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EDITORIAL

Annie Darwin's death, the evolution of tuberculosis and the need for systems epidemiology

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When Charles Darwin's daughter Anne Elizabeth ('Annie', Photograph 1) died at the age of 10 years on April 23, 1851 her parents were devastated. Charles Darwin was a devoted father and constantly concerned about the health of his 10 children. His concerns were also motivated by fear of the consequences of marriage between relatives: Emma Wedgewood, his wife, was also his first cousin.[1] The possible adverse effects of consanguineous marriage, which was not uncommon in England at that time, were a matter of debate. Annie's death, and self-fertilization experiments in plants, made him suspect that 'marriage between near relations is likewise injurious'.[2] In 1870, Darwin motivated his mathematician son George to study the prevalence of close-kin marriages in patients in asylums in comparison with the prevalence of the general population. The study, which is reprinted in this issue of the journal,[3] with several commentaries,[1,2,4,5] was first published in 1875 and concluded that 'the evil [of marriages between cousins] has been often much exaggerated' and that 'under favourable conditions of life, the apparent ill-effects were frequently almost nil'.[3]

Indeed, Annie died after a lingering illness, most likely of tuberculosis (TB) caused by *Mycobacterium tuberculosis*,[6] and not of the consequences of a high coefficient of inbreeding (the *F* coefficient that features in one commentary[2]). Of note, although

Photograph 1 Daguerreotype photograph of Anne Elizabeth ('Annie') Darwin 1849. Annie Darwin died in 1851, probably of tuberculosis. © English Heritage Photo Library. Reproduced with permission

Darwin may have been aware of the studies by his contemporaries, Pasteur and Koch, he did not consider the role of microbes and infectious diseases in his work.[7] *M. tuberculosis* would, however, surely have

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been of interest. This obligate human pathogen has co-evolved with humans for millennia[8] and has been extremely successful: today one-third of the world's population is estimated to be infected and 1.7 million people die from TB each year, more than anytime during previous human history.[9,10] Co-infection with HIV is an important risk factor for TB, increasing the lifetime risk of progression from infection to active disease from 5% per lifetime to 5% per year,[11] which is a particular problem in sub-Saharan Africa. Moreover, the emergence of bacterial strains resistant to most current antimicrobial drugs threatens to make TB untreatable.[9] Edmonds and colleagues,[12] in this issue, document the staggeringly high incidence of TB in HIV-infected children in Kinshasa, Democratic Republic of Congo: 20.4 per 100 person-years. Anti-retroviral therapy halved the incidence of TB, but as Boulle and Eley emphasize in their commentary,[13] additional interventions are needed to control TB in this population, including efforts to improve the diagnosis of TB in children co-infected with HIV.

Darwin would of course understand: the theory of evolution which he outlined in his seminal work *On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life* is also 'the modern story of TB'.[14] The recent emergence of HIV and the introduction of effective drugs represent selection pressures that *M. tuberculosis* has not experienced for most of its evolutionary history. As one consequence of the widespread (and not always well supervised) use of drugs, resistant strains have developed. Many drug resistance-conferring mutations in *M. tuberculosis* lead to a reduction in bacterial fitness, although compensatory evolution may mitigate fitness defects.[15] In HIV-infected, immune-compromised hosts even strains with high-cost resistance mutations could be propagating efficiently, which might explain why drug-resistant TB has been associated with HIV co-infection.[16,17] TB patients could thus serve as a 'breeding ground' for highly compensated drug-resistant strains, with an increased capacity to spread in the general population. To date, no study has addressed this disturbing possibility. The strain genetic background has also been shown to influence the fitness of drug-resistant *M. tuberculosis*. For example, the Beijing lineage has been associated with drug resistance,[18] suggesting that this lineage might be 'pre-adapted' to resistance. Importantly, Beijing has also been associated with HIV[19,20] and is now emerging in South Africa, probably as a consequence of the HIV epidemic.[21,22]

Genomics, the study of the genomes of organisms, is becoming increasingly important for communicable

