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PERSPECTIVES

Endogamy, consanguinity and community genetics

A. H. BITTLES*

Centre for Human Genetics, Edith Cowan University, 100 Joondalup Drive, Perth, WA 6027, Australia

The population of India is composed of many thousands of subpopulations, divided by geography, language, religion and caste or biraderi (patrilineage) boundaries, with endogamous marriage the norm. The net effect has been the creation of multiple genetic isolates with individual mutation profiles, but to date the clinical consequences of this highly complex differentiation have been largely ignored. In contrast, the topic of consanguinity continues to attract attention among medical and population geneticists, clinicians and social scientists. The significant progress made in India in improving childhood nutritional status and combating infectious disease means that genetic disorders have assumed ever-increasing importance. In populations where consanguineous marriage is widely practised, recessive genetic disorders will continue to gain greater prominence in the overall spectrum of ill health. At the same time this increase will in part be negated by urbanization and the move to smaller family sizes, which predictably will result in a decline in the prevalence of consanguineous unions. Developing an understanding of these changes will require a wide-ranging and multidisciplinary investigative approach for which community genetics is ideally suited.

Introduction

It can reasonably be claimed that India has long led the world in the field of community genetics. Beginning with the Census of India 1871 and continuing until the 1931 Census, information on the prevalence of blindness, deafness, insanity and leprosy were routinely collected and analysed on state and national bases, with additional information obtained on diseases specific to certain areas, e.g. filariasis in Travancore. In particular years and states the data also were collected with caste as basis. Thus in the 1921 Census of Punjab, which at that time comprised the present-day Indian states of Punjab and Haryana and the Pakistan province of Punjab, data on prevalence of deaf-mutism were collected across four geographical subdivisions, and for 13 Hindu and two Sikh castes and 17 Muslim *biraderi*s (patrilineages) (Census of India 1921, 1923).

From a genetic perspective the population of India is unique in its size and level of subdivision, with 15 major languages and six main religions. Within the majority Hindu community there are an estimated 3000 major castes, 1055 scheduled castes and 572 schedules tribes (Bhasin *et al*. 1992), and the Muslim population of over 130 million is similarly subdivided into Sunni, Shia, Ismaili and Dawoodi Bohra communities, and *biraderi*s that are based on traditional social and occupational divisions (Shami *et al*. 1994). The net result is that the national population of 1050 million (PRB 2002) is composed of some 50,000 to 60,000 essentially endogamous subpopulations (Gadgil *et al*. 1998).

Although mitochondrial DNA data have suggested that the founding female population of India was small (Roychoudhury *et al*. 2000), analysis of modern Indian populations has confirmed the continuing high level of gene differentiation (Majumder *et al*. 1999), with marked divisions according to caste ranks (Bamshad *et al*. 2001). While there is evidence of some female gene flow between castes (Bamshad *et al*. 1998), male gene flow across ethnic boundaries appears to have been negligible (Bamshad *et al*. 1998; Bhattacharya *et al*. 1999). Studies of this nature are, however, still in their infancy and in many cases they depend on quite broad population subclassifications. A hint of the possible levels of complexity of genetic subdivision was provided by the 1901 Census of India, which enumerated 101 Brahmin subgroups in the state of Mysore alone, although no information was provided as to whether or not marriage was permissible or had occurred between these different subgroups (Census of India, Mysore 1903).

India also is subdivided into two major regions with respect to a preference for or avoidance of consanguineous marriage, a subject that strongly attracted the attention of J. B. S. Haldane (Haldane 1963). The interest expressed by Haldane was instrumental both in the inclusion of a subsurvey on consanguinity within the 1961 Census of India (Roychoudhury 1976) and in numerous subsequent studies into the prevalence of both consan-

*E-mail: a.bittles@ecu.edu.au.

guineous and affinal marriage (Chakravarti 1968; Roychoudhury 1976, 1979; Singh and Tyagi 1987).

