Environmental Health Policy

HERITABLE ANOMALIES AMONG THE INHABITANTS OF REGIONS OF NORMAL AND HIGH BACKGROUND RADIATION IN KERALA: RESULTS OF A COHORT STUDY, 1988–1994

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In a genetic epidemiological and fertility survey among 70,000 inhabitants in a high-background radiation region (HBRR) and normal radiation region (NRR) in Kerala, India, 985 persons were found to have heritable anomalies. Suggested etiologies for the anomalies were chromosomal and Mendelian, 15 percent; multifactorial, 60 percent; and congenital, 25 percent. There was a statistically significant increase of Down syndrome, autosomal dominant anomalies, and multifactorial diseases and an insignificant increase of autosomal recessive and X-linked recessive anomalies in the HBRR. The total fertility rate was 3.85 per couple; 9 percent of live-born children were reported dead. The rate of untoward pregnancy outcome—death of the offspring or presence of an anomaly in a living child—was 6.4 percent among the unrelated couples in the NRR, with one spouse born outside the area of current residence ("migrant"). Considering this as the base, the excess relative risks in the other groups are: "NRR-nonmigrant," 35 percent; "HBRR-nonmigrant," 69 percent; "NRR-consanguineous," 76 percent; and "NBRR-consanguineous," 157 percent. Ionizing radiation, consanguinity, and nearness of birthplace of the spouse are risk factors for the death of offspring and for anomalies. The higher risk among the "nonmigrant" couples may be due to geographic inbreeding. The findings are suggestive of an autosomal recessive etiology for the majority of the multifactorial anomalies.

The role of genetic factors in health and well-being has been recognized for a long time. However, there are no comprehensive baseline data on morbidity load due to genes for any human population. Muller (1) demonstrated the mutagenic effect of ionizing radiation in fruit flies in 1928. In the single largest

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prospective study of 150,000 children born in Hiroshima-Nagasaki during 1948–1964, no statistically significant increase of any untoward pregnancy outcome was found for children born to parents exposed to ionizing radiation from the bombs (2). In short, no reliable evidence is available based on sufficient human data about either spontaneous or radiation-induced morbidity load attributable to genes. The United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) relies on the background incidence estimated from ad hoc surveys conducted in industrial towns where a majority of the population is West European or West European in origin (3). African-Asian peoples are different from West Europeans in rate of inbreeding, lifestyles, and exposure to mutagens. There are no data for these people, who account for three-fourths of the global population.

About 200,000 people live in high-background radiation regions (HBRR) in India. Sources of radiation are thorium, uranium, and their radioactive daughters contained in the mineral monazite. Rich surface deposits of monazite are found in the coastal districts of Ganjam in Orissa State, Kanyakumari in Tamilnadu State, and Kollam (earlier Quilon) in Kerala State. Other well-known HBRRs are in China, Brazil, France, Italy, Iran, Madagascar, and Nigeria. In 1957, the World Health Organization (WHO) identified the Kerala HBRR (mean background radiation 650 millirad/year (mR/yr)) and adjoining villages in a normal-radiation region (NRR) as the ideal setting for studying the radiation-induced and spontaneous genetic load in human beings (4, p. 13).

Results of the biological studies conducted in some of the HBRRs show mixed results. A cytogenetic study in the Brazilian HBRR with background radiation of 640 mR/yr showed a significant increase in chromosome aberrations (5). Wei and colleagues (6) reported a higher incidence of Down syndrome, chromosomal aberrations, and reactivity of T lymphocytes in Yanjiang County of China. Gopal-Ayengar and colleagues (7) observed a higher incidence of cytological abnormalities and pollen sterility in four species of wild plants from the Kerala HBRR. However, Gruneberg and associates (8) found no difference in musculoskeletal abnormalities in rats (*Rattus rattus I.*) from the HBRR and NRR. In a cytogenetic study of 1,482 adults and infants from the Kerala HBRR and NRR, there was a 50 percent excess of aberrations among the subjects from the HBRR (9, 10). Nevertheless, in a survey of 2,381 couples from the HBRR and NRR, Gopal-Ayengar and colleagues (11) did not find any difference in rates of fertility, mortality, and twinning. Kochupillai and colleagues (12) reported a higher incidence of Down syndrome and severe mental retardation in the Kerala HBRR. George and co-workers (13) did not find any significant increase of Down syndrome and other congenital anomalies in 3,000 infants born to parents from the HBRR.

All three human health studies in the Kerala HBRR were based on small samples and sought data on limited endpoints. There are no data on total, visible genetic load in the entire population settled in the Kerala HBRR or in a population

living in an NRR. In this article, we report the findings of a cohort-type study conducted during 1988–1994 to measure the prevalence of heritable anomalies and to assess the reproductive performance of couples in the Kerala HBRR and a comparable NRR.

STUDY POPULATIONS AND METHODS

Land and People

The study area (Kerala HBRR) is a coastal strip, which is part of four revenue villages: Alapat, Panmana, Chavara, and Neendakara, in Karunagappalli *taluk* (subdistrict) of Kollam district. The strip is an island with Neendakara and Kayamkulam estuaries in the south and the north, Ashtamudi-Kayamkulam back-waters in the east, and the Arabian Sea in the west. The control NRR consists of four coastal villages: Ambalapuzha, Purakkad, and Punnapra in Ambalapuzha *taluk* of Alapuzha (earlier Alleppey) district and a fishing village in Kollam municipality in Kollam district. The study area has no hospital or health center. The HBRR can be seen during the Kollam-Alapuzha boat ride, which is a popular tourist itinerary. The national highway forms the eastern boundary of the NRR. The study and control areas had seaports frequently mentioned in the chronicles of medieval travelers and traders. The majority of the inhabitants belong to three castes: Dheevarar, Catholics, and the Ezhavar. The traditional occupation of the first two groups is fishing; the Ezhavar were traditionally farmers, toddy-tapers, and jaggery-makers. There are no differences in food habits, lifestyle, customs, and rituals between the study and control populations.

The southern portion of the HBRR once housed the headquarters of the Indo-Norwegian Project, which initiated the mechanization of Indian fishers during the 1950s. The Project also had a health care component with a hospital and community health service, which functioned as long as the Norwegians were there. It also assisted in implementing water supply schemes in the HBRR and other parts of Kerala. Since the 1980s, the birthplace and the ashram of Mata Amritanandamayi situated in the HBRR have been receiving thousands of devotees from India and abroad. Kerala's coastal villages have a high population density (2,000 persons per square kilometer) and poor infrastructure. Until the middle of the last century, there was an acute shortage of safe drinking water and a high incidence of water-borne diseases. In 1953, "half the population had to carry water from wells more than 200 yards away. Many women carried water from public wells up to two miles away. . . . An examination in 1954 revealed that about 90 percent of those examined were infected with hook worms, round worms or other intestinal parasites" (14). Availability of safe drinking water, mechanization of fishing, expansion of the market, universal immunization, and hospital delivery have been instrumental in reducing maternal and child mortality since the 1960s. The infant mortality rate in Kerala was 25 per 1,000 births during the 1980s (15).

The secondary data on health and morbidity for the state are very limited. Births and deaths taking place in hospitals are registered with the local authorities. The parish registers have details of births, marriages, and deaths spanning more than a century. However, there is no registry for stillbirths, congenital anomalies, or cancer.