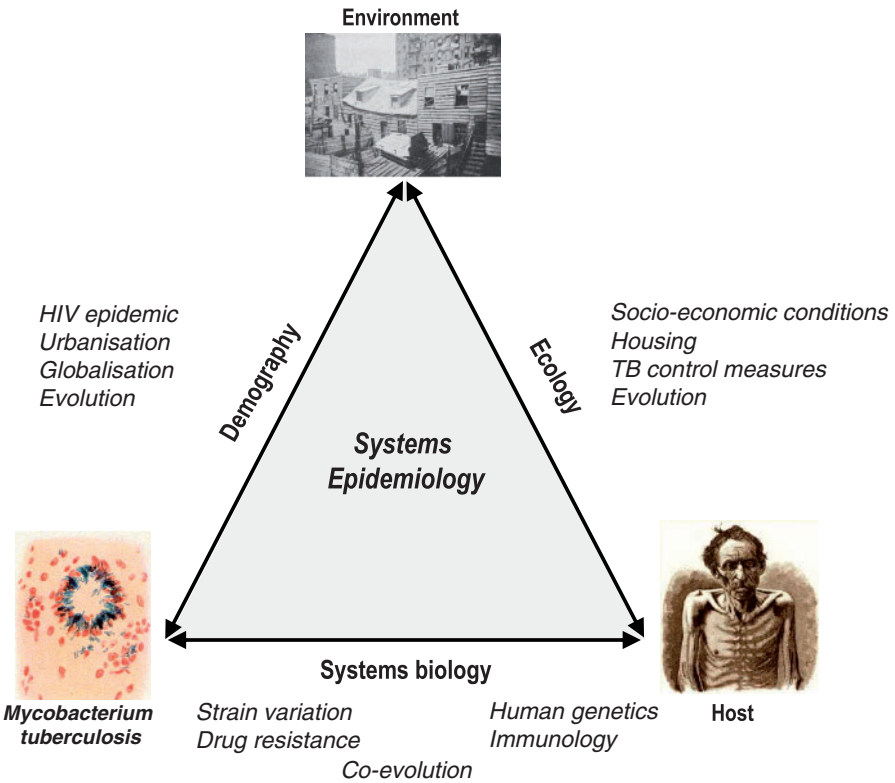

Figure 1 A 'systems epidemiology' approach to tuberculosis, which integrates demography, ecology and systems biology. Picture credits: Drawing from Koch R. Die Aetiologie der Tuberkulose. Berliner Klinische Wochenschrift, 1882; Dens of Death. Photograph from Riis JA. The Battle with the Slum. New York: MacMillan Company, 1902; Drawing of man with tuberculosis (source unknown).

disease epidemiology and control. Infectious diseases result from complex interactions between microbes, host and the environment, which are subject to evolutionary pressures and ecological changes (Figure 1). Genetic and immunological studies can answer fundamental questions about host–pathogen interaction, pathogenesis, host genetic susceptibility and the factors influencing response to treatment and prognosis.[23] Humans show remarkable variation in their response to infectious agents. For example, particular human gene polymorphisms explain some of the variation among individuals who differ in their ability to control HIV infection.[24,25] In addition to host genetic diversity, genetic variation within particular microbial species can influence the outcome of infection and disease. In *M. tuberculosis*, for example, a recent study demonstrated that the rate of progression to active TB depended on the bacterial lineage.[26] Other studies showed *M. tuberculosis* lineages to be associated with different clinical manifestations of TB.[27,28]

Both the recent changes in the human host (i.e. the emergence of HIV) and in the bacterium (i.e. the emergence of drug resistance) will influence the evolutionary trajectory of *M. tuberculosis*. We urgently need a better understanding of the genetic diversity and evolution of *M. tuberculosis* and the epidemiological and clinical consequences. How does co-infection affect the genetic population structure and evolution of *M. tuberculosis* in sub-Saharan Africa? What are the clinical and epidemiological implications of these effects? Does HIV co-infection influence the frequency and distribution of antimicrobial resistance-conferring mutations in *M. tuberculosis*? Do the clinical correlates of *M. tuberculosis* genetic diversity and the transmission dynamics of *M. tuberculosis* differ depending on HIV status and degree of HIV-induced immunodeficiency?

Improved understanding of the complex interactions between genetically diverse hosts and pathogens in changing environments will require new multidisciplinary approaches. In particular, the integration of systems biology with population sciences and ecology, in what might be described as 'systems epidemiology' is promising (Figure 1).[29] This involves combining genomic and evolutionary analyses of the host and the pathogen, with immunology, molecular and clinical epidemiology, and mathematical modelling. 'Darwinian Medicine', where evolutionary biology and biomedicine interact to enhance our understanding of both biological and evolutionary processes, is part of this concept.[30] If successful, such an integrated approach will inform the development of new diagnostics, drugs and vaccines, and guide future public health interventions. Thus, even though Charles Darwin might not have fully appreciated the significance of infectious microbes at the time, his legacy will play a crucial role in addressing challenges such as the dual epidemics of HIV and TB.

Conflict of interest: None declared.

References

[1] Kuper A. Commentary: A Darwin family concern. *Int J Epidemiol* 2009;**38:**1439–42.

[2] Brittle AH. Commentary: the background and outcomes of the first cousin marriage controversy in Great Britain. *Int J Epidemiol* 2009;**38:**1453–58.

[3] Darwin GH. Reprints and reflections: marriages between first cousins in England and their effects. *Int J Epidemiol* 2009;**38:**1429–39.

[4] Stoltenberg C. Commentary: of the same blood. *Int J Epidemiol* 2009;**38:**1442–47.

[5] Evans A. Commentary: Darwin's origin: the Irish connection. *Int J Epidemiol* 2009;**38:**1448–52.

[6] Keynes R. *Annie's Box: Charles Darwin, His Daughter, and Human Evolution*. London: Fourth Estate Publishers, 2001.

[7] Lederberg J. J. B. S. Haldane (1949) on infectious disease and evolution. *Genetics* 1999;**153:**1–3.

[8] Hershberg R, Lipatov M, Small PM *et al*. High functional diversity in *Mycobacterium tuberculosis* driven by genetic drift and human demography. *PLoS Biol* 2008;**6:**e311.

[9] World Health Organization. WHO report 2008. Global tuberculosis control. Geneva: WHO, 2008.

[10] Corbett EL, Watt CJ, Walker N *et al*. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003;**163:**1009–21.

[11] Selwyn PA, Alcabes P, Hartel D *et al*. Clinical manifestations and predictors of disease progression in drug users with human immunodeficiency virus infection. *N Engl J Med* 1992;**327:**1697–703.

[12] Edmonds A, Lusiama J, Napravnik S, Kitetele F, Van Rie A, Behets F. Anti-retroviral therapy reduces incident tuberculosis in HIV-infected children. *Int J Epidemiol* 2009;**38:**1612–21.

[13] Boulle A, Eley B. Commentary: reducing HIV-associated tuberculosis in children. *Int J Epidemiol* 2009;**38:**1621–23.

[14] Iseman MD. Extensively drug-resistant *Mycobacterium tuberculosis*: Charles Darwin would understand. *Clin Infect Dis* 2007;**45:**1415–16.

[15] Gagneux S, Long CD, Small PM, Van T, Schoolnik GK, Bohannan BJ. The competitive cost of antibiotic resistance in *Mycobacterium tuberculosis*. *Science* 2006;**312:** 1944–46.