As indicated in figure 1, based on the 1992–1993 National Family and Health Survey (IIPS 1995), unions between biological kin are uncommon in the northern, eastern and northeastern states because of a general prohibition on consanguineous marriage in the majority Hindu population. The prohibition is believed to date back to approximately 200 BC and forbids the marriage of a man with the daughter of his father's sister or of his mother's sister, or of his mother's brother (Kapadia 1958; Sanghvi 1966; Rao 1984). Among Hindus of North India, the descendants of Indo-European-speaking populations who are thought to have entered the Indian subcontinent around 2000 BC, pedigrees are examined over an average of seven generations for males and five generations for females to ensure avoidance of a consanguineous union. By comparison, uncle–niece marriage and first-cousin unions between a man and his maternal uncle's daughter (mother's brother's daughter) have a long tradition in South India (Sastri 1976).

Because of their traditional status consanguineous unions are regarded as customary for the peoples of southern India, i.e. those living south of the Narmada river. Cross-cousin marriage was recognized in the Hindu Marriage Act of 1955, and the legality of uncle–niece unions was subsequently confirmed in the Hindu Code Bill of 1984 (Appaji Rao *et al*. 2002). As a result, consanguineous unions increase in prevalence in the states south of the Narmada, with the highest rates reported in Andhra Pradesh, Karnataka and Tamil Nadu (table 1). Kerala is an exception, in part because of the strict avoidance of consanguineous marriage among members of the Christian Syrian Orthodox church and, as indicated

