EDITORIAL / VAN DIE REDAKSIE

Has Tay-Sachs disease become more common?

Tay-Sachs disease (TSD), although rare, is of great interest, since it is about 100 times more common among Ashkenazi Jews than it is among Sephardi and Oriental Jews, and non-Jews.[1,2] The reasons for this are obscure.[3,4] Equally enigmatic is the widespread impression, at the end of last century, that 'it seemed as though the disease waited until the carriers immigrated to America or England, before appearing'.[5,6] This makes little sense, and has therefore been ignored by geneticists.[7] Nevertheless, we believe it warrants investigation. Of particular concern is the possible effect incest taboos might have had in small, relatively isolated, feudal communities, compared with the marriage patterns in large cities.

In small isolates, kin constitues a considerable fraction of the available mates. Since a large proportion of TSD genes in an isolate resides among the kin of carriers, incest taboos substantially lower the risk of genetic disease in such isolates.[7] The question we wished to answer, therefore, was: is this effect great enough to have given rise to the abovementioned rumour?

A computer was used to simulate the genetic effects of the move from a rural isolate to a large metropolis. Each simulation consisted of two parts. The first part aimed at recreating the patchy TSD-carrier distribution which is believed to have characterised the East European Ashkenazi communities immediately before emigration to the West.[8,9] Rather than impose an arbitrary, and therefore possibly misleading, TSD-carrier rate distribution on our simulated pre-emigration feudal communities, we allowed genetic drift and selection to operate for 20 generations and, as a result, determined by more 'natural' means the immediate pre-migration TSD population genetic profiles of the investigation proper. Each community started, therefore, with identical TSD carrier rates which had been adjusted (for the population as a whole) to produce an average, overall carrier rate in generation 20 approximately equal to that of the Ashkenazi Jews of today.[9] The second part of the simulation (the investigation proper) modelled the migration of these populations to the West, where the genetic isolation between the separate communities was suddenly removed.

Part I of the programme focused on a generation of 10 000 unrelated diploid individuals who were all simultaneously of marriageable age. This population was subdivided into 200 isolates of equal size. Ten per cent of these individuals were carriers of the TSD gene. Marriages were contracted only between members of the same isolate. The number of surviving offspring per couple had a negative binomial distribution,[5,10] with a mean of 2,2 (SD ±1,85) surviving children per couple.[11,12] Marriages between siblings in this and all subsequent generations were prohibited. TSD homozygotes died without reproducing. There were no new mutations. No limits were placed on the growth or extinction of isolates, as it was felt that this probably best approximated the actual population dynamics of East European Jewish communities. The immediate pre-emigration populations of our experiment proper therefore consisted of communities of widely varying sizes and with widely varying TSD carrier rates.

The young (unmarried) individuals of the 20th generation then immigrated *en masse*, as it were, to the West. Here the genetic isolation between the separate communities was suddenly removed. The taboo on sibling marriages persisted. This effectively meant that mating suddenly became 'random' in a very large population. The incidence of TSD births among the offspring from this generation was compared with the TSD frequency immediately before 'emigration'.

The TSD carrier frequencies in generation 20 varied from 2,82% to 3,02%, depending on initial isolate size and average fertility rate (both of which we could vary). These are slightly lower than the 4% carrier frequency of TSD among the Ashkenazim who immigrated to America.[9] However, we also simulated the effect of reproductive compensation.[3,4,7,13] This increased the carrier frequency in generation 20 to 4,65%, which is closer to the actual incidence of TSD carriers among present-day Ashkenazim.

The incidence of TSD births was, in all cases, 4 - 5 times lower after 'emigration' than immediately before 'emigration'. Isolates of the initial 50 marriageable members, with a mean fertility rate of 2,2 surviving offspring per couple, had 104,6 TSD children per 100 000 births in generation 20, and 20,6 per 100 000 in generation 21. Smaller isolates had 78,8 TSD births per 100 000 in generation 20, and 19,1 per 100 000 in generation 21. A high fertility rate produced 88,3 and 23,8 TSD births per 100 000 respectively. With reproductive compensation the incidence of TSD fell from 314,6 to 91,0 per 100 000 births on release from genetic isolation.