[16] Gandhi NR, Moll A, Sturm AW *et al*. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006;**368:**1575–80.

[17] Raviglione MC, Smith IM. XDR tuberculosis–implications for global public health. *N Engl J Med* 2007; **356:**656–59.

[18] Borrell S, Gagneux S. Infectiousness of drug-resistant *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2009;**13:** 1456–66.

[19] Middelkoop K, Bekker LG, Mathema B *et al*. Molecular epidemiology of *Mycobacterium tuberculosis* in a South African community with high HIV prevalence. *J Infect Dis* 2009;**200:**1207–11.

[20] Caws M, Thwaites G, Stepniewska K *et al*. Beijing genotype of *Mycobacterium tuberculosis* is significantly associated with human immunodeficiency virus infection and multidrug resistance in cases of tuberculous meningitis. *J Clin Microbiol* 2006;**44:**3934–39.

[21] Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs–worldwide, 2000–2004 *MMWR Morb Mortal Wkly Rep* 2006;**55:**301–5.

[22] Cowley D, Govender D, February B *et al*. Recent and rapid emergence of W-Beijing strains of *Mycobacterium tuberculosis* in Cape Town, South Africa. *Clin Infect Dis* 2008;**47:** 1252–59.

[23] Cooke GS, Hill AV. Genetics of susceptibility to human infectious disease. *Nat Rev Genet* 2001;**2:**967–77.

[24] Fellay J, Shianna KV, Ge D *et al*. A whole-genome association study of major determinants for host control of HIV-1. *Science* 2007;**317:**944–47.

[25] Telenti A. Adaptation, co-evolution, and human susceptibility to HIV-1 infection. *Infect Genet Evol* 2005;**5:**327–34.

[26] de Jong BC, Hill PC, Aiken A *et al*. Progression to active tuberculosis, but not transmission, varies by *Mycobacterium tuberculosis* lineage in the Gambia. *J Infect Dis* 2008.

[27] Caws M, Thwaites G, Dunstan S *et al*. The influence of host and bacterial genotype on the development of disseminated disease with *Mycobacterium tuberculosis*. *PLoS Pathog* 2008;**4:**e1000034.

[28] Thwaites G, Caws M, Chau TT *et al*. Relationship between *Mycobacterium tuberculosis* genotype and the clinical phenotype of pulmonary and meningeal tuberculosis. *J Clin Microbiol* 2008;**46:**1363–68.

[29] Comas I, Gagneux S. The past and future of tuberculosis research. *PLoS Pathog* 2009;**5:**e1000600.

[30] Shanks N, Pyles RA. Evolution and medicine: the long reach of ''Dr. Darwin''. *Philos Ethics Humanit Med* 2007; **2:**4.

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REPRINTS AND REFLECTIONS

Marriages between first cousins in England and their effects[1]

George H Darwin

I. The Proportion of First-Cousin Marriages to all Marriages

It is well known that when the Census Act, 1871, was passing through the House of Commons, an attempt was made by Sir J. Lubbock, Dr Playfair, and others, to have a question inserted with respect to the prevalence of cousin marriages, under the idea that when we were in possession of such statistics we should be able to arrive at a satisfactory conclusion as to whether these marriages are, as has been suspected, deleterious to the bodily and mental constitution of the offspring. It is unfortunately equally well known that the proposal was rejected, amidst the scornful laughter of the House, on the ground that the idle curiosity of philosophers was not to be satisfied.

It was urged, that when we had these statistics it would be possible to discover, by inquiry in asylums, whether the percentage of the offspring of consanguineous marriages amongst the diseased was greater than that in the healthy population, and thus to settle the question as to the injuriousness of such marriages. The difficulty of this subsequent part of the inquiry was, I fear, much underrated by those who advocated the introduction of these questions into the census. It may possibly have been right to reject the proposal on the ground that every additional question diminishes the trustworthiness of the answers to the rest, but in any case the tone taken by many members of the House shows how little they are permeated with the idea of the importance of inheritance to the human race.

In the summer of 1873 the idea occurred to me that it might be in some measure possible to fill up this hiatus in our national statistics. In looking through the marriages announced in the *Pall Mall Gazette*, I noticed one between persons of the same surname; now as the number of surnames in England is very large, it occurred to me that the number of such marriages would afford a clue to the number of first-cousin marriages.

In order to estimate what proportion of such marriages should be attributed to mere chance, I obtained the ''Registrar-General's Annual Report'' for 1853, where the frequency of the various surnames is given. I here found that there were nearly 33,000 surnames registered, and that the fifty commonest names embraced 18 per cent. of all the population. It appear that one in 73 is a Smith, one in 76 a Jones, one in 115 a Williams, one in 148 a Taylor, one in 162 a Davies, one in 174 a Brown, and the last in the list is one Griffiths in 529. Now it is clear that in one marriage in 73 one of the parties will be a Smith, and if there were no cause which tended to make persons of the same surname marry, there would be one in 73^2, or 5,329 marriages, in which both parties were Smiths. Therefore the probability of a Smith—Smith marriage *due to mere chance is* $\frac{1}{5329}$; similarly the chance of a Jones-Jones, a Davies-Davies and a Griffiths-Griffiths marriage would be $\frac{1}{76^2}$, $\frac{1}{162^2}$ and $\frac{1}{529^2}$, respectively. And the sum of fifty such fractions would give the probability of a *chance* marriage, between persons of the same surname, who owned one of these fifty commonest names. The sum of these fifty fractions I find to be 0.0009207, or 0.9207 per thousand. It might, however, be urged that if we were to take more than fifty of the common names, this proportion would be found to be much increased. I therefore drew a horizontal straight line, and at equal distances along it I erected ordinates proportional to $\frac{1}{73^2}$, $\frac{1}{76^2}$, . . . , $\frac{1}{529^2}$, The upper ends of these ordinates were found to lie in a curve of great regularity, remarkably like a rectangular hyperbola, of which my horizontal straight line was one asymptote; and the ordinate corresponding to Griffiths was exceedingly short. Observing the great regularity of the curve, I continued it beyond the fiftieth surname by eye, until it sensibly coincided with the asymptote, at a point about where the hundred and twenty-fifth name would have stood, and then I cut out the whole (drawn on thick paper) and weighed the part corresponding to the fifty surnames, and the conjectural part. The conjectural addition was found to weigh rather more than one-tenth of the other part; and as the chance of same-name marriages is proportional to the areas cut out, I think I may venture confidently to assert that in England and Wales about one marriage in a thousand takes place in which the parties are of the same surname, and have been uninfluenced by any relationship between them bringing them together. Now it will appear