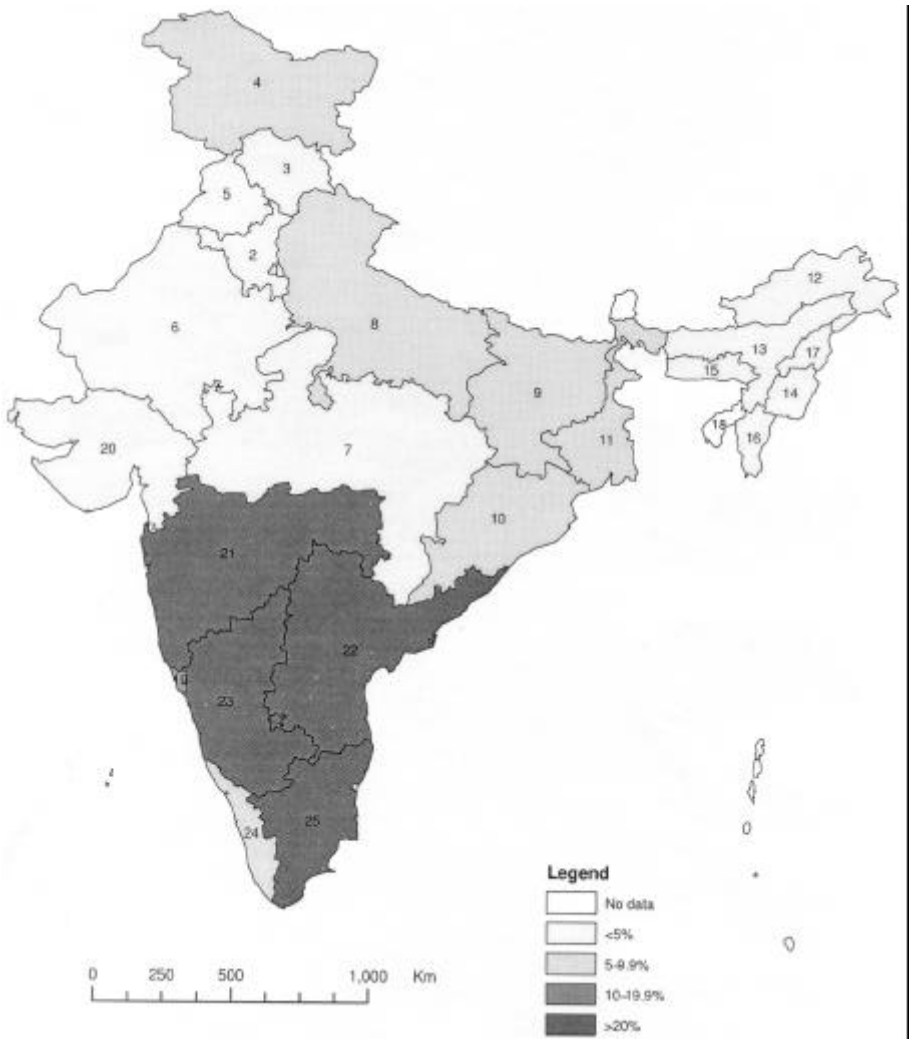

Figure 1. Map of India, indicating prevalence of consanguineous marriage from 0% to 20+% by state reported in the 1992–1993 National Family and Health Survey (IIPS 1995). The numbering of the states corresponds to that in table 1.

below, by lower levels of consanguinity in a long-established local Muslim community. There also is evidence that the levels of consanguineous marriage within the Hindu community have decreased since the 1961 Census of India (Roychoudhury 1976), although high levels of consanguineous marriage have continued among tribal groups (Joseph and Mathew 1991).

No comparable north–south division exists in the Muslim population of India. Although consanguineous marriage is common in all Indian Muslim communities, the *Quran* contains no specific guidance that could be interpreted as encouraging consanguinity (Hussain 1999). Indeed, according to one of the *hadith*, a recorded pronouncement of the Prophet Muhammad, cousin marriages were better discouraged. On the other hand the Prophet married his daughter Fatima to Ali, his paternal first cousin and ward. Thus, for Muslims, cousin marriage could be interpreted as following the *sunnah*, i.e. the deeds of the Prophet.

Variations are seen in the levels of consanguineous unions contracted in different branches of Islam and between specific communities. While 43.4% of marriages in the Shia community of Lucknow in North India were consanguineous (Basu 1975), the comparable figure was less than 10% among the *Mappillas* of Kerala, the descendents of Arab traders who settled in the southwest of India from the eighth century AD (Bittles and Hussain 2000). In fact, within the Indian subcontinent the clearest division in rates of Muslim consanguineous marriage is seen between Islamic communities in India and their Pakistani coreligionists (Hussain and Bittles 1998; Bittles and Hussain 2000), which emphasizes the important influence of local and regional customs in the arrangement of marriage contracts.

The net result of the various religious preferences and prohibitions with respect to consanguinity are summarized in table 2. While consanguineous unions were reported in all religions, at national level the highest rates were observed in the Muslim and Buddhist communities and the lowest among Sikhs and Jains.

The genetic effects of consanguineous marriage

It can be argued that all humans are to some extent inbred, as evidenced by a simple calculation of the impossibly

Table 1. Consanguineous marriage in India by state, 1992–1993.

Region	State	Consanguineous marriage (%)	Mean coefficient of inbreeding (a)
North	1. Delhi	4.3	0.0023
	2. Haryana	1.0	0.0004
	3. Himachal Pradesh	0.8	0.0003
	4. Jammu and Kashmir*	8.0	0.0049
	5. Punjab	0.9	0.0006
	6. Rajasthan	1.3	0.0006
Central	7. Madhya Pradesh	4.1	0.0025
	8. Uttar Pradesh	7.5	0.0044
East	9. Bihar	5.0	0.0032
	10. Orissa	5.7	0.0035
	11. West Bengal	5.0	0.0030
Northeast	12. Arunachal Pradesh	3.9	0.0029
	13. Assam	1.7	0.0010
	14. Manipur	2.1	0.0013
	15. Meghalaya	2.7	0.0018
	16. Mizoram	0.5	0.0002
	17. Nagaland	1.5	0.0009
	18. Tripura	1.9	0.0010
West	19. Goa	10.6	0.0066
	20. Gujarat	4.9	0.0029
	21. Maharashtra	21.0	0.0131
South	22. Andhra Pradesh	30.8	0.0212
	23. Karnataka	29.7	0.0180
	24. Kerala	7.5	0.0042
All-India		11.9	0.0075

*Data were collected only in Jammu region.