Dosimetry

A. P. Suresan and M. Muralikrishna measured the external radiation with a portable gamma counter, at 10 and 100 centimeters above ground, at 100 points in the NRR and 2,070 points in the HBRR. The geometric mean of the readings was calculated for each of the 26 local council (*panchayat*) wards in the HBRR. Bernd Lehman of Strahlentelex, Berlin, read the thermoluminescent dosimeters exposed for 30 days in 43 houses. R. T. H. Van de Laar studied the concentration of radionuclides in fish. Radon monitoring was done in 10 houses in the HBRR. Drinking water samples were analyzed for radionuclides by the International Water Tribunal, Amsterdam.

Sampling and Primary Survey

The support of priests, village leaders, and social workers was solicited for the survey, the stated objective being an assessment of the health status of the coastal people. All households of permanent residents in the HBRR were listed, using the electoral rolls and housing records held by the local government. The primary investigators were women from the same village who had 10 or more years of schooling. They canvassed a pretested schedule consisting of three parts: part I, socioeconomic and demographic data; part II, fertility history of all couples; and part III, information on morphological or functional abnormalities in any of the family members. Re-survey was done in 10 percent of the households by another investigator to check for errors and investigator bias. Fertility data include birthplace of each spouse, consanguinity, age at menarche, marriage, pregnancies, and menopause, and pregnancy outcomes and contraceptive history.

Medical Investigations

In the primary survey, 4,555 persons (2,767 from the HBRR) were reported to be suffering from one or more anomalies listed in part III of the schedule. A team consisting of the medical investigator, a nurse, and a research assistant examined 4,530 persons from both areas. The team also collected anthropometric measurements, prenatal and postnatal history, and details of prior diagnosis and therapy. With the twin objectives of eliminating false negatives and perfecting etiology, the team also documented details of each affected person's

blood relative(s) having the same or a different anomaly. All relatives reported as anomalous were examined. A total of 1,121 persons (from both areas) with complex syndromes were referred to one of the 13 postgraduate consultants in medicine, pediatrics, surgery, orthopedics, otolaryngology, ophthalmology, and dermatology. Karyograms, urinaminograms, audiograms, and X-rays were also done where necessary. Twenty-five persons (11 from the HBRR) could not be examined despite repeated house visits.

S. Shyam and S. N. Shibu provided software support. Statistical analysis was done using Epi Info Version 6.0 (16).

Cytogenetic Study

Fifty-four subjects and their parents volunteered for the cytogenetic study. Of the 117 samples of peripheral blood (fixed in EDTA and heparin) sent to the All India Institute of Medical Sciences, Delhi, 105 were successfully cultured. Cells harvested after 48 hours of culture were scored for satellite association. Fragile sites expressed in folic acid- and thymidine-deficient medium were scored after 96 hours of culture.

RESULTS

Dosimetry

Dosimetric findings have been published in detail elsewhere (17). The estimated annual exposure in the NRR at 10 cm above ground was within the narrow range of 85 to 110 mR/yr, with a geometric mean of 100 mR/yr. In the HBRR, the geometric means of the estimated annual dose at 10 cm and 100 cm above ground were 735 and 563 mR/yr, respectively. The northern and eastern areas had lower readings than southern and western areas. The mean annual exposure at 100 cm above ground was 235 mR in the northern-most ward versus 1,273 mR in the extreme south. Thermoluminescent dosimetry readings did not differ from those of the gamma counter. Concentrations of radon/thoron in houses and radionuclides in drinking water samples were within normal limits. Concentrations of radium-226 and radium-228 in sardines—the main type of fish eaten in the area—were 0.04 and 0.07 becquerels per kilogram (Bq/kg) of fresh weight, respectively. No difference was seen in fish caught in the sea off the HBRR and NRR. The clam meat harvested from the backwaters near the HBRR had 1.27 Bq/kg of radium-226 and 4.3 Bq/kg of radium-228 (18).

Demographic Data

There were 38,685 persons in 6,782 households in the HBRR and 31,550 persons in 5,677 households in the NRR. Three-fourths of the households had a single

family and one-fifth had two families. One-fourth of the households had one or more grandchildren. The caste composition of the HBRR population (NRR in parentheses) was Dheevarar 52.0 percent (48.6 percent), Ezhavar 16 percent (24 percent), Catholics 21.9 percent (21.0 percent), and other 10 percent (6.6 percent). The socioeconomic class of each household was assessed from ownership of land and fishing gear, type of house, and occupation of family members. With modernization of fishing, class division has arisen among the fishing communities. The high-income group constituted 7 percent of the households in the NRR versus 14 percent in the HBRR. More sociodemographic data are given in the Appendix (p. 511).

The nonmigrant population (35,305 in the HBRR and 27,675 in the NRR) is used as the denominator for estimating the prevalence of anomalies. In both areas, 89 percent of males and 72 percent of females were born in the house where they lived at the time of the survey. Migrants from outside the areas constituted 4.7 percent of the males and 12.6 percent of the females in the HBRR and 6.7 percent of the males and 19.8 percent of the females in the NRR. Outmigration takes place once in life, usually after marriage; repeat migration is rare. In the three major castes, the youngest son inherits the family house, which, in a sense, is permanent; the other sons usually set up their homes near the family house. Patrilocality is the norm; only 387 households had a resident son-in-law. Because of population pressure and poor communication facilities, many families from the HBRR had moved out to the eastern villages. In the NRR, where sea erosion is not a serious problem, poor families from the east have settled on the unowned land beyond the high-tide line.

Genetic and Congenital Anomalies: Total Caseload

Anomalies attributable to maternal infection by teratogenic agents, difficult labor, and accidents/illness were excluded. The anomalies were coded according to WHO's International Classification of Diseases (ICD) (19). We found 985 nonmigrant persons with genetic or congenital anomalies, 631 in the HBRR and 354 in the NRR; 236 persons had multiple anomalies, with a maximum of four diagnoses scored. The sex ratio (males per 1,000 females) of patients was 1,369 in the HBRR and 1,186 in the NRR. Mean age at the time of the survey was 14 years for persons with Down syndrome, 20 years for persons with other anomalies, and 26 years for those without anomalies. Maternal age at pregnancy of the proband for the HBRR (NRR in parentheses) was below 25 years for 47.7 percent (44.6 percent), 25 to 34 years for 43.6 percent (46.6 percent), and 35 to 44 years for 8.7 percent (8.8 percent). Mean maternal age at birth was 34 years for children with Down syndrome and 25 years for other anomalies. We found no difference in mean maternal age for normal children and children with anomalies other than Down syndrome.

Cytogenetic Study

Among the 5,648 metaphases scored, the percentages of cells with DD, DG, and GG satellite associations were 7, 13, and 1 percent, respectively, in samples from the HBRR and 2, 6, and 1 percent in samples from the NRR. The difference between areas is significant at the 0.0006 level. Frequency of fragile sites was also higher among the subjects from the HBRR ($P < 0.05$). For structural aberrations, there is no difference between the areas (20).