Darwin GH, Marriages between first cousins in England and their effects. Fortnightly Review 1875; 24:22–41.

presently that far more than one marriage in a thousand is between persons of the same surname; and as I do not profess to have attained results of an accuracy comparable to 0.1 per cent., I am entitled to say that same-name marriages, when they take place, are due to consanguinity of the parties. If it permitted such accuracy, the method pursued would, however, include a compensation for this disturbing cause.

With the help of an assistant the marriages announced in the *Pall Mall Gazette* in the years 1869–72, and part of 1873, were counted, and were found to be 18,528. Out of these 232 were between persons of the same surname, that is 1.25 per cent. were same-name marriages. The same marriage is occasionally announced twice over, but as there can be no reason to suppose that this course has been pursued oftener or seldomer with same-name marriages than with others, the result will not be vitiated thereby. In order to utilise this result it now became necessary to determine-

(1) What proportion of this 1.25 per cent. were marriages between first cousins.
(2) What proportion marriages between first cousins of the same surname bear to those between first cousins of different surnames.

If these two points could be discovered, the percentage of first-cousin marriages *in the upper classes* could be at once determined. I have endeavoured to find out these proportions in several ways.

An assistant was employed to count the marriages of the *men* in the pedigrees of the English and Irish families occupying about 700 pages of ''Burke's Landed Gentry,'' marking every case where the marriage was ''same-name''. I then tried in every such case to discover, from a consideration of the pedigree, whether the marriage had been between first cousins. I found that in a certain number of cases I was unable to discover this. The total number of pedigrees in the 700 pages was about 1,300; and of these I had to exclude 71, thinking that by only including family trees where I could discover the relationship of the parties, I should not obtain an unfair selection of the whole. The marriages of the men alone were included, because, had I included those of the women, many marriages would have been counted twice over – once in the pedigree under consideration, and again in that of the husband. In this way, then, I found out of 9,549 marriages given by Burke 72 were same-name first-cousin marriages, and 72 were same-name marriages not between first cousins. This gives the percentage of same-name marriages as 1.5 (not strikingly different from the 1.25 deduced from the *Pall Mall Gazette*), and of this percentage 0.75 is to be attributed to first-cousin marriages.

I further collected in the same way 1,989 marriages from the ''English and Irish Peerage,'' and of these 18 were same-name first-cousin marriages, or 0.9 per cent. The number of same-name marriages not being first-cousin marriages was not, however, compared in this case. It will be observed, that the proportion is nearly 0.2 per cent. higher than with the ''Landed Gentry,'' and as the nobility are known to marry much *inter se*, this was perhaps to be expected; however, 2,000 is too small a number on which to base a conclusion on this head with safety. The Peerage and Burke combined give 90 out of 11,538, or 0.78 per cent., of same-name first-cousin marriages.

The next step was to send out a large number of circulars (about 800) to members of the upper middle and upper classes, in which I requested each person to give me the names of any members of the following classes, who married their first-cousins; viz., (1) the uncles, aunts, father, and mother of the person; (2) the brothers, sisters, and the person himself; (3) the first cousins of the person. I further asked for the names of any persons in the above classes who contracted same-name marriages *not* with first cousins. I confined my question to near relations, because, had the more distant ones been included, a risk was run of getting a selected set of marriages – a risk which I am inclined to suspect was not avoided, as will hereafter appear.

In about 300 of the circulars, I further asked for the total number of marriages contracted by the persons included in the Classes 1, 2, and 3. Care was taken to exclude, as far as possible, those persons who had cousins in common, so that each answer should embrace a fresh field. I must here return my thanks to the many persons who so kindly filled in and returned the circulars.

The following result was obtained:-

TABLE A

Same-Name First-Cousin Marriages	Different-Name First-Cousin Marriages	Same name *not* First-Cousin Marriages
66	182	29

From 181 circulars returned in which the total number of marriages in each class was given, the following was the result:-

TABLE B

Total Number of Marriages	Total Number of First-Cousin Marriages	Percentage of First-Cousin Marriages	Percentage of Same-Name marriages, whether Cousin or not Cousin
3,663	125	3.41	1.38[2]

Persons having no cousin marriages to fill in were asked to return the circular blank in those cases where the total number of marriages was not asked for. Of such blank returns, together with those where

the total number of marriages was not given, 207 came back to me; and the results derived from them were found to agree closely with those in Table B.

From Table A it is seen that there were 182 different-name cousin marriages to 66 same-name cousin marriages; *i.e.* for every same-name cousin marriage there were 2¾ different-name cousin marriages.

