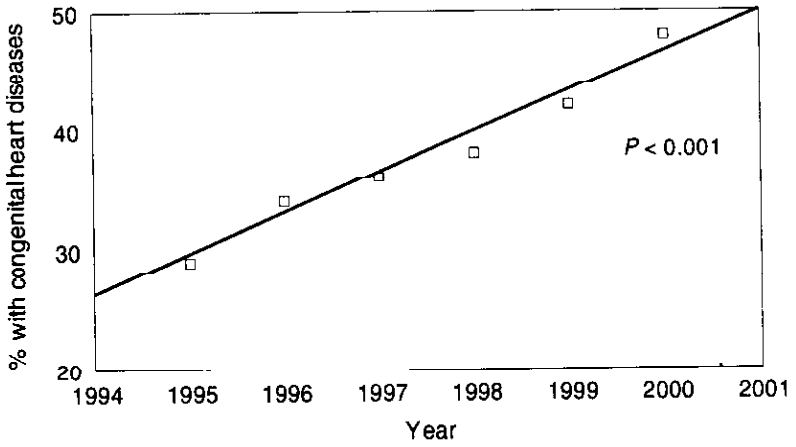

Figure 1 **Annual incidence of congenital heart diseases per 100 infants with Down syndrome in Alexandria, Egypt**

Also patients with diabetic mothers on insulin were significantly associated with increased risk of CHD (OR = 4.5, 95% CI: 1.7–12.3). No significant association was found between CHD and maternal age, paternal age, birth order, irradiation, infection, fever and history of more than three abortions. Increased risk of GIA was found only with history of maternal fever (OR = 5.1, 95% CI: 1.3–19.5).

After considering the statistical contribution of each variable, the final logistic regression analysis model showed the following factors to be independently asso-

Table 3 **Univariate analysis of biological and genetic risk factors for major associated congenital defects in infants with Down syndrome, Alexandria, Egypt (1995–2000)**

Risk factor	CHD (n = 198)			GIA (n = 33)			Controls (n = 206)	
	No.	%	OR (95% CI)	No.	%	OR (95% CI)	No.	%
Sex								
Male®	126	63.6	1.0	18	54.5	1.0	117	56.8
Female	72	36.4	0.8 (0.5–1.1)	15	45.5	1.1 (0.5–2.3)	89	43.2
Birth order								
1st®	58	29.3	1.0	9	27.3	1.0	67	32.5
2nd	47	23.7	1.1 (0.6–1.9)	8	24.2	1.2 (0.4–3.6)	51	24.8
≥ 3rd	93	47.0	1.2 (0.8–2.0)	16	48.5	1.4 (0.5–3.6)	88	42.7
Maternal age (years)								
< 25 ®	28	14.1	1.0	8	24.2	1.0	40	19.4
25–34	94	47.5	1.6 (0.9–3.0)	7	21.2	0.4 (0.1–1.4)	83	40.3
≥ 35	76	38.4	1.3 (0.7–2.4)	18	54.5	1.1 (0.4–3.0)	83	40.3
Paternal age (years)								
< 25 ®	5	2.5	1.0	3	9.1	1.0	5	2.5
25–34	80	40.4	0.9 (0.2–3.8)	11	33.3	0.2 (0.04–1.3)	87	42.2
≥ 35	113	57.1	1.0 (0.2–4.1)	19	57.6	0.1 (0.02–0.8)	114	55.3
Parental consanguinity								
No®	80	40.4	1.0	29	87.9	1.0	181	87.9
Yes	118	59.6	10.7 (6.4–17.7)	4	12.1	1.0 (0.3–3.1)	25	12.1
Maternal parents' consanguinity								
No®	95	48.0	1.0	23	69.7	1.0	142	68.9
Yes	103	52.0	2.4 (1.6–3.6)	10	30.3	0.9 (0.4–2.1)	64	31.1
Paternal parents' consanguinity								
No®	167	84.3	1.0	30	90.9	1.0	193	93.7
Yes	31	15.7	2.8 (1.4–5.4)	3	9.1	1.5 (0.4–5.5)	13	6.3

® = *reference category.*
CHD = congenital heart diseases. *GIA = gastrointestinal anomalies.*
OR = odds ratio. *CI = confidence interval.*

Table 4 **Univariate analysis of environmental risk factors for major associated congenital defects in infants with Down syndrome, Alexandria, Egypt (1995–2000)**