Etiological Classification of Anomalies

We assigned the mode of inheritance according to Victor A. McKusick's *Catalogue of Autosomal Dominant, Autosomal Recessive and X-Linked Phenotypes* (21). The catalogue lists 2,208 traits, of which 1,443 are dominant, 626 recessive, and 138 X-linked recessive. Anomalies of non-allelic heterogeneity (traits that can be inherited in any one of the Mendelian modes or caused as a teratogenic effect) were not considered Mendelian. Sporadic cases of arthrogryposis multiplex congenita, Sturge-Weber syndrome, myopia, Cornelia de Lange syndrome, congenital optic atrophy, craniostenosis, and precocious puberty were thus excluded. We found 232 anomalous persons in 99 clusters of blood relatives. In 56 clusters, two or more blood relatives had the same multifactorial anomaly. The affected relatives belonged to the same generation in 54 percent and two generations in 44 percent of the clusters. We considered five clusters (rows 32 to 36 of Table 1), in which one parent and a child had the same anomaly, as dominantly transmitted. Sporadic cases with no affected blood relative are possibly fresh (de novo) mutations. We selected persons less than 30 years of age to assess the load due to de novo mutation. There were two mother-child pairs having the same multifactorial anomaly, not listed in McKusick's registry. These mothers were considered to have a de novo mutation, as their parents and other relatives were reported as unaffected.

Details of autosomal dominant anomalies are given in Table 1. "Total persons in population" shows the number of anomalous persons in the study and control areas. Probands belonging to the same extended family were considered part of one family, and the number of families thus counted is given under "No. of extended families." Of the 36 dominant traits (including five phenotypes observed in parents and children), 30 were seen in the HBRR and 18 in the NRR. Details for persons below age 30 suffering from a presumed de novo mutation are given in Table 2 (p. 492), and details of autosomal recessive and X-linked recessive anomalies in Table 3 (p. 493). Our caseload includes eight autosomal recessive and five X-linked recessive traits listed in McKusick's catalogue. Table 4 (p. 494) lists chromosomal disorders, congenital anomalies (ICD 740–757), and diseases of multifactorial etiology. The latter group includes mental retardation, deafness, cerebral palsy, epilepsy, and blindness.

Table 1

Autosomal dominant anomalies in Kerala HBRR and NRR, 1988–1994

McKusick registry no.[a]		Trait	Total persons in population		No. of extended families	
			NRR	HBRR	NRR	HBRR
1	*10080	Achondroplasia	1	0	1	0
2	*10630	Ankylosing spondylitis	0	1	0	1
3	*11810	Klippel-Feil syndrome	0	1	0	1
4	*11821	Charcot-Marie-Tooth disease II	2	1	1	1
5	*11960	Cleidocranial dysostosis	0	1	0	1
6	*12020	Coloboma of iris, choroid and retina	1	1	1	1
7	*12105	Contractural arachnodactyly	0	1	0	1
8	*12690	Dupuytren contracture	0	1	0	1
9	*13370	Exostoses, multiple	7	1	1	1
10	*13510	Fibrodysplasia ossificans	1	0	1	0
11	*14670	Ichthyosis vulgaris	0	2	0	1
12	*15470	Marfan syndrome	1	4	1	1
13	*16070	Myopia (familial)	2	5	1	1
14	*16090	Myotonic dystrophy	1	7	1	2
15	*16220	Neurofibromatosis	1	4	1	4
16	*16440	Olivopontocerebellar atrophy type I	0	1	0	1
17	*16470	Olivopontocerebellar atrophy type V	2	0	1	0
18	*16620	Osteogenesis imperfecta tarda	1	0	1	0
19	*16680	Otosclerosis	1	4	1	3
20	*17280	Piebald trait	0	1	0	1
21	*17420	Polydactyly, postaxial	6	8	5	7
22	*17830	Ptosis, hereditary	3	7	3	6
23	*18020	Retinoblastoma	0	1	0	1
24	*18260	Spastic paraplegia	0	1	0	1
25	*18590	Syndactyly type I	4	2	3	2
26	*18610	Syndactyly type III	0	3	0	3
27	*19110	Tuberous sclerosis	0	1	0	1
28	13250	Epistaxis, hereditary	0	4	0	1
29	16810	Paralysis agitans, juvenile hunt	0	1	0	1
30	17440	Polydactyly, preaxial I	4	8	4	5
31	17627	Prader-Willi syndrome	1	0	1	0

Table 1 (Cont'd.)

McKusick registry no.[a]		Trait	Total persons in population		No. of extended families	
			NRR	HBRR	NRR	HBRR
32	318.1	Mental retardation	2	0	1	0
33	318.1	Mental retardation congenital cataract	0	2	0	1
34	389.1	Sensory neural deafness	0	2	0	1
35	553.1	Paraumbilical hernia	0	3	0	1
36	754.5	Clubfoot	0	2	0	1
		Total cases	41	81	29	54

[a]Traits in rows 32 to 36 are not in McKusick's registry; their ICD numbers are given instead. Asterisks here and in Tables 2 and 3 indicate McKusick has established mode of inheritance.

Summary data and statistics for anomalies, classified into five etiologic groups, are given in Table 5 (p. 495). The prevalence of all groups is higher in the HBRR. Of these, the difference is significant for Down syndrome, autosomal dominant disorders, and anomalies of multifactorial origin. Cleft lip and/or cleft palate is the only congenital anomaly with a significant increase in the HBRR (relative risk (RR) = 2.49, $\chi^2 = 6.66$, df = 2, and $P = 0.009$). For de novo dominant cases, there is an excess risk of 65 percent in the HBRR, but the difference is not significant. The difference in the case of autosomal recessive and X-linked anomalies is also not significant. Since the anomalous persons have a lower survival chance, the prevalence based on total population underestimates the actual risk; this is partially offset in the following analysis, which is based on a smaller subset of patients for whom parental details were available.

Fertility and Untoward Pregnancy Outcomes

Background Details. Fertility data were collected from 12,943 married women under 60 years of age. We considered 8,068 couples for this analysis, after excluding the following categories: (*a*) birthplace of husband not known—these are either widows or divorcees; (*b*) no live birth; (*c*) belonging to one of 12 minority castes; (*d*) both spouses born outside the area of current residence; and (*e*) married after 1984. Couples in (*c*) and (*d*) were excluded because these groups were small. Those married after 1984 were excluded because the majority of anomalies reported in this series are of childhood or late onset. Mean age at marriage of the wife was 17 years during the 1950s and 21 years during the 1980s;

Table 2

Autosomal dominant anomalies—presumed de novo cases, Kerala HBRR and NRR, 1988–1994

McKusick registry no.[a]		Trait	No. of cases NRR	No. of cases HBRR
1	*10080	Achondroplasia	1	0
2	*11810	Klippel-Feil syndrome	0	1
3	*11960	Cleidocranial dysostosis	0	1
4	*12020	Coloboma iris, retina	1	0
5	*12105	Contractural arachnodactyly	0	1
6	*15470	Marfan syndrome	1	0
7	*16220	Neurofibromatosis	1	1
8	*17280	Piebald trait	0	1
9	*17420	Polydactyly, postaxial	1	2
10	*17830	Ptosis, hereditary	1	1
11	*18020	Retinoblastoma	0	1
12	*18260	Spastic paraplegia	0	1
13	*18590	Syndactyly type I	1	1
14	*18610	Syndactyly type III	0	1
15	*19110	Tuberous sclerosis	0	1
16	17627	Prader-Willi syndrome	1	0
17	318.1	Mental retardation, congenital cataract	0	1
18	389.1	Sensory neural deafness	0	1
		Total cases	8	15
	Nonmigrant population <30 years		20,151	24,388

[a]Traits in rows 17 to 18 are not in McKusick's registry; their ICD numbers are given instead.

on average, husbands were seven years older than their wives. Mean maternal age at the first and the last pregnancies was 18 and 41 before 1950 versus 22 and 26 after 1980. For the above indices, we found no difference between study and control areas. Rate of consanguineous marriage was 12 percent in the NRR and 10.7 percent in the HBRR. Until the mid 1960s, abstinence and breast-feeding were the only contraceptives available. By the 1980s, almost everybody had accepted the small-family norm; the average couple had two children in quick succession, after which the wife underwent tubectomy. The incidence of induced abortion, though legalized, was very low. Contraceptive pills were not part of the national family planning package and nobody reported using them.