And again there were 66 same-name cousin marriages to 29 same-name-not-cousin marriages; that is rather more than two to one. This last result disagrees so much with that obtained from Burke and the Peerage, where the proportion was, as above stated, found to be as 1 to 1, that I am inclined to suspect that I had either a run of luck against me, or more probably that a considerable number of marriages between persons of the same surname, not being first cousins, escaped the notice of my correspondents. This latter belief is somewhat confirmed by what follows. If, however, I combine the results obtained from Burke with those from my circulars, I obtain the following:-

$$\frac{\text{Same} - \text{name cousin} - \text{marriages}}{\textit{All same} - \textit{name marriages}} = \frac{142}{249} = .57$$

And in default of anything more satisfactory I am compelled to accept this result as the first of my two requisite factors.

As to the second factor, - the proportion 2¾: 1 for different-name cousin marriages to same-name cousin marriages is, I fear, also unsatisfactory. But before entering on this point I will indicate the sources of error in my returns:-

(1) The sensitiveness of persons in answering the question in cases where there are cousin marriages, particularly when any ill results may have accrued.
(2) The non-return by persons who had no such marriages to fill in, and who would say, "I have no information, what is the use of returning this?"[3]
(3) The ignorance of persons of the marriages of their relations. This ignorance would be more likely to affect the returns of different-name marriages than of same-name ones. I feel convinced that this has operated to some extent, as will be seen hereafter.
(4) In the cases of same-name marriages, persons would be more likely to know of the marriages between first cousins than of other such marriages. The discrepancy between Burke and my circulars leads me to believe that this too has operated.

I have been much surprised to find how very little people know of the marriages of their relations, even so close as those comprised in my three classes. As it is clear that the marriages contracted by a man's uncles and aunts, and by his brothers and sisters, would be less likely to escape his notice than would those contracted by his first cousins, I made an analysis of my circulars, including only the first two classes, viz: (1) uncles, aunts, father, and mother; (2) brothers and sisters and the person himself. And the results from this analysis made a nearer approach to those derived from Burke. But even then it seemed so unsatisfactory, that I feel sure that the indirect method, to which I now proceed, is on the whole more reliable.

It is possible to discover the proportion between the same-name and different-name marriages in an entirely different way, and this I have tried to do. A man's first cousins may be divided into four groups, viz: the children of (*a*) his father's brothers, (*b*) of his father's sisters, (*c*) his mother's brothers, (*d*) his mother's sisters. Of these four groups only (*a*) will in general bear the same surname as the person himself. On the average the number of marriageable daughters in each family of each of the four groups will be the same. Were the four groups then equally numerous, we might expect that the same-name would bear to the different-name marriages the proportion of one to three. Since, however, a man cannot marry his sisters, this cannot hold good; for the classes (*a*) and (*d*) are clearly on the average smaller than (*b*) and (*c*), and the proportion we wish to discover is $\frac{(a)}{(b)+(c)+(d)}$, which must evidently be less than $\frac{1}{3}$. To take a numerical example: A's father is one of 3 brothers, who married and have children, and A's father had 2 sisters, who married and have children. A's mother had 1 brother, who married and has children, and was one of 5 sisters, who married and have children. Then clearly the class

(a) consists of 2 families.
(b) consists of 2 families.
(c) consists of 1 family.
(d) consists of 4 families

So that the above fraction becomes $\frac{2}{2+1+4} = \frac{2}{7}$. In this case we may conclude that if A marries a first cousin, it is 5 to 2 that he will marry one of a different surname. In another case the numbers might have been different, and therefore the fraction and the betting also different. And what we wish to discover is the *average* value of this fraction. But for the various members of a large community there will be a very large number of such fractions, and some will occur more frequently than others; so that in finding this average value, each fraction should have its proper weight assigned to it.

In order to assign the weight to - say the above fraction $\frac{2}{7}$, we must take a thousand families and find in how many of them there were 3 sons and 2 daughters who married and had children, and in how many there were 1 son and 5 daughters who married and had children. Having sufficiently indicated how the required proportion depends on probabilities, I may state that I sent out a number of circulars to

members of the upper middle, and upper classes, and obtained and classified statistics with respect to a considerable number of families. I treated the question in four different ways. It might be supposed that a man, who had five families of first cousins in relation to himself, would be five times as likely to marry a first cousin as a man who had only one such family, or again it might be supposed that he would be only equally likely. The truth, however, will certainly lie between these suppositions. The question, when treated from this point of view, leads to the result that $\frac{\text{Same-name cousin-marriages}}{\text{Different-name first-cousin marriages}}$ is greater than $\frac{1}{4.44}$ and less than $\frac{1}{4.12}$. So that the true proportion would be about $\frac{1}{4\frac{1}{4}}$.

The two other methods are founded on the same grouping of families, and depend on the fact that my class (*a*) will on the average be equal in number to class (*d*), and class (*b*) to class (*c*), and all that is necessary is to find what value should be assigned to the ratio (*a*) or (*d*): (*b*) or (*c*). It would be tedious to indicate the precise method employed, but suffice it to say, that after a correction for the greater prevalence of the second marriages of men than of women, the result comes out that $\frac{\text{Same-name cousin-marriages}}{\text{Different-name first-cousin marriages}}$ is greater than $\frac{1}{4.23}$ and less than $\frac{1}{4.14}$, so that the proportion would be really about $\frac{1}{4\frac{1}{6}}$; a result which differs but very slightly from that given by the two other methods.

The amount of arithmetical labour was so great that I was obliged to make an approximation, which would, however, hardly affect the results, but as far as it went it would make the above fractions too small.