Table 2. Consanguineous marriage in India by religion, 1992–1993.

Religion	Consanguineous marriage (%)	Mean coefficient of inbreeding (a)
Hindu	10.6	0.0068
Muslim	23.3	0.0141
Christian	10.3	0.0068
Sikh	1.5	0.0009
Jain	4.3	0.0024
Buddhist	17.1	0.0107
Others	8.7	0.0053

large number of human ancestors implied if all matings had occurred with non-kin in past generations. The term consanguinity is used to describe unions between couples who are known to share genes inherited from one or more common ancestors. Globally, the most common form of consanguineous marriage is between first cousins, who are predicted to have 12.5% of their genes in common, and so on average their progeny will be homozygous at 6.25% of gene loci, equivalent to a coefficient of inbreeding (F) of 0.0625 (Bittles 2001). Thus comparable values for uncle–niece or double first-cousin progeny are $F = 0.125$, and for second cousins $F = 0.0156$. At the population level the mean coefficient of inbreeding (a) can be calculated according to the formula

$$a = \Sigma p_i F_i ,$$

where the summation is over the proportion of individuals p_i in each consanguinity category F_i. The highest a value reported for an Indian community was 0.0449 in Pondicherry, where 20.2% of the marriages were uncle–niece unions and 31.3% between first cousins (Puri *et al*. 1978). Composite figures for different Indian communities and comparable data on other populations worldwide have been compiled and are available in Bittles (1998) and at the website http://www.consang.net.

In many well-established communities there is a long, unbroken history of consanguineous unions. Under these circumstances the cumulative level of inbreeding may be significantly higher than the value calculated for a single generation. A correction can be applied to account for the effects of ancestral inbreeding using the formula

$$F = \sum (½)^n (1 + F_A),$$

where F_A is the ancestor's inbreeding coefficient, n is the number of individuals in the path connecting the parents of the individual, and the summation is taken over each path in the pedigree that goes through a common ancestor.

For most purposes a marriage is regarded as consanguineous if it has been contracted between spouses who are related as second cousins or closer ($F = 0.0156$), since the levels of homozygosity in marriages beyond second cousin ($F < 0.0156$) differ only to a minor degree from those observed in the general population. In a large majority of clinical studies only the effects of consanguinity in the current generation are considered. As indicated above this may underestimate the actual level of homozygosity in an individual, but the decision is taken largely on practical grounds as in many communities the family pedigrees show complex multiple pathways of consanguinity that are difficult and very time-consuming to interpret.

The preference for consanguineous unions

The highest rates of consanguineous marriage in South India are usually reported in traditional rural areas and among the poorest and least educated groups. However, close kin marriage is commonplace even in Brahmin communities (Srinivasan and Mukherjee 1976), and it may be strongly favoured among major land-owning families as a means of ensuring the maintenance of their estates. The only communities in which consanguinity appears to be specifically avoided are those with origins in North India, and which continue to follow the traditions of that region (Appaji Rao *et al*. 1998).

Both social and economic reasons are given for the popularity of consanguineous unions (Bittles *et al*. 1991; Bittles 1994). It is believed that consanguineous marriage helps to strengthen family ties, and at the same time health or financial uncertainties that could arise through marriage with a partner from another family or community will be avoided. Premarital arrangements are greatly simplified in consanguineous unions, and the relationship of a couple, especially the bride, with their in-laws (and family relatives) is expected to be more congenial. Economic considerations also are important and, in communities where either dowry or bride-wealth payments are the norm, the arrangement of a marriage within the family reduces or even abolishes the associated financial costs (Badaruddoza and Afzal 1995).