Table 3

X-linked recessive and autosomal recessive anomalies, Kerala HBRR and NRR, 1988–1994

McKusick registry no.[a]		Trait	Total persons in population	
			NRR	HBRR
X-linked recessive				
1	*30670	Hemophilia A	0	4
2	*30690	Hemophilia B	0	1
3	*30810	Ichthyosis, X-linked	1	0
4	*31010	Muscular dystrophy, Becker	1	0
5	*31020	Muscular dystrophy, Pseudohypertrophic	1	0
		Total X-linked recessive	3	5
Autosomal recessive				
1	25330	Muscular atrophy, infantile I	0	2
2	26250	Pituitary dwarfism	0	2
3	27880	Xerodermic idiocy of de Sanctis and Cacchione	0	1
4	*20890	Ataxia-telangiectasia	0	1
5	*20990	Bardet-Biedl syndrome	1	0
6	*25300	Mucopolysaccharidosis type 4A	1	0
7	*27460	Pendred syndrome	0	1
8	*27690	Usher syndrome[a]	0	4
		Total autosomal recessive	2	11

[a] All persons with Usher syndrome belonged to one family.

Outcomes. We found 31,097 live births to 8,068 couples. For about one-fourth of the couples (1,952) one or more of their children died in infancy or later. Of these couples, 642 experienced multiple deaths, and in one family 10 out of 13 children had died. There were 593 couples with one or more children suffering from a heritable anomaly listed in Tables 1 to 4. Mean age of the children with and without anomalies was 14.5 (SD = 9.1) and 15.7 (SD = 10) years, respectively. The reported rate of prenatal loss (abortion and stillbirth) was only 3 percent of the total pregnancies, which seems to be a gross underreporting attributable to memory lapse or recall bias. Since there is no difference between exposure and outcome groups, data on prenatal loss was not analyzed.

The outcomes under consideration here are live births, infant and child mortality, and genetic/congenital anomalies. The anomalies have been classified based on etiology as in Table 5. Of the untoward outcomes under consideration, the etiology of Down syndrome and Mendelian traits is well known. Involvement

Table 4

Chromosomal, congenital, and multifactorial anomalies, Kerala HBRR and NRR, 1988–1994

ICD No.		Trait	Total persons in population: NRR	Total persons in population: HBRR
Chromosomal anomaly				
1	758.0	Down syndrome	5	18
Congenital anomalies (ICD 740.0–757.9)				
2	749	Cleft lip and/or palate	11	35
3	754.5 & 754.6	Varus and valgus deformities of feet	31	43
4	743	Congenital anomalies of eye	13	18
5	745–747	Congenital heart disease	24	40
6	740–757	Other congenital anomalies	42	44
		Total congenital	121	180
Multifactorial disorders				
7	318.1	Mental retardation	51	85
8	389.1	Deafness	42	64
9	343	Cerebral palsy	13	25
10	345	Epilepsy	25	46
11	362–378	Blindness and anomalies of eye	22	37
12		Other anomalies of CNS	30	72
		Total multifactorial	183	329
		Total anomalies	309	527
	Total nonmigrant population		27,606	35,308
	Nonmigrant population <25 years		16,326	19,576

of gene(s) is suspected in congenital and multifactorial anomalies, although the precise mechanism is not clear. There is more uncertainty in the case of infant and child mortality. Although the majority of deaths in this series, especially those before the 1970s, were due to poverty, not all deaths can be thus explained. We found 225 couples with multiple infant/child deaths (40 percent or more of their live-born children). The percentage of couples experiencing the death of one child or of less than 40 percent of live-born children declined from 29 percent in the pre-1958 wedded couples to 4.1 percent in the post-1978 wedded couples. At the same time, those reporting multiple child deaths with a mortality rate higher than

Table 5

All heritable anomalies diagnosed, Kerala HBRR and NRR, 1988–1994: etiological classification, summary, and statistics

	Etiology group	Persons alive		Prevalence per 10,000			Chi square	*P*
		NRR	HBRR	NRR	HBRR	RR[a]		
1	Chromosomal—Down syndrome[b]	5	18	3.1	9.2	3	4.31	0.037
2	Autosomal dominant anomalies—all	41	81	14.9	22.9	1.62	6.27	0.012
3	Autosomal dominant anomalies—presumed de novo cases[c]	8	15	4.0	6.2	1.65	0.94	0.33
4	Autosomal and X-linked recessives[d]	5	16	1.8	4.5			
5	Congenital anomalies (ICD 740–757)	121	180	43.8	51.0	1.1	0.6	0.44
6	Multifactorial anomlies	183	329	66.3	93.2	1.41	13.55	0.0002
7	Total anomalies	354	631	128.2	178.7			
8	Total nonmigrant population	27,606	35,308					
9	Nonmigrant population <25 years	16,326	19,576					
10	Nonmigrant population <30 years	20,151	24,388					

[a]Relative risk in the HBRR.
[b]Prevalence of Down syndrome based on population below 25 years of age.
[c]Prevalence of dominant new cases based on population below 30 years of age.
[d]Grouped because of small numbers.

40 percent remained more or less constant at 2.7 percent to 2.9 percent across the decades. We suspect the involvement of genes in this segment and so included it in the anomalous group.

Temporal Changes. Table 6 provides data for couples classified into three marriage cohorts: pre-1958, 1958–1974, and 1975–1984. A sharp decline is evident in rates of fertility, child mortality, and anomalies per couple. When all anomalies (including multiple deaths) are considered together, 12.3 percent of couples in the pre-1958 cohort were affected versus 6.3 percent in the post-1974 cohort. The number of children with heritable anomalies per 1,000 couples declined from

Table 6

Pregnancy outcome by year of marriage, couples from Kerala HBRR and NRR (combined), 1988–1994

Year of marriage	Number					Rate per 1,000 couples				Rate per 1,000 births		
	No. of couples	Total live births	Total deaths	Congenital anom.	Replace-ment	Births	Deaths	Congenital anom.	Replace-ment	Deaths	Congenital anom.	Replace-ment
Pre-1958	1,559	10,052	1,430	196	8,428	6,448	917	126	5,406	142	19	838
1958–74	2,775	11,390	987	223	10,181	4,105	356	80	3,669	87	20	894
Post-1974	3,734	9,655	467	237	8,952	2,586	125	63	2,397	48	25	927
Total	8,068	31,097	2,884	656	27,561	3,854	357	81	3,416	93	21	886

Note: Replacement = live births – (congenital anomalies + deaths); congenital anom. = all heritable anomalies.

124 in the pre-1958 group to 63 in the post-1974 group. When we used total births as the denominator, the rate of children with anomalies was 18 and 23 per 1,000 births for the pre-1958 and post-1974 groups, respectively.