I think on the whole it may be asserted, that the same-name first-cousin marriages are to the different-name first-cousin marriages as 1 to 4. It may perhaps be worth mentioning that a second grouping of families from ''Burke's Landed Gentry'' led to almost identical results, notwithstanding the bias introduced by the fact that the eldest sons have a constant premium on marriage.

It appears to me on the whole that this latter result is considerably more reliable than that from my circulars, and this, as before stated, I can only explain on the supposition that many different-name marriages have escaped notice. The whole is very perplexing, and may perhaps be held to make all my results valueless. My final result then for the two required factors is, that-

$$\frac{\text{Same - name cousin - marriages}}{\textit{All same - name marriages}} = .57$$

And

$$\frac{\text{Same - name cousin - marriages}}{\text{Different - name first - cousin marriages}} = \frac{1}{4}$$

If this be applied to the percentage 1.25 of the *Pall Mall Gazette*, we get 3.54, or 3½ per cent., as the proportion of first-cousin marriages to all marriages in the middle classes. If it be applied to the peerage we get 4½ per cent., and for the landed gentry 3¾ per cent., and for both combined $3\frac{9}{10}$ per cent. To sum up, the direct statistical method gives from $3\frac{1}{5}$ to $3\frac{2}{5}$ per cent., or including only the classes (1) and (2), comprising uncles, aunts, brothers, and sisters, $4\frac{1}{2}$ per cent., the indirect method $3\frac{1}{2}$ per cent.; and the partly indirect and partly statistical, founded on the Peerage and Burke, gives $3\frac{9}{10}$. There is, however, some reason to suppose that the proportion is really higher amongst the landed classes. There is a serious discrepancy between the direct and indirect methods as to the proportion of same-name and different-name marriages, which goes far to invalidate the results.

Whether, however, these proportions are actually correct or not, there can be little doubt, that if the area taken is large enough the percentage of first-cousin marriages in any class is proportional to the percentage of same-name marriages; so that if the latter is, say, only half the former, the cousin marriages are also only half. I therefore obtained from the General Registry of Marriages at Somerset House a return of the proportion of same-name marriages in 1872 in various districts, namely, (1) London, (2) large towns, viz., Bradford, Leeds, Manchester, Portsmouth, Southampton, Exeter, Plymouth, Birmingham, Northampton, &c., and (3) Agricultural districts of Hampshire, Devonshire, Middlesex, Herts, Bucks, Oxon, Northampton, Huntingdon, Bedford, and Cambridge. I must take this opportunity of returning my warm thanks to the superintendent of the statistical department, Dr. Farr, for the very great kindness both he and Mr. N. A. Humphreys, of the General Registry Office, have shown in helping me in this inquiry by every way in their power. The following Tables, in which the third column is introduced for the sake of comparison with the statistics from the *Pall Mall Gazette*, give the results:

	Number of Marriages Registered	Per Cent. of same-name Marriages	Approximate Ratio to the Number (1.25) from *Pall Mall Gazette*	Per Cent. of First Cousin Marriages as deduced by previous method
I. Metropolitan District	33,155	0.55	½	1½
II. Urban Districts	22,346	0.71	$\frac{7}{12}$	2
III. Rural Districts	13,391	0.79	$\frac{2}{3}$	2¼

It thus appears that in London, comprising all classes, the cousin marriages are about half what they are in the upper middle class, that is, probably 1½ per cent. In urban districts they are about $\frac{7}{12}$ths of what they are in the upper middle classes, that is probably 2 per cent. In rural districts they are about two-thirds of what they are in the upper middle classes, that is probably 2¼ per cent. In the middle and upper middle class or in the landed gentry probably 3½ per cent. In the aristocracy probably 4½ per cent. This is in accordance with what might have been expected *à priori*: for the aristocracy hold together very much, the landed gentry slightly less, the business class again less. And beginning from the other end, London is an enormous community, recruited from every part of England; the large towns form communities, only one degree less heterogenous; and the country is still less heterogeneous. I am, however, somewhat surprised at finding the proportion in the rural population so small, for one would imagine that agricultural labourers would hold together very closely.[4]

Persons accustomed to deal with statistics will be able to judge, better than myself, what degree of reliance is to be placed on the previous results. My one *impression* is that there is not an error of one per cent. in asserting that amongst the aristocracy the proportion of first-cousin marriages to all marriages is 4½ per cent., and that for the upper middle classes, and the urban and rural districts the error in the percentages is somewhat less, and lastly for London decidedly less. But this is an impression that I hardly know how to justify, and I therefore leave an ample field for adverse criticism.

II. Inquiries in Asylums

I now pass on to the second part of my inquiry, namely, the endeavour to discover, by collecting statistics in asylums, whether first-cousin marriages are injurious or not.

The method I intended to pursue was as follows: to get the superintendents of asylums to ask each one of the patients under their charge, either personally or through their subordinates, the question, ''Were your father and mother first cousins or not?'' In the case of the insane, I thought, in my ignorance, that those who had charge of them would have so intimate a knowledge of the character of each individual case as to be able to sift those whose answers could be depended on from those who were quite untrustworthy. In this it appears that I was mistaken, as will be shown by the remarks sent me by the various gentlemen who so kindly took up this inquiry. I cannot help thinking, however, that they under value the statistics which they have collected for me. I must take this opportunity to return my warm thanks to all the gentlemen mentioned below for the immense pains they have been at in collecting these results. I could hardly have believed that so many men, much occupied by their business, could have shown a stranger so much kindness, more especially as many of them seemed convinced that their labours were almost in vain. To Dr. W. Lauder Lindsay, Dr. Crichton Browne, Dr. Maudsley, and Dr. Scott, I must return my especial thanks for the really extraordinary vigour with which they took up the subject, and gave me every help in their power. I have also to thank Dr. Wilkie Burman, of Devizes; Dr. Bacon, of Fulbourn; Dr Shuttleworth, of Lancaster; and Dr. Clouston, of Edinburgh, for their kind offers of help. The table of results is as follows:-