The results show that large decreases in the incidence of TSD homozygosity occur when small communities are suddenly relieved of their genetic isolation, even in the presence of strict incest taboos. It is doubtful whether this finding could easily be reversed by factors we have overlooked or chosen to ignore (e.g. a reluctance to marry first cousins). The major reason for this phenomenon is the inevitably patchy dispersion of rare genes among the small isolates. Such highly patchy distributions occur even if there is some mobility between neighbourhoods.[13] Since the homozygosity rate of a gene is proportional to the square of its allelic frequency (assuming panmixis), it follows that the average homozygosity rate of two separate isolates (i.e. the homozygosity rate in the pre-migration population) is $(a^2 + b^2)/2$, where a and b are the allelic frequencies of the gene in the two communities. (In very small isolates, adjustments have to be made for the fact that a and b have discrete rather than continuous values.) If these communities merge (as in our post-migration population), the new homozygosity rate is $(a + b)/2^2$. When $a = b$ then $(a^2 + b^2)/2 = ((a + b)/2)^2$. In other words, in the absence of incest taboos, the incidence of lethal homozygosity before and after emigration would be exactly equal. Thus, if the TSD-carrier rate remained, or was by chance, exactly equally distributed between isolates (a virtual impossibility), then incest taboos would cause a lower homozygosity rate in the pre-migration population than in the post-migration population.

If, however, a and b are not equal then $((a + b)/2)^2 < (a^2 + b^2)/2$. In other words, the new, combined homozygosity rate is lower than the arithmetic mean of the two separate homozygosity rates. The greater the difference between a and b, the greater the discrepancy between $((a + b)/2)^2$ and $(a^2 + b^2)/2$. Incest taboos in the pre-migration population cannot negate such major discrepancies.[7]

It is therefore puzzling that the impression should have arisen that there was an increase in the incidence of TSD when the Ashkenazim emigrated from the Baltic states to the West. We believe that among the reasons for this false impression was the fact that the Western doctors were seeing increasing numbers of TSD babies as more and more Jewish immigrants arrived from eastern Europe. Second- and third-hand reporting of this situation, possibly by distressed patients and relatives of TSD babies, or by a sensation-seeking press, resulted in an inadvertent misrepresentation. It is also possible that

EDITORIAL / VAN DIE REDAKSIE

the immigrants, predominantly in their late teens and early twenties,[12] had not paid much attention to the circumstances of infant deaths at home. Had they not emigrated, and been asked whether TSD babies were known in the community, they would almost certainly have consulted the older generation and been given an affirmative reply. In their new country such consultation was impossible, and what should have been a 'don't know' answer became a nostalgic denial.

PHILLIP C. HAMPTON
STEPHEN R. SCHACH
Department of Computer Science
Vanderbilt University
Nashville, Tenn.
USA

JOHAN H. KOESLAG
Department of Medical Physiology and Biochemistry
University of Stellenbosch
Tygerberg, CP

1. McKusick VA. *Mendelian Inheritance*. Baltimore: Johns Hopkins University Press, 1978: 678.
2. Mourant AE, Kopec AC. *The Genetics of the Jews*. Oxford: Clarendon Press, 1978: 45-56.
3. Koeslag JH, Schach SR. Tay-Sachs disease and the role of reproductive compensation in the maintenance of ethnic variations in the incidence of autosomal recessive disease. *Ann Hum Genet* 1984; **48:** 275-281.
4. Koeslag JH, Schach SR. On the perpetuation of relic genes having an inviable homozygote. *Ann Hum Genet* 1985; **49:** 291-302.
5. Aronson SM. Epidemiology. In: Volk BW, ed. *Tay-Sachs' Disease*. New York: Grune & Stratton, 1964: 45-56.
6. Myrianthopoulos NC, Aronson SM. Population dynamics of Tay-Sachs disease: I. Reproductive fitness and selection. *Am J Hum Genet* 1966; **18:** 313-327.
7. McCormick DB, Schach SR, Koeslag JH. Marital mores as a mechanism for the maintenance of ethnic variations of lethal gene frequencies. *Am J Hum Genet* 1986; **39:** 477-488.
8. Fraikor AL. Tay-Sachs disease: genetic drift among the Ashkenazim Jews. *Soc Biol* 1977; **24:** 117-134.
9. Petersen GM, Rotter JI, Cantor RM, *et al*. The Tay-Sachs disease gene in North American Jewish populations: geographic variations and origin. *Am J Hum Genet* 1983; **35:** 1258-1269.
10. Cavalli-Sforza LL, Bodmer WF. *The Genetics of Human Populations*. San Francisco: Freeman, 1971: 311-314.
11. Kuchemann CF, Boyce AJ, Harrison GA. A demographic and genetic study of a group of Oxfordshire villages. *Hum Biol* 1967; **39:** 251-276.
12. Hofsten E, Lundstrom H. *Swedish Population History*. Stockholm: Statistika Centralbyrn, 1976: 139-149.
13. McKusick KB, Schach SR, Koeslag JH. Social mechanisms in the population genetics of Tay-Sachs and other lethal autosomal recessive diseases. *Am J Med Genet* 1990; **36:** 178-182.