Although the most common form of consanguineous marriage in all major societies is between first cousins, the importance of customary influences is apparent from variations in the specific types of first-cousin marriage contracted. While marriage to mother's brother's daughter is the strongly preferred form of consanguineous union among South Indian Hindus (Rao and Inbaraj 1977), all four types of first-cousin union, i.e. to father's brother's daughter, to father's sister's daughter, to mother's brother's daughter, and to mother's sister daughter, are arranged in South Asian Muslim communities.

The influence of consanguinity on fertility and mortality

An overall assessment of the genetic influence on prenatal losses within consanguineous unions is difficult, as

the information available is usually dependent on maternal recall, which often proves to be inaccurate (Wilcox and Horney 1984). The outcomes also may be dependent on nongenetic factors, such as maternal age, birth order and birth interval, factors that have seldom been incorporated into the study design. Where data have been available, primary infertility appeared to be reduced and there was little general evidence of increased numbers of miscarriages or stillbirths (Bittles 2001). Thus a meta-analysis conducted on 30 populations showed that at levels of consanguinity from $F = 0.0156$ to $F = 0.125$ the mean number of live births was higher in consanguineous than nonconsanguineous unions, and for first-cousin marriages ($F = 0.0625$) the fertility differential was significant at $P < 0.0001$ (Bittles *et al*. 2002).

Most studies in India have indicated that early postnatal mortality is higher in the progeny of consanguineous unions, owing to the expression of deleterious recessive genes. Consanguinity-associated deaths are largely concentrated during the first year of life (Hussain *et al*. 2001), and multiple deaths have been reported in specific consanguineous families in proportion to the level of parental genetic relatedness (Bittles *et al*. 1991). Following a hypothesis by Sanghvi (1966), there is a body of opinion which suggests that through time the practice of consanguineous marriage would have led to the effective elimination of recessive lethal alleles from the gene pool. As with investigations into the association between consanguinity and prenatal losses, many earlier studies were hindered by a lack of control for important sociodemographic variables, and in some cases the sample sizes were unrealistically small to adequately test any hypothesis. Where appropriate clinical and laboratory investigations have been conducted there has been no convincing evidence of a consanguinity-associated 'cleansing' of the gene pool.

There has been a marked downward revision in the estimates of excess consanguinity-associated mortality through time (Bittles and Makov 1988), which principally results from better sampling techniques, including partial control for nongenetic variables. The most recent representative mortality estimate is based on a multinational study of over 600,000 pregnancies and live births, in which 10 of the 38 populations studied were from India and nine were from Pakistan (Bittles and Neel 1994). The analysis showed that, from approximately the sixth month of pregnancy to a median age of 10 years, deaths in first-cousin progeny exceeded mortality in nonconsanguineous progeny by an average of 44/1000 births. Even this figure may, however, be exaggerated as few if any of the constituent surveys in the analysis had explicitly included control for potential confounding sociodemographic factors, e.g. maternal age, maternal education, birth order and birth interval.

The mean coefficient of inbreeding for the total population of India in the 1992–1993 National Family and Health Survey (IIPS 1995) was $a = 0.0075$ (table 1). The data of Bittles and Neel (1994), where consanguinity-associated mortality to approximately 10 years of age averaged 44/1000 births at $F = 0.0625$, would suggest that on a national basis consanguinity would be a contributory factor in 5.2/1000 deaths. To place this figure in partial perspective, the rate of under-five-year mortality in India over a comparable study period was 109.3/1000 (IIPS 1995).

Consanguinity and morbidity

A comprehensive listing of genetic disorders that have been diagnosed in the progeny of consanguineous couples is available at the website http://www.consang.net. The diagnosis of birth defects in India may overlap with and reflect late foetal and neonatal survival rates, and the data that are available were almost exclusively collected in the major cities, whereas the majority of the population is rural. For these reasons the reported prevalence rates may be unrepresentative of the numbers of affected cases in the country as a whole.