"Exposure" and Inbreeding Groups. Based on place of current residence, birthplace, and consanguinity, couples were classified into six "exposure" groups. The first four groups consist of unrelated couples in both areas. In the first and third groups (labeled "nonmigrant"), both spouses were born in the area where they resided at the time of the survey. In the second and fourth groups ("migrant" groups), one of the spouses was born in the area of residence and the other was an immigrant from outside the area. The fifth and sixth groups consist of related couples in the study and control areas, respectively. Details of couples and their anomalies are given in Table 7: A, raw data; B, proportion of outcomes in 1,000 couples; and C, relative risks and other statistics.

Confounders. Caste and year of marriage have also influenced these outcomes. To quantify the interaction, we grouped all anomalies together and classified the couples as anomalous and non-anomalous. In the stratified analysis using caste as the second variable, the Mantel-Haenszel (MH) corrected odds ratio (OR) is 1.28 (95 percent confidence interval (CI) = 1.09–1.51, $\chi^2 = 6.17$, and $P = 0.0457$) versus the crude OR of 1.32. There is no indication of confounding by year of marriage, as both the crude and the MH-corrected OR are 1.32.

The Main Findings. The findings can be summarized as follows:

1. The relative risk for chromosomal, autosomal dominant, and multifactorial anomalies is higher in the HBRR.
2. For congenital anomalies (ICD 740–757), there is no difference between the areas. Within the study and control areas, "nonmigrant" couples have 51 percent and 61 percent excess relative risk (ERR), respectively, in comparison to "migrant" couples. The ERR among the related versus the unrelated couples is 96 percent in the HBRR and 41 percent in the NRR.
3. Rates of multifactorial anomalies and multiple deaths are higher in the HBRR. Again, the related and the nonmigrant couples have higher risk than the migrants and the unrelated, respectively. The rates among the migrants in both areas are more or less the same.
4. If all untoward outcomes other than Down syndrome and Mendelian anomalies are grouped together, 6.4 percent of the unrelated "migrants" in the NRR are affected versus 16.4 percent of the related couples in the HBRR.

Vital Rates. Table 8 (p. 500) compares the reproductive performance of couples classified on outcome, consanguinity, and migration status. The "unaffected"

Table 7

Couples with an untoward pregnancy outcome by birthplace and consanguinity, Kerala HBRR and NRR, 1988–1994

	Unrelated couples					
	NRR		HBRR		Related couples	
Outcome	Migrant	Settled	Migrant	Settled	NRR	HBRR
A. Data						
Down syndrome	0	2	2	8	0	1
Autosomal dominant anomalies	8	12	11	32	2	4
Congenital anomalies (ICD 740–757)	27	43	20	69	13	16
Multifactorial and autosomal recessive anomalies	40	60	33	137	20	34
Multiple deaths	36	41	24	89	14	21
Recessive, multifactorial, congenital anomalies, and multiple deaths	103	144	77	295	47	71
All anomalies and multiple deaths	111	158	90	335	49	76
Total births	5,674	6,504	4,193	11,090	1,714	1,922
Total couples	1,606	1,667	1,206	2,737	419	433
B. Proportion in 1,000 couples						
Down syndrome	0.0	1.2	1.7	2.9	0.0	2.3
Autosomal dominant anomalies	5.0	7.2	9.1	11.7	4.8	9.2
Congenital anomalies (ICD 740–757)	16.8	25.8	16.6	25.2	31.0	37.0
Multifactorial and autosomal recessive anomalies	24.9	36.0	27.4	50.1	47.7	78.5
Multiple deaths	22.4	24.6	19.9	32.5	33.4	48.5
Recessive, multifactorial, congenital anomalies, and multiple deaths	64.1	86.4	63.8	107.8	112.2	164.0
All anomalies and multiple deaths	69.1	94.8	74.6	122.4	116.9	175.5

		95% CI			
	RR	Lower	Upper	Chi square	*P*
C. Statistics					
Study vs. control (unrelated)					
Down syndrome	4.16	0.85	27.83	2.92	0.0876
Autosomal dominant anomalies	1.81	1	3.31	3.86	0.0490
Multifactorial anomalies	1.42	1.09	1.86	7.16	0.0070
All anomalies	1.35	1.14	1.59	13.19	0.0003
Settled vs. migrants, both areas (unrelated)					
Congenital anomalies (ICD 740–757)	1.54	1.07	2.21	5.65	0.0174
Multifactorial anomalies	1.73	1.3	2.31	15.26	0.0000
Multiple deaths	1.4	1.01	1.93	4.17	0.0412
All anomalies	1.62	1.35	1.93	29.9	0.0000
Related vs. unrelated (both areas)					
Congenital anomalies (ICD 740–757)	1.56	1.02	2.39	4.31	0.0378
Multifactorial anomalies	1.64	1.18	2.27	9.37	0.0022
Multiple deaths	1.58	1.07	2.33	5.58	0.0181
All anomalies	1.63	1.32	2.02	21.5	0.0000

Note: Settled = both spouses born and living in the same area (unrelated only); migrant = one spouse born in the same area and the other born outside the area (unrelated only).

Table 8

Vital rates by consanguinity, migration, and outcome status, Kerala HBRR and NRR (combined), 1988–1994

Consanguinity, migration, and outcome status	Number					Per 1,000 couples			Replacement per 1,000	
	Couples	Live births	Deaths	Congenital anom.	Replace-ment	TFR	Deaths	Congenital anom.	Couples	Births
Unaffected										
Related	516	1,750	—	—	1,750	3,391	—	—	3,391	1,000
Unrelated settled	3,043	10,169	—	—	10,169	3,342	—	—	3,342	1,000
Unrelated migrant	2,134	6,510	—	—	6,510	3,051	—	—	3,051	1,000
Deaths only										
Related	211	1,193	276	—	917	5,654	1,308	—	4,346	769
Unrelated settled	868	4,876	1,091	—	3,785	5,618	1,257	—	4,361	776
Unrelated migrant	477	2,449	580	—	1,869	5,134	1,216	—	3,918	763
Anomalies and multiple deaths										
Related	125	693	178	100	415	5,544	1,424	800	3,320	599
Unrelated settled	493	2,549	563	402	1,584	5,170	1,142	815	3,213	621
Unrelated migrant	201	908	196	150	562	4,517	975	746	2,796	619
Total										
Unrelated	7,216	27,461	2,430	552	24,479	3,806	337	76	3,392	891
Related	852	3,636	454	100	3,082	4,268	533	117	3,617	848

Note: TFR = total fertility rate (number of live-born children per couple); congenital anom. = all heritable anomalies; replacement = alive and healthy (non-anomalous children).

couples are those who reported that all their live-born children were alive and non-anomalous. The "mortality" group consists of couples who experienced the death of one child or less than 40 percent of all live-born children. Couples with a child suffering from an anomaly or those who experienced multiple child deaths—more than 40 percent of their live-born children—form the "anomalous" group. "Replacement" refers to the live and non-anomalous children. Since there is no difference between the areas, data for both areas have been grouped together. Couples in the "mortality" and the "anomalous" groups had, on the average, two more live births than the "unaffected" group. The "mortality" group had 30 percent more healthy survivors than the other two groups. If reproductive efficiency is measured with total births as the denominator, the score (alive and non-anomalous children as percentage of total births) is 62 percent for the "anomalous" group and 77 percent for the "mortality" group.