Spotting the melanoma

The incidence of cutaneous malignant melanoma is increasing in all countries where reliable epidemiological statistics are available.[1] Worldwide data show an average rise in incidence of 7% per year, equivalent to a doubling every decade. Fourfold increases over a 10-year period have been reported in some groups.[2] The highest incidence of melanoma is in Queensland, Australia, largely as a result of ultraviolet exposure in a fair-skinned population. Although recent data from a population-based study in Cape Town indicate a lower incidence than in Australia, the annual incidence is disconcertingly high. During the past two decades, the mortality rate for melanoma in the USA increased faster than that of any other tumour, with a devastating impact, especially on young and middle-aged adults.[3] The most accurate prognostic factor for the individual patient is the tumour thickness of the primary lesion.[4] There is a strong correlation between the degree of tumour invasion and ultimate survival.[5] Biologically early or thin melanoma (less than 0,76 mm) is curable with conservative surgery, while locally advanced lesions have a relatively poorer prognosis and disseminated disease is invariably fatal.

Early recognition of melanoma is the most critical aspect of management and may be life-saving. Any change in the colour, size or shape of a pigmented lesion is of fundamental importance. Irregularity is the key physical sign. The ABCD guide to melanoma should be familiar to all clinicians: A for Asymmetry, B for irregular Borders, C for variegation of Colour, and D for increasing Diameter. Others have suggested more refined guidelines which include a 7-point checklist to avoid false positives.[6] However, no lesion causing anxiety should be excluded from referral. Many lesions mimic primary cutaneous melanoma including common melanocytic and dysplastic naevi, pigmented basal cell carcinomas, seborrhoeic keratoses, vascular lesions such as pyogenic granulomas and haemangiomas and solar lentigines. Amelanotic melanomas are notoriously difficult to diagnose as a result of atypical presentation. When there is any doubt about the diagnosis, an excision biopsy should be performed. The best diagnostic biopsy for small suspicious tumours is a complete full-thickness, tridimensional excision with a small margin of normal skin. An exception to this is a lesion too large for excision biopsy. Shave biopsies may result in the misdiagnosis of melanoma and compromise accurate staging of the tumour. A tissue sample should be taken for histological evaluation before cautery of any undiagnosed lesion. The histological assessment of problematic melanocytic lesions should be referred to an experienced dermatopathologist.

Failure to appreciate the significance of a new or changing pigmented lesion is the principal factor impeding early diagnosis.[7,8] Early detection should ensure less advanced disease at presentation and a more favourable prognosis.[9,10] Patient delay in seeking medical attention is the major factor in the late diagnosis of cutaneous melanoma in British, North American and South African studies.[9,11,12] In the Cape Town prospective evaluation of 250 patients with stage I melanoma, a mean of 11,1 months elapsed before definitive diagnosis.[12] The major delay (9,8 months) was the interval between the patient's noticing a new or changing lesion and his seeking professional advice. In addition, the perception that minor symptoms or changes in a lesion are not cancer-related and do not require medical attention is evident in that 46% of patients responded only after noticing ulceration, bleeding or the appearance of a lump in a pigmented lesion, i.e. late features in the progression of melanoma. These findings suggest that most patients with cutaneous melanoma are unable to distinguish between sinister and innocuous pigmented skin lesions. Certainly, in the early curable phase of biological evolution, signs may be subtle and melanoma may provide few clues that arouse suspicion or alarm the patient. Previous studies examining the underlying causes of delay in seeking medical opinion suggest that patients are often unaware of or minimise the potential seriousness of their condition;[10] this confirms that patients react more quickly to the late signs of melanoma than to the early, subtle signs. The relationship between delay and awareness of melanoma is not, however, a function of age, education or socio-economic status.[7,10] Clearly, patients require specific education in order for them to respond to the early signs of melanoma by seeking medical consultation; this is, after all, when they are most likely to be cured.

EDITORIAL / VAN DIE REDAKSIE

Clinicians, too, do not always identify early melanoma or precursor lesions accurately.[13,14] While in the majority of consultations in the Cape Town study the practitioner correctly identified a melanoma or recognised the lesion as suspicious and responded promptly, in 12% of cases the doctor's evaluation and reaction were inappropriate, with an ensuing delay in treatment.[12] Other studies have reported professional delays in 13 - 21% of cases.[9,11] The inability to recognise lesions that are curable in their early stages and invariably fatal when advanced has major clinical implications and requires attention. This may be a reflection of inadequate training in the diagnosis of skin lesions and emphasises the need for effective education programmes for health care providers. Of significance is the beneficial consequence of an incidental discovery of an asymptomatic melanoma during routine skin examination.[12] The mean depth of asymptomatic, incidentally identified melanomas was 0,9 mm compared with the 1,7 mm of symptomatic melanomas.[12] This finding strongly supports careful routine skin surveillance, particularly in susceptible at-risk patients.[15]

Given the importance of early detection and treatment (especially of biologically early melanoma) in lowering the mortality and morbidity rates associated with this disease, effective public education campaigns designed to increase awareness of the signs of melanoma, the need to screen regularly and the appropriate action to take when noticing suspicious changes, are crucial. Experience in Australia and Scotland has demonstrated that sustained professional and public skin cancer education programmes can reduce the number of deaths from melanoma substantially by detecting the disease early and increasing the proportion of thin to thick melanoma at presentation.[16,17] Evidence for the effectiveness of mass media and public educational campaigns in other countries is the resultant decrease in sun exposure among targeted populations as well as the increased use of sunscreens.