Many different types of genetic disorders have been reported to be more common among consanguineous progeny, for example congenital disorders (Centerwall and Centerwall 1966; Asha Bai *et al*. 1981; Agarwal *et al*. 1991), including neural tube defects (Kulkarni *et al*. 1989; Jain *et al*. 1993) and congenital heart defects (Jain *et al*. 1993; Badaruddoza *et al*. 1994; Gnanalingham *et al*. 1999). Autosomal recessive hearing loss disorders (Chen *et al*. 1997) and visual defects such as early-onset retinal dystrophies (Rahi *et al*. 1995), primary congenital glaucoma (Panicker *et al*. 2002) and anophthalmos (Hornby *et al*. 2001) also are present at increased prevalence. However, there is a paucity of national or even state-level data for all genetic types of disorder, which makes derivation of credible prevalence rates virtually impossible.

A topic that has so far received little attention is the possible effect of consanguinity on adult-onset disease. Little comment can usefully be made because of the overall lack of information but, for example, a preliminary prediction that breast cancer appeared to be more common in females born to consanguineous parents in Pakistan (Shami *et al*. 1991) has recently been supported by studies on early-onset cases, i.e. patients under 40 years (Liede *et al*. 2002). Also, in a French-Canadian isolate a significant association between consanguinity, expression of the *APOE-4* allele and late-onset Alzheimer's disease has been identified (Vézina *et al*. 1999). Given the extremely high prevalence of premature coronary heart disease in South Asian males, an urgent detailed investigation of the possible role of recessive genes as predisposing disease factors would appear to be warranted.

Discussion

While caste endogamy remains largely unchanged throughout India, data on trends in the prevalence of consanguineous marriage in predominantly Hindu South India are somewhat contradictory, with some studies suggesting a decline (Audinarayana and Krishnamoorthy 2000) and others that there has been no recent change (Bittles *et al*. 1993). In the Muslim population of India there has been no evidence of a reduction in consanguineous marriage during the last 40 years (Hussain and Bittles 2000). Nonetheless, it is probable that increased urbanization and the gradual shift to smaller family sizes will impose constraints on consanguineous marriage in future generations. In this respect, a reduced prevalence of uncle–niece marriages would appear to be especially likely because of unacceptable age differentials between the potential partners (Radha Rama Devi *et al*. 1982).

The excess risk that an autosomal recessive disorder will be expressed in the progeny of a consanguineous union is inversely proportional to the frequency of the disease allele in the gene pool (Bittles 2001). For this reason, during the last decade many disease genes that are rare in the general population have been identified and their chromosomal locations mapped by studying highly inbred families with multiple affected members. As previously discussed, in India the population is subdivided into many thousands of endogamous communities that through time have evolved into distinctive breeding pools. Whether or not a mutation will appear in all communities or be restricted to a single subcaste or *biraderi* will be dependent on the origin and the age of the community. At least three major migrations into the Indian subcontinent have been identified (Gadgil *et al*. 1998; Roychoudhury *et al*. 2000), but across historical time there almost certainly were other, smaller migrations involving one or several subpopulations.

Four basic classes can be defined with respect to the age of mutations (table 3). For example, mutations that occurred over 100 generations ago may conceivably be found in all Hindu castes, whereas those of more recent origin probably have restricted distribution and may be unique to specific subcastes. The smaller the community the greater the probability that founder effect and genetic drift will exert a significant influence on the distribution patterns of specific mutations. Therefore, even in the absence of preferential consanguineous marriage, genetic isolation often results in an increased frequency of community-specific genetic diseases. This fact is commonly overlooked, with the consequent general assumption that where an autosomal recessive disease is present in a family or community at high frequency consanguinity is necessarily implicated.