The Estimated Birth Incidence

We have kept couples at the center of the above analysis because they are the ones who receive the genetic insult, and the children happen to be the medium through which its effect is manifested. In order to facilitate comparison with other databases, we estimated incidence using total births as the denominator (Table 9). This requires life tables of persons with anomalies. From a literature survey of 351 Mendelian traits, Costa and colleagues (22) estimated 57.5 percent premature mortality, "most often in the pre and intra-reproductive age group." The proportion of survivors among persons with anomalies was about two-thirds of the liveborn in Northern Ireland (23) and in British Columbia (24). Considering the differences in socioeconomic status and health care facilities in our series, we have assumed a lower survival rate of 50 percent for the affected persons in this study. The estimated birth incidence is given in the last two columns of Table 9.

DISCUSSION

Limitations of the Study

The ideal methodology for this study would have been a complete medical examination of all the inhabitants. Given the medical personnel constraints, WHO suggested a middle course of action: examination of all persons by a trained nurse (25). Since more than two-thirds of the people are away at school or at work during the daytime, even this would have been too time consuming. Hence, we opted to ask the mothers/wives to identify the persons with anomalies in their families. The respondents knew the primary investigators and were not short of time for interviews. Moreover, a visit by the medical team was generally welcomed. Incidentally, more than 40 percent of the households reported an anomaly.

Table 9

Heritable anomalies, Kerala HBRR and NRR, 1988–1994, rate per 10,000 births (observed and estimated)

	Persons alive		Rate per 10,000 birth			
			Observed		Estimated[a]	
Anomalies	NRR	HBRR	NRR	HBRR	NRR	HBRR
Down syndrome	2	11	1.4	6.4	2.9	12.8
Autosomal dominant traits	25	51	18.0	29.6	36.0	59.3
X-linked recessive traits[b]	2	5	2.9	5.6	5.8	11.2
Autosomal recessive traits	2	11	1.4	6.4	2.9	12.8
Congenital anomalies	88	110	63.3	63.9	126.7	127.9
Multifactorial anomalies	125	220	90.0	127.9	180.0	255.7
Congenital and multi-factorial anomalies	213	330	153.3	191.8	306.7	383.6
Total	244	408	175.6	237.1	351.3	474.3
Total births	13,892	17,205				
Total male births	6,930	8,892				

[a] Assuming a 50 percent chance of survival for child with anomaly.
[b] X-linked recessives estimated on male births.

Overreporting by mothers who were aware of the hazards in the study hypothesis could be a source of bias. To offset this, the hypothesis of the study was not disclosed. The majority of the population is ignorant about radiation and its health hazards; there has not been any popular agitation or media campaign on this topic.

The area of residence is not the only independent variable in the analysis. As Verma observes, "Indian parents readily accept the birth of an abnormal child as the hand of destiny or their fate" (26). Underreporting due to ignorance about an anomaly corrected during childhood cannot be totally ruled out. This bias could have been operative in such anomalies as phymosis, polydactyly, and so forth, if the respondents were not the mothers.

Because many of the traits are rare and complex, diagnostic expertise is crucial in such a study, which is primarily based on clinical examination. The diagnosis by the consultant was considered final—there was no review. Given the different consultants in medicine, pediatrics, and surgery, diagnostic bias cannot be ruled out. Diagnosis of mental retardation was clinic-based; no measurement of IQ was done.

Because genes differ in their expressivity and penetrance, assignment of sporadicity is difficult in the absence of molecular genetic investigations. Mere absence

of the trait in parents or other relatives is not conclusive evidence of de novo mutation, since the unaffected parents could be germinal mosaics.

Genetically Significant Exposure

Besides the external radiation from beta particles and gamma rays from the soil, there is the possibility of internal exposure through air, water, and food. Soman (27) estimated the per capita daily uptake of radium-228 by the study population as 4.72 Bq. Based on the average consumption of sardines, Van de Laar (18) estimated the daily intake as less than 0.01 Bq per person. Since the coastal land is less fertile and farming and husbandry are restricted to small pockets, the internal exposure is mainly from poultry products, fish, and accidental ingestion of fine grains of monazite in childhood. Because of various uncertainties, we have not estimated the genetically significant dose. Incidentally, universal schooling, better homes with raised platforms, more built-in and cemented space, and more items of furniture have reduced the exposure in recent times.

Changes in Health Status and Other Exposures

At the time of the survey, the HBRR population was not as "Malthusian" as suggested by Gopal-Ayengar in 1957 (28). However, unnecessary exposure to X-rays and teratogenic drugs such as thalidomide is negligible. There is no known occupational or other environmental exposure to modern toxins. Since 1965, the people of Kerala (including the study and control populations) have been exposed to pesticide residues in food. Among men, 38 percent in the HBRR and 32 percent in the NRR were either tobacco chewers or smokers. The percentage of tobacco chewers among women was 60 percent in the HBRR and 56 percent in NRR (29). Consumption of alcohol among young men increased after the 1970s. Both study and control populations were affected by filariasis; the endemicity rate was 44 percent in the NRR and 6 percent in the HBRR in 1931 (30). Public health measures employed against filariasis during the 1950s consisted of application of crude oil on mosquito breeding grounds, mass treatment of people by the drug Hetrazan, and spraying of houses with pesticide (BHC) once every four months (31). The coastal areas in southern Kerala also have a higher incidence of endomyocardial fibrosis (32) (two cases in the HBRR) and calcific pancreatitis (33). Among the hospital admissions in 1956, the incidence of toxemia of pregnancy was less than 3 percent in the HBRR (34). According to Kochupillai (35), this condition was rare during the 1960s in the NRR also.

Validation and Comparisons

Background Demographic Data. The results of this study have been validated by comparison with several earlier studies in this area and in other parts of the

state. Demographic data at the village level are available in the census reports. Fertility rates for the HBRR and NRR are available from two earlier studies (11, 12). The annual reports of the Indo-Norwegian Project hospital are rich source materials for morbidity data in the HBRR during the 1950s and 1960s. The Centre for Development Studies, Trivandrum, has been monitoring the demographic transition in Kerala (36). We also collected details of baptisms, marriages, and burials from six parishes in the HBRR and NRR. Comparisons among all these sources reveal no major difference in fertility indicators.

Background Incidence of Down Syndrome. The "global" incidence of Down syndrome is 12 per 10,000 births (3, p. 32). Aggregating the results of birth monitoring in several Indian cities, Verma and co-workers (37) also found a similar incidence. Stevenson and colleagues (38) diagnosed only one case of Down syndrome among 66,000 infants born to Indian parents in Bombay, Calcutta, Singapore, and Kuala Lumpur. There were a few hospital-based birth-monitoring programs in Kerala. In the first series, no case of Down syndrome occurred among 3,721 consecutive births at Calicut in 1964 (39). In a series from Trivandrum medical college in 1975, the incidence was 8.4 per 10,000 live births (Sugunabai, cited in 40). In a survey of 43,600 hospital births in Quilon and Trivandrum districts during 1985–1990, the incidence almost halved to 4.8 per 10,000 (13). We found in the present series an estimated birth incidence of Down syndrome of 3 and 13 per 10,000 births in the NRR and HBRR, respectively. The incidence in the NRR is comparable to the Quilon-Trivandrum series.