Risk factor	CHD (n = 198)			GIA (n = 33)			Controls (n = 200)	
	No	%	OR (95% CI)	No.	%	OR (95% CI)	No.	%
Drugs								
Aspirin	4	21.7	2.6 (1.4–4.6)	4	12.1	1.3 (0.4–4.0)	20	9.7
Antibiotics	20	10.1	2.4 (1.2–4.6)	2	6.1	0.9 (0.2–4.1)	14	6.8
Female sex hormone	19	9.6	4.3 (1.6–11.7)	3	9.1	4.0 (0.9–17.7)	8	3.9
Contraceptive pills	36	19.2	3.4 (1.8–6.4)	1	3.0	0.4 (0.05–3.4)	18	8.7
Medical problems								
Infection	6	3.0	1.9 (0.8–4.5)	0	0.0	–	8	3.9
Fever	12	6.1	0.7 (0.2–2.4)	5	15.2	5.1 (1.3–19.6)	7	3.4
Hypertension	3	1.5	0.8 (0.2–3.5)	0	0.0	–	4	1.9
Diabetes mellitus	20	10.1	4.5 (1.7–12.3)	3	9.1	5.1 (0.9–28.6)	4	1.9
Irradiation	4	2.0	0.8 (0.2–3.1)	1	3.0	1.3 (0.1–11.1)	5	2.4
Abortion								
No®	104	52.5	1.0	17	51.5	1.0	129	62.6
Yes, < 3 times	89	44.9	1.5 (1.0–2.3)	16	48.5	1.6 (0.7–3.7)	74	35.9
Yes, ≥ 3 times	5	2.5	2.1 (0.4–11.2)	0	0.0	–	3	1.5

® = reference category.
CHD = congenital heart diseases. *GIA = gastrointestinal anomalies.*
OR = odds ratio. *CI = confidence interval.*

ciated with an increased risk of CHD in patients with DS: parental consanguinity (OR = 7.5, 95% CI: 4.3–15.1), maternal parents' consanguinity (OR = 2.1, 95% CI: 1.3–3.4), maternal exposure to antibiotics during pregnancy (OR = 2.5, 95% CI: 1.1–5.5), oral contraceptive pills (OR = 3.4, 95% CI: 1.6–7.5) and diabetic mother (OR = 5.1, 95% CI: 1.6–15.8). Only one factor increased the risk of GIA, namely maternal fever during pregnancy (OR – 12.5, 95% CI: 7.2–63.9) (Table 5).

Discussion

The strength of this study lies in the relatively large sample size of infants with DS. Its limitation lies in the fact that some associations were based on only a small number of cases.

DS is a major cause of mental retardation, congenital heart problems and gastrointestinal malformations [*11*]. In Egypt, the incidence of DS is 1 in 1000 live births [*12*].

In our study, congenital anomalies were detected in 59.9% of patients with DS. In a series of 705 DS patients reported in Cairo, approximately 50% had associated anomalies [*13*]. Stoll et al. reported a frequency of 61.8% congenital anomalies among 246 individuals with DS in France [*14*]. Torfs and Christianson [*6*] reported a frequency of 56.0% in a survey of 687 cases in the United States of America, while Sipek et al. [*15*] found a frequency of 37.3% among

4933 cases with DS in the Czech Republic. In epidemiological studies of DS-associated defects, prevalence rates vary substantially according to the secular time, the definitions and ascertainment method used, in addition to genetic and environmental factors [*4–6*].

CHD are present in about 40%–45% of DS patients [*16*]. They have been reported in two cases of partial duplications that include the distal region of q21q22 [*2,17*], but have not been reported in any cases that do not include this region [*18*]. CHD were the most common congenital anomalies in patients with DS in our study (38.5%). Two recent Egyptian studies reported 38.7% and 36.8% CHD among individuals with DS [*19,20*]. Stoll et al. [*14*] found CHD in 46.2%, while Kallen et al. [*7*] reported a frequency of 26%. Two other studies, one covering 11 years of ascertainment of DS by the California Birth Defects Monitoring Program [*6*] and another of 171 DS infants in Texas [*21*], found cardiac defects in more than half of the patients.

The results of our study indicate that AVSD was the commonest type of CHD among patients with DS, followed by atrial septal defect and then patent ductus arteriosus. On comparing our results with those of other studies, atrioventricular canal lesions, ventricular septal defect and patent ductus arteriosus were the most frequent lesions in France [*14*]. Another study performed in the United States of America reported that the most frequent lesions were atrioventricular canal and tetralogy of Fallot [*22*]. Evidence of wide variations in the frequency of CHD and their forms suggests that environmental factors can play an important role in the etiology of CHD among DS individuals.

GIA occur in 1 in 10 000–40 000 live births but in 1%–7% of DS infants with full trisomy. Furthermore, infants with DS constitute about 35% of infants with GIA [*11*]. In our study, the frequency of GIA was 6.4%. This is higher than that reported by Khoury and Erickson (5%) [*23*]. However, it is lower than that reported by Torfs

Table 5 **Multiple logistic regression analysis of risk factors of major associated defects in infants with Down syndrome, Alexandria, Egypt (1995–2000)**

Risk factor	Congenital heart diseases (n = 198)		Gastrointestinal anomalies (n = 33)	
	OR	95% CI	OR	95% CI
Parental consanguinity	7.5	4.3–15.1	Removed	
Maternal parents' consanguinity	2.1	1.3–3.4	Removed	
Antibiotics	2.5	1.1–5.5	Removed	
Contraceptive pills	3.4	1.6–7.5	Removed	
Fever (> 38 °C)	Removed		12.5	7.2–63.9
Diabetes mellitus	5.1	1.6–15.6	Removed	

OR = odds ratio.
CI = confidence interval.

and Christianson (7.5%) [*22*] and Bell et al. (12%) [*24*]. Our value is in agreement with that of Stoll et al. (6%) [*14*].