English and Welsh Asylums	Number of Patients	Answers to "were Parents First Cousins?"	Offspring of First Cousin	Observations
1. West Riding, Wakefield (lunatics and idiots) Dr. Crichton Browne	1,407	655	31	Examination conducted with great care; cases of doubt excluded. Almost all who gave answers were lunatic and not idiotic.
2. Hanwell (lunatics) Dr. Rayner	380	255	2 or 3	Only those are given as trustworthy where the history of the patient could be ascertained. Amongst the males there were twelve cases of doubtful consanguinity, but whether first cousins or not, is not stated.
3. Warneford, Oxford (lunatic) Dr. Byewater Ward	59	20	–	Patients of the farmer and tradesmen class.
4. Mickleover, Derby (lunatics) Dr. Murray Lindsay	364	198	4	Dr. Lindsay thinks these statistics worth little.
5. Metropolitan District, Caterham (lunatics) Dr. Adam	1,904	560	20	Statistics very imperfect; trustworthiness of answers uncertain.
6. Glamorgan County (lunatics) Dr. Yellowlees	492	218	9	Statistics worth little. Of those who did not answer, 137 were ignorant, and 137 incapable.
7. Chester County (lunatics) Dr. Lawrence	About 450	225	3	Patients of the labouring class.

8. County Lunatic, Snenton, Nottingham Dr. Phillimore	390	200	4 or 9	Statistics to be little depended on.
9. Grove Hall, Bow Dr. Mickle	427	181	8	Patients old soldiers.
10. Hatton, Warwick Dr. Oscar Woods	537	258	8 or 9	Patients, labourers and artisans. The offspring of first cousins belonged to seven families. Examinations conducted with great care.
11. Earlswood, Surrey (idiot) Dr. Grabham	–	1,388	53	Facts derived from parents, and therefore tolerably trustworthy.
12. Broadmoor Criminal (lunatic) Dr. Orange	370	150	2	Dr. Orange places little reliance on these results.
Totals for England and Wales	8,170 very nearly	4,308	149 or 142	Between 3.46 and 3.20 per cent. of the patients who answered said they were offspring of first-cousin marriages.
Scotch Asylums				
1. Montrose (lunatic) Dr. Howden	406	141	8	Dr. Howden thinks the inquiry useless. No inquiry was made of the idiots in this asylum.
2. Crichton Royal Institution, Dumfries Dr Gilchrist	146	51	4	
3. Southern Counties, Dumfries Dr. Anderson	318	200	8	
4. Murray Royal Institution, Perth Dr. Lauder Lindsay	80	44	4	Dr. Lindsay thinks the results very doubtful. The failure to get answers was due to incapacity and refusal.
5. Perth District, Murthly Dr. McIntosh	220	78	3	Patients paupers.
Totals	1,179	514	27	5.25 per cent. of the patients who answered said that they were offspring of first-cousin marriages.
Irish Asylums				
1. Maryborough Through Dr. Courtenay	217	–	2	Patients agricultural labourers.
2. Limerick District Dr. Courtenay	434	–	3	Twenty patients of better class; the rest labourers.
Totals	651	–	5	No information as to numbers who failed to answer. Dr. C considers these statistics of little value. Roman Catholics do not marry first cousins. 0.77 per cent. of all the patients say they are offspring of first-cousin marriages.

The columns of observations show how very unsatisfactory the collectors consider these results. From various circumstances, it appears that the results from Earlswood, Hatton, and the West Riding Asylums are considerably more trustworthy than the others.

Including, then only these three asylums, it appears that, out of 2,301 patients, 90 or 91 were offspring of first cousins, that is 3.9 per cent. The fact that this agrees pretty closely with the 3.4 per cent. deduced from the whole table, leads me to think that the trustworthiness of the results collected has been under-estimated by the collectors themselves.

At Hanwell, where also there were some circumstances leading one to believe in tolerable accuracy, the percentage is very small, and this agrees well with what I should have been led to expect, from the small percentage of cousin marriages I found in London, by the methods of the first part of this paper. It is to be observed, however, that there were twelve cases reported of doubtful *consanguinity*.

It will be seen that the percentage of offspring of first-cousin marriages is so nearly that of such marriages in the general population, that one can only draw the negative conclusion that, as far as insanity and idiocy go, no evil *has been shown* to accrue from consanguineous marriages.

From the high percentage (5¼) of offspring of first-cousin marriages in the Scotch asylums, I should be led to believe that such marriages are more frequent in Scotland than in England and Wales, and from the mountainous nature of the country this was perhaps to be expected.

The methods of the first part of this paper throw no light on the question as far as concerns Scotland.

From the two Irish asylums no results whatever can be deduced.

But, whatever the value of these statistics may be, the opinion of prominent medical men, who have had especial advantages of observation, and are many of them also men of science, cannot be without interest.

Dr Crichton Browne writes to me that the investigation was impossible in the case of idiots, except through the medium of the parents. ''It has always seemed to me that the great danger attending such marriages consists in the intensification of the morbid constitutional tendencies, which they favour. Hereditary diseases and cachexiae are much more likely to be shared by cousins than by persons who are in no way related... (and these) are transmitted with more than double intensity when they are common to both parents... They seem to be the square or cube of the combined volume... Even healthy temperaments, when common to both parents often come out as decided cachexiae in the children.'' He adds, that persons of similar temperaments ought not to intermarry. Elsewhere he tells me that he did not at first make sufficient allowance for the ignorance ''and stupidity of my patients.'' In such an investigation, congenital effects, he says, should be distinguished from the acquired. I fear, however, that I must leave this to some hands more skilful than mine.