Studies on Radiation-Induced Down Syndrome. In Hiroshima-Nagasaki, the birth incidence of Down syndrome was 5.4 and 12.7 per 10,000 among the children of exposed and unexposed mothers, respectively (41). The control group also included persons who were exposed to residual radiation from fission and activation products. In 13 studies of Down syndrome and parental exposure to radiation summarized by Denniston (42), there was a statistically significant increase in four studies. Of the remaining nine studies, five were in the positive direction, two showed no difference, and two were counter to the study hypothesis. In the Chinese HBRR study, an excess risk was found among exposed, older mothers (6). In our present series, 63 percent of the children with Down syndrome in the HBRR and 80 percent in the NRR were born to mothers aged above 30 years, indicating that the higher risk is confined to older mothers.

Mendelian Anomalies: Estimated "Global" Incidence. Unlike Down syndrome, the data available on Mendelian anomalies are extremely limited. In the absence of data from a single population, the standard-setting agencies rely on ad hoc surveys conducted by different authors in different populations. Sankaranarayanan observes that "although the estimates provide us some insights into the load of Mendelian disease in the human species, [they] represent a

synthesis of information from different populations. Therefore, they do not reflect the profile of the aggregate burden of such diseases in any specific human population; ideally, it is this which is required to project risks in context" (43). In 1977, Carter (44) estimated an incidence of 65 per 10,000 births for 24 "common" traits. In recent surveys, the incidence of 38 traits is given as 100 per 10,000 births, of which BRCA1-associated cancers (of the breast and ovary) and hypercholesterolemia account for 45 cases (45). We did not seek data on cancer or hypercholesterolemia. The estimated birth incidence of Mendelian anomalies is 36 and 59 per 10,000 births in the NRR and HBRR, respectively, which are comparable to the observed "global" incidence minus BRCA1-linked cancers and hypercholesterolemia.

Autosomal Dominant Anomalies: Observed Incidence in Hawaii, Hungary, and Boston. The observed incidence of dominant anomalies per 10,000 births in three birth-monitoring programs is: Hawaii 2.4 (46), Boston 3.6 (47), and Hungary 5.5 (43, 48). The numbers of traits detected in these programs are: Hawaii 8, Boston 16, and Hungary 17. The estimated incidence per 10,000 births in our series is 36 in the NRR and 59 in the HBRR, and the number of traits detected is 18 and 30 for the NRR and HBRR, respectively. Achondroplasia and aniridia are the most common traits in the three birth-monitoring programs cited above. Incidence of achondroplasia per 10,000 was 0.29 in Boston, 0.56 in Hungary, and 1.12 in Hawaii. In short, the traits are not common nor is the incidence uniform in the birth-monitoring programs. In comparison with the other birth-monitoring programs, the number of traits and the incidence are higher in our series.

Mendelian and Multifactorial Anomalies: Observed Incidence in British Columbia. There is a close similarity between the demographic situation in our series and that in British Columbia, where a health surveillance registry (HSR) for birth anomalies has been in place since 1953 (24). In 1984, the HSR had details of 154,000 handicapped persons, of whom 79,000 were born outside the province. A summary of the British Columbia data is given in Table 10. The incidence per 10,000 births of all anomalies with "an important genetic component" was 530 in British Columbia. The estimated incidence in Kerala is 351 in the NRR and 474 in the HBRR. The incidence of autosomal dominant anomalies in British Columbia is only one-fourth of the estimated incidence in the NRR in our series. Detection rate is said to be satisfactory during the second decade in the British Columbia registry, when the incidence of all anomalies registered a 33 percent increase. This increase, however, was not uniform across etiological groups. While Mendelian and chromosomal anomalies increased by 16 percent, four multifactorial diseases (diabetes, mild mental retardation, schizophrenia, and epilepsy) decreased by 35 percent and all other multifactorial anomalies increased by 200 percent. During the study period, the fertility rate per 10,000 Canadian couples declined from 1,000 in 1954 to 550 in 1984 (49; 50, Table 26). There was a

Table 10

Etiological distribution of anomalies, British Columbia, 1953–1984

	Rate per 10,000 births, by year of birth				Increase (1952–63 = 100)	
Etiology group	1952–63	1964–73	1974–83	1952–84	1964–73	1974–83
Autosomal dominant	8.7	10.0	8.2	8.9	116	94
Autosomal recessive	9.2	11.8	9.6	10.1	128	105
X-linked recessive	3.6	3.8	2.7	3.4	107	75
Chromosomal	14.9	16.3	14.6	15.2	110	98
Mendelian and chromosomal	36.3	42.0	35.1	37.6	116	97
Diabetes, epilepsy, etc.	42.0	27.5	27.5	32.1	65	65
Other multifactorial	97.1	290.5	293.3	219.1	299	302
Others	269.8	391.7	434.7	360.4	145	161
Raw Data						
Handicapped total	19,476	25,909	29,919	75,304	133	154
Birth total	437,503	344,665	387,705	1169,873	79	89

Source: Baird et al. (24, Tables 1–6).

parallel decline in late fetal mortality from 150 to 80 per 10,000 live births (50, Table 43; 51). Since more than half the handicapped persons listed in the HSR were born outside British Columbia, there was apparently a high rate of immigration during the period. However, the beneficial effect of pan mixing is not visible in British Columbia. On the contrary, the rate of anomalies has increased over time. British Columbia's HSR is the only database of children born to two generations of parents. The selective increase of multifactorial anomalies may be indicative of underdiagnosis during the second and third decades. However, diagnostic bias alone cannot explain the phenomenal increase over the second and third decades.

An Autosomal Recessive Etiology for Multifactorial Anomalies and Multiple Deaths? In our study, for multifactorial anomalies including congenital anomalies (ICD 740–757) and for multiple deaths, we found a significant ERR among the related and the "nonmigrant" couples. The higher risk of the former group is known to be due to recessive genes. Many of the nonmigrant couples may have common ancestors beyond the grandparents. "Geographic" inbreeding has been recognized as a risk factor in Brazil by Freire-Mala (52). As such, it is tempting to consider a recessive hypothesis for the ERR among the "nonmigrant" couples in our series. If so, the majority of the multifactorial anomalies and multiple deaths

seem to be recessively inherited. Let us assume a recessive etiology for 314 couples in our series; these couples had 1,472 live births, with 341 anomalous and 921 non-anomalous children. Under the recessive hypothesis, the anomalous children (25 percent of the total live births) would be homozygous for the gene; about 50 percent of the children would be heterozygous (obligate carriers); and the remaining 25 percent would be homozygous unaffected (without the gene). With three live and unaffected children per sibship, all the participating spouses would get a chance to keep their mutant gene afloat through the two heterozygous offspring. Zygotes homozygous for recessive lethal genes would have died in utero or during early infancy. Since the "mortality" group has the highest replacement rate, the gene is in a position of advantage here also. In other words, it is the end of the road for the "selected" (dead or seriously handicapped) children, not for the couples or for the gene. Reproductive compensation by consanguineous couples has been reported by Schull and Neel (53) in Japan and Bittles and co-workers (54) in Karnataka, South India. *Homo sapiens* can adapt to a reproductive emergency by increasing the number of births, and in the modern era the species has technology on its side.