Khoury and Erickson reported that the frequency of CHD rose from 20% to 50%, but that GIA remained stable with time (5%) [*23*], which is similar to our result. Either improved ascertainment and/or a true increase that might be attributed to other risk factors (genetic or environmental) can explain our findings of increased rate of CHD.

In Egypt, there are a number of possible factors that might increase the risk of several additional birth defects for the trisomy 21 fetus: genetic factors (such as consanguinity), environmental factors (maternal radiation, use of medications during pregnancy whether prescribed or "over the counter", and exposure to environmental pollution), and cultural factors (low accessibility to genetic counselling).

We failed to demonstrate a significant association between sex, birth order, maternal age, paternal age and any DS-associated defect. This concurs with the finding of others [*22,23*].

There are no studies of the possible relationship between parental consanguinity and any DS-associated defects in the literature. Our study showed an increased frequency of parental consanguinity among patients with DS. Also, there was a sevenfold increase in relative risk of CHD among DS babies born to consanguineous parents. This finding suggests that homozygosity at certain loci may play a part in the development of CHD among DS infants. As regards grandparents, there was a strong association between CHD and maternal parents' consanguinity. This result indicates that the presence of homozygous predisposing genetic element(s) may manifest itself on association with certain endogenous or exogenous environmental factors. This finding strengthens the belief that consanguinity not only increases the risk of homozygosity for deleterious recessives or intermediates, but also increases the risk of having offspring with multifactorial disorders [*25*].

Because DS is the result of developmental errors that occur prior to conception, drugs used during pregnancy may have an effect on the *in utero* survival of the trisomic conceptus and influence the birth defect among DS infants [*26*]. We found a strong association between antibiotics use and CHD risk. Some antibiotics have been reported as being harmful to the fetus [*27*]. It has been suggested that fetuses with DS may be more susceptible to the effects of teratogenic agents because of a generalized instability in growth and development as well as a disruption in homeostatic mechanisms [*28*].

Some of the epidemiological data have led to speculation that contraceptive pills may be an important factor in the etiology of DS [*29,30*]. In our study, women who had ever used oral contraceptives during pregnancy showed an increased risk of having a child with CHD. However, more accurate information on formulations was not available. Among non-DS infants, contraceptive pills have been found to be teratogenic to the fetus during the period of cardiovascular embryogenesis [*31*].

We found that maternal fever during the first trimester was not associated with CHD, in contrast to reports of other investigators [*21.32*]. The association between maternal fever and GIA has been previously reported [*23*], a finding with which our study concurs.

Several maternal disorders have been identified in which the risk of fetal malformations is increased including diabetes and phenylketonuria [*33*]. The risk of congenital malformations in the pregnancies of dia-

betic women is two-to-three times higher than that in the general population [*34*]. There was a strong association between maternal diabetes and CHD in our study. The relation between diabetes and DS has been discussed by Janerich and Brachen [*26*] and by Narchi and Kulaylat [*34*], who concluded that DS should be added to the congenital malformations already known to occur more frequently in infants of diabetic mothers.

Conclusion

Our results suggest that consanguinity put the trisomy 21 embryo at increased risk of CHD. There is a strong tendency for specific birth defects to recur in DS, indicating that specific, persistent causal factors are at work. Although genetic explanations have usually been preferred, we find strong, if indirect, evidence that some environmental factors during early pregnancy can interact with chromosomal imbalance to increase the risk of several additional birth defects, suggesting that important environmental teratogens have yet to be discovered.

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Through children's eyes: a collection of drawings and stories from the Global School Contest on Mental Health

World Health Day 2001 was devoted to mental health with the theme "Stop Exclusion: Dare to Care". As part of the celebration of World Health Day a school contest was organized in which young people were asked to show in pictures and words their understanding of what it means to suffer from a mental illness and what could be done to reduce stigma. We have not adequately recognized that children themselves can be affected by a mental or brain disorder, or that they can be marked by a mental disorder affecting a loved one in the family. Open discussion is a necessary part of prevention and of successful treatment. The aim of this book is to foster such discussions.

This publication is a selection of the national winning pictures and stories chosen to illustrate some of the common mental health concerns among the young people who participated in the contest. It is designed to be read by young people, and used by adults to facilitate discussions in schools and community settings about emotions, mental and brain disorders, and stigma. The book is intended to provide materials that can be of interest to a wide range of age groups. A discussion guide explaining how to use this book as well as a listing of WHO programmes and resources are provided at the end of this document. The document can be ordered from: WHO Marketing and Dissemination, CH-1211 Geneva 27, Switzerland. Fax: +22 7914857, E-mail: bookorders@who.int. The selling price is: Sw.fr. 15 (Sw.fr. 10.50 in developing countries). It is also available free on the Internet at: http://whqlibdoc.who.int/hq/2001/who_nmh_msd_whd_01.2.pdf