The situation is somewhat different in the Muslim population of India, because of the conversions from Hinduism that occurred from the twelfth to the nineteenth centuries AD (Hussain and Bittles 2000) and the various waves of invasion by peoples from Central Asia. The 1921 Census of Punjab also indicated the occurrence of inter-*biraderi* marriages and hence some gene pool admixture. As a result, it seems probable that the levels of genetic differentiation between *biraderi*s would be less pronounced than those between castes. Nonetheless, genomic studies in Pakistan have demonstrated highly significant differences between Muslim *biraderi*s at both autosomal and Y-chromosome loci (Wang *et al*. 2000).

Table 3. The time scale of human mutations.

Period	Generations	Years
Modern	≤ 10	≤ 250
Historical	> 10–100	250–2500
Pre-historical	> 100–4000	2500–100,000
Ancient	> 4000	> 100,000

The presence of multiple discrete subpopulations creates substantial practical difficulties in the compilation of national disease registers, and in the organization of screening programmes for specific genetic disorders. On the positive side, once a specific mutation has been identified within a consanguineous pedigree, case ascertainment in other family members can be greatly simplified (Ahmed *et al*. 2002; Modell and Darr 2002). This applies within communities that are effective genetic isolates, whether or not consanguinity is involved. Thus in a rural South Indian community it was possible to rapidly identify the causative mutation for the autosomal dominant disorder familial adenomatous polyposis coli, and to efficiently counsel and test all persons at risk (Savithri *et al*. 2000). It should, however, be stressed that genetic heterogeneity may persist even where a recessive disorder is known to be common within a particular inbred subpopulation, with no guarantee that all affected members are homozygous for the same mutation. Furthermore, in many consanguineous isolates there is the possibility that two or more mutant alleles are segregating within a family, which greatly complicates diagnosis and genetic counselling (Bittles 2001).

The total burden of disease in a population can increase significantly as populations progress in economic terms, with ameliorative treatment of formerly lethal genetic disorders placing an ever-increasing demand on family resources (Bittles 2001). Thus, although consanguineous marriage may remain culturally desirable, a major shift in balance between the social and economic benefits associated with intrafamilial marriage and adverse health outcomes can be predicted. These changes are already under way in India, and new diagnostic, counselling and treatment skills need to be rapidly developed in conjunction with appropriate community education programmes.

A multidisciplinary research team in North America has recently recommended that for neonatal and early-childhood investigations the progeny of first-cousin marriages should be treated in a manner comparable to the treatment of children of nonconsanguineous parents (Bennett *et al*. 2002). This advice also applies in India, although once again the enormous complexity of the population subdivisions may make any form of all-encompassing recommendation difficult to sustain. While India still has major problems in dealing with infectious diseases and nutritional disorders, genetic disease already presents as a significant, although largely underestimated, problem. The time is now appropriate to determine the prevalence of the major genetic diseases in different parts of the country, and in the various major communities, and to invest in the training of specialist medical, scientific, nursing and counselling staff.

Acknowledgements and dedication

This paper is dedicated to the memory of Professor Vulimiri Ramalingaswami, F.R.S., and is based on the Inaugural Professor V. Ramalingaswami Lecture delivered at the Symposium on Community Genetics in Developing Countries, held in the Indian Institute of Science, Bangalore, on 16 January 2002 with generous support from the Sir Dorabji Tata Trust. Professor Ramalingaswami first came to international attention though his outstanding work on iodine deficiency disorders in the Himalayan region of India. His breadth of knowledge and administrative skills were acknowledged by his appointment as Director-General of the Indian Council of Medical Research, and in his subsequent secondment to UNICEF in New York. Throughout his long and highly distinguished career Professor Ramalingaswami led by personal example. His deeply compassionate nature, sincerity and great personal charm will always be remembered by his colleagues and by those who were fortunate to be counted among his friends.

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