Recent laudable major educational campaigns in this country have been directed at primary (risk reduction) and secondary (early detection) prevention, incorporating both high-risk and population-based strategies. Identification of patients at high risk for cutaneous malignant melanoma allows efforts at prevention to be targeted and achieve more effective results. The risk factors for primary cutaneous malignant melanoma are any changing mole, dysplastic naevi (if there is family history of dysplatic naevi and melanoma), previous melanoma, large numbers of benign naevi, immunosuppression, excessive intermittent sun exposure and phenotypic factors such as sun sensitivity and inability to tan. Educational campaigns require clear, simple and focused messages stressing the increased risk of melanoma related to excessive sun exposure particularly in childhood, the clinical appearance of early melanoma, the excellent prognosis associated with detection and treatment of early melanoma and the need for regular skin examinations by self, surrogate, spouse or surgeon.

Early detection and prompt treatment is the most important factor in reducing the number of deaths from melanoma. The inability of most patients to recognise early changes and the delayed response of many demonstrate the need for increased sustained public education efforts. Melanoma offers an opportunity for the early detection and cure of a malignant disease; this, in large measure, is a realistic and attainable goal. Our responsibility is to seize the initiative and ensure that both the public and clinicians are enabled to take advantage of this unique opportunity.

J. E. J. KRIGE
N. SAXE

Departments of Surgery and Dermatology
Groote Schuur Hospital and
University of Cape Town

1. Balch CM, Milton GW. *Cutaneous Melanoma: Clinical Management and Treatment Results Worldwide*. Philadelphia: JB Lippincott, 1985.
2. Swerdlow AJ. Epidemiology of cutaneous malignant melanoma. In: Mackie RM, ed. *Clinics in Oncology: Melanoma*. Vol. 3. London: WB Saunders, 1984: 407-437.
3. Kopf AW, Rigel DS, Friedman RJ. The rising incidence and mortality rate of malignant melanoma. *J Dermatol Surg Oncol* 1982; **8:** 760-761.
4. Breslow A. Tumor thickness, level of invasion and node dissection in stage I cutaneous melanoma. *Ann Surg* 1975; **182:** 572-577.
5. Russell RCG. Malignant melanoma. *Br J Surg* 1986; **73:** 773-774.
6. MacKie RM. Clinical recognition of early invasive malignant melanoma. *BMJ* 1990; **301:** 1005-1006.
7. Rampen FHJ, Rumke P, Hart AAM. Patients' and doctors' delay in the diagnosis and treatment of cutaneous melanoma. *Eur J Surg Oncol* 1989; **15:** 143-148.
8. Cassileth BR, Temoshok L, Frederick BE, *et al.* Patient and physician delay in melanoma diagnosis. *J Am Acad Dermatol* 1988; **18:** 591-598.
9. Doherty VR, MacKie RM. Reasons for poor prognosis in British patients with cutaneous malignant melanoma. *BMJ* 1986; **292:** 987-989.
10. Temoshok L, DiClemente RJ, Sweet DM, *et al.* Factors related to patient delay in seeking medical attention for cutaneous malignant melanoma. *Cancer* 1984; **54:** 3048-3058.
11. Cassileth BR, Clark WH, Heiberger RM, March V, Tenaglia A. Relationship between patients' early recognition of melanoma and depth of invasion. *Cancer* 1982; **49:** 198-200.
12. Krige JEJ, Isaacs S, Hudson DA, King HS, Strover RM, Johnson CA. Delay in the diagnosis of malignant melanoma. *Cancer* 1991; **68:** 2064-2068.
13. Kofp AW, Mintzis M, Bart RS. Diagnostic accuracy in malignant melanoma. *Arch Dermatol* 1975; **111:** 1291-1292.
14. Cassileth BR, Clark WH, Lusk EJ, *et al.* How well do physicians recognize melanoma and other problem lesions? *J Am Acad Dermatol* 1986; **14:** 555-560.
15. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. *Lancet* 1989; **2:** 487-490.
16. Smith T. The Queensland melanoma project: an exercise in health education. *BMJ* 1979; **1:** 253-254.
17. Doherty VR, MacKie RM. Experience of a public education programme on early detection of cutaneous malignant melanoma. *BMJ* 1988; **297:** 388-391.