Of six comparative studies of consanguineous and non-consanguineous couples in South India, four findings were in the direction of the hypothesis and two were counter to the hypothesis (55–57). According to Sanghvi and colleagues (58), certain genetic defects are "extruded" in the process of continuous inbreeding, which explains the negative results. This possibility is ruled out by Bittles and colleagues (54). Considering the mechanism of reproductive compensation noted above, "genetic cleansing" seems to be a remote possibility.

The inbreeding coefficient among different populations is given in Table 11. The southeastern coastal states in India have a very high inbreeding coefficient. Likewise, Buddhists, Hindus, and Muslims the world over have a higher degree of inbreeding than do Christians. Freire-Mala (52) has suggested that under increased mutation pressure, the frequency of recessive traits would increase linearly with the inbreeding coefficient. The background incidence of autosomal recessive anomalies was 25 per 10,000 births as reported by UNSCEAR (3, p. 131) and BEIR (Biological Effects of Ionizing Radiation) (59, p. 91). The latest estimate by Sankaranarayanan (43) is 75 per 10,000 births. According to UNSCEAR and BEIR, the increase of recessive anomalies in the first generation after exposure (to ionizing radiation) would be minimal, while others (e.g., Bertell (60) and Neel (quoted in 59, p. 80)) think otherwise. Since all the disease data considered by these agencies are from populations with an inbreeding coefficient of less than 0.001, the "global" estimate of spontaneous and radiation-induced recessive disorders may not be relevant for Asian-African peoples.

The Estimated Total Genetic Load in the Study Population. A study of this type can reveal only a fraction of the total genetic load in the population. The undetected load will include late-onset multifactorial anomalies (such as diabetes),

Table 11

Inbreeding coefficient of various populations

Population	Inbreeding coefficient
Europe	0.001
Japan	0.006
Northeastern Brazil	0.009
India	
This study—both areas	0.006
Kerala Hindus	0.001–0.010
Kerala Muslims	0.011–0.020
Tamil Nadu, Andhra Pradesh, and Rajasthan Hindus	0.021–0.030

Sources: Europe, Japan, and Brazil: Nelson and Holmes (47); India: I. C. Verma, A new perspective for congenital malformations in India. In *Genetic Research in India,* ed. I. C. Verma, pp. 178–187. Sagar, New Delhi, 1986.

traits causing prenatal or pre-reproductive mortality, and changes in continuously distributed variables such as IQ and anthropometric indices. If these were also included, a high proportion of the couples could be said to be harboring a "genetic" problem.

An important finding of our study is that the distribution of the recognized Mendelian traits is not different from that in West European populations. The population of 63,000 includes 163 persons with 43 recognized Mendelian traits. The prevalence is similar to the estimates based on ad hoc surveys, despite the differences in methodology and setting. While the incidence of the recognized autosomal recessive anomalies is less than one-tenth that of the dominant traits, many of the multifactorial anomalies appear to be recessively inherited. The actual load of recessive anomalies in the study populations seems to be much higher than the UNSCEAR estimate.

CONCLUSIONS AND RECOMMENDATIONS

The mean cumulative exposure to external radiation during the reproductive life of people living in the high-background radiation regions is 18 rads for women and 22 rads for men, six times the exposure in the normal radiation region. In the case of Down syndrome, we are confirming an earlier observation that was based on a smaller sample. Since the excess risk of Down syndrome is confined to older couples only, this effect is almost invisible under the existing fertility situation.

There is a statistically significant increase in the prevalence of all dominant anomalies. When we consider cases resulting from presumed de novo mutation in the previous generation, we find a nonsignificant increase in the HBRR. Given that most of the detected anomalies are milder ones, accompanied by more or less normal reproductive fitness, the observed load could be the result of mutations over several generations. In other words, there is no conclusive evidence that exposure in one generation reduces the reproductive fitness of the population in the HBRR.

For multifactorial anomalies, which account for more than four-fifths of the caseload, we find a significant excess risk in the HBRR. At the same time, the unrelated migrant couples in the HBRR have a lower risk than their related and nonmigrant counterparts in the NRR. It seems that both populations can reduce the risk by choosing partners from outside the circle of blood relatives and same-villagers.

Measures for reducing population exposure—such as providing houses with raised platforms for hut-dwellers, clubs, and community halls, and cement floors for drying fish—are recommended, following the dictum that, for radiation exposure, every dose is an overdose. Considering the pressure on land, it may not be possible to resettle residents in a normal (NRR) area.

Apart from a few schools for the deaf and blind, there is hardly any rehabilitation or medical support for the handicapped in the study area. Given the high incidence of anomalies, more training and work centers for the "diffabled" are required. Parents are concerned about the care of affected children, especially after the parents' retirement and death. As of now, the investment in welfare for the handicapped by the government and by the corporate sector is very marginal.

An estimated 20 percent of the couples in our series can be considered as having a "genetic" problem. Although this study is based on three ethnic groups unique to Kerala, there are some similarities between the population in this study and the rest of the country. More than half the population in South India is similar to the Kerala groups in terms of the size of the castes and the degree of inbreeding. The coefficient of inbreeding is higher in other south Indian states, where uncle-niece unions are also common. For such communities, seeking geographically and genetically distant partners may bring in a considerable amount of relief from anomalies. Education, occupational mobility, and construction of roads are some cheap and effective ways for improving the reproductive fitness of closely inbred communities.

Since the 1950s, caste has been excluded from official census and health statistics in India. Almost all marriages of Indians (including Christians and Muslims) are within the same caste. Given that genes have been implicated in almost all health problems, publication of fertility, mortality, and morbidity data by caste would help communities adopt genetically sound strategies.

There is no reliable database on the spontaneous incidence of single-gene anomalies in human populations. The genetic risk of ionizing radiation is estimated from animal data. WHO recommended detailed prospective studies in the Kerala HBRR some four decades ago, but this has not yet been done. About 200,000 people are living in Indian HBRRs with different radiation levels, food habits, and socioeconomic status. Pregnancy monitoring, genealogical studies of families with affected persons, and molecular genetic studies in the NRRs and HBRRs may reveal the spontaneous as well as radiation-induced genetic load in human beings. Lack of noise from other mutagens, a low rate of outmigration, and the cooperation of the people are other positive factors found in the Indian regions that could aid such studies.

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APPENDIX

Sociodemographic Indices, Kerala HBRR and NRR, 1988

	Percent of total population			
	Male		Female	
Socioeconomic variables	HBRR	NRR	HBRR	NRR
Broad age groups				
0–14	30.5	30.2	30.1	31.5
15–54	59.7	58.8	59.0	57.3
≥55	9.8	11.0	10.9	11.2
Educational status, age group 8–59				
Illiterate	0.2	0.5	0.2	0.3
8–10 years of school	34.0	35.0	29.0	33.0
>10 years of school	1.3	1.9	1.1	1.9
Employment, age group 17–59				
Fishing	55.0	52.0		
Other	20.0	18.0	6.6	4.8
Unemployed	25.0	30.0	93.4	95.2
Marital status				
Married[a]	73.0	70.0	78.0	79.0

	Percent of total households	
	HBRR	NRR
Details of households[b]		
Land holdings		
No land	17.0	14.0
Above 50 cents	3.0	2.8
Households owning fishing gear (all types)	14.0	7.0
Households using loan for fishing gear	9.5	4.7
House with thatched walls and roof	43.0	41.0
Household income <Rs 20,000	60.0	59.0

[a]Women age >17 years, men age >20 years.
[b]A household is an economic unit, with one head and one hearth.

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