Dr. Howden, of Montrose, says: ''As regards insanity, my own impression is, that unless there exists a hereditary predisposition the marriage of cousins has *no effect* in producing it... Neither in insanity nor in any other abnormal propensity do two plus two produce four; there is always another factor at work neutralising intensification and bringing things back to the normal.'' Dr. Howden thus disagrees with Dr. Crichton Browne, who, I take it, would maintain that, in insanity, two plus two makes more, and not less, than four.

Dr. Lauder Lindsay is of opinion that the ill-effects of cousin marriage, including insanity, are much less than represented. He urges the ''impossibility'' of obtaining trustworthy answers from the patients themselves; and even the results of personal inquiries from the nearest relatives of the patients would be liable to much error. Several of my correspondents expressed a belief that consanguinity of parents was more potent in producing idiocy than insanity. The results from Earlswood do not seem, however, to confirm this, and here the results sent seemed peculiarly trustworthy.

I had intended to pursue my inquiries in hospitals and asylums for other diseases, but the attempt which I made with respect to deaf mutes has shown me that the difficulties which arise are so great that it is almost useless to persevere in this course any further. I will now give the results which I have collected.

The first return relates to the College for the Blind at Worcester. The results were communicated through the kindness of the Rev. Robert Blair and Mr. S. S. Foster. The college is small, and only 20 cases are recorded, and particulars of each case were sent. Of these, 20, the offspring of first cousins were one, and of second cousins one case of 2 brothers. Of the 20 cases, 2 were due to accidents. Thus, out of 17 families, there was one case of offspring of first cousins.

Dr. Scott, of Exeter, has informed me that out of 241 families, in which there were children born deaf and dumb, there were 7 cases of first-cousin marriage. In three or four of these families there were more than one child so afflicted.

Dr. Scott also kindly offered to place me in communication with the superintendents of a number of institutions for the deaf and dumb, and having availed myself of his kindness, I have collected the following answers.

Mr. Arthur Hopper, of the Deaf and Dumb School near Birmingham, conducted an inquiry with the utmost care. He tells me that out of 122 pupils he has received information about the parentage of all but 9. The 113 pupils, whose parentage is known, belonged to 109 families; of these 113, there were deaf from accident or disease 37, and of 10 the cause of deafness was unknown. Of these 10 pupils and the 66 congenitally deaf, not one was the offspring of a *consanguineous* marriage. Of the 37 who became deaf from disease, one was the offspring of first cousins. I am not informed whether the cases where several were deaf in a family belonged to the congenital cases, but it is almost certain to be so, and in any case I will assume (as the most unfavourable assumption) that it is so. Thus, out of 62 congenitally deaf families, not one was the offspring of even a consanguineous marriage. If we were to assume the 10 other cases to be cases of congenital deafness, it would be, not one in 72 congenitally deaf families was the offspring of a consanguineous marriage.

Mr. Patterson, of the Manchester School for Deaf Mutes, kindly informs me that his 130 pupils belong to 123 families. Concerning 8 of these families no information could be obtained; in 67 such families the deaf-mutism results from disease; in 63 it was congenital; and only one family was the offspring of first cousins.

Mr. Neill, of the Northern Counties Institution, at Newcastle-on-Tyne says, ''350 have been admitted into this institution, and I do not think more than 6 of the parents were cousins. In one family whose parents were cousins there were 4 deaf mutes.''

I have thus accurate information with respect to 366 families (i.e. $241 + 62 + 63$), and out of these 8 were offspring of first cousins; that is to say, nearly 2.2 per cent. were offspring of first cousins. And, including the 350 cases at Newcastle, the percentage is $\frac{1400}{716}$, or 1.9 per cent. It is curious to notice that I deduced 2 per cent. as the proportion of first-cousin marriages in urban districts, other than London. Thus as far as these meagre results go, no evil in the direction of deaf-mutism would appear to arise from first–cousin

marriages. The failure to collect more statistics of this kind does not arise from any inability to get at the best sources of information; on the contrary, I have on all hands the kindest assurances of willingness to help me.

Mr. David Buxton, of the Liverpool School, says the mode of investigation is simply impracticable; but he has sent me several pamphlets on the subject, his own excellent paper amongst the number.

Mr. William Sleight, of the Brighton School, tells me that the children know nothing, and the parents are unwilling to communicate the fact inquired after, and says, ''As far as I have been able to ascertain, about 7 per cent. of born deaf children are the offspring of parents who were cousins.'' (Query, first cousins?)

Mr. Patterson also writes to me that he is of opinion that, ''though the result of the marriage of near relatives may not be seen in the deafness of their immediate offspring, yet the result is a deterioration of the constitution of the offspring, which may show itself in deafness in a few generations.''

Mr. Neill, who has been engaged in the tuition of the deaf and dumb for forty years, thinks the cases of offspring of cousins so afflicted are fewer than is supposed. He also gives me facts showing how strongly heritable congenital deafness is where both parents are deaf-mutes; marriages are, moreover, by no means uncommon between pupils of these institutions.

To sum up the results of the whole investigation: It seems probable that in England, among the aristocracy and gentry, about 4 per cent. of all marriages are between first cousins; in the country and smaller towns between 2 and 3 per cent; and in London perhaps as few as 1½ per cent. Probably 3 per cent. is a superior limit for the whole population. Turning to lunatic and idiot asylums, probably between 3 and 4 per cent. of the patients are offspring of first cousins. Taking into account the uncertainty of my methods of finding the proportion of such marriages in the general population, the percentage of such offspring in asylums is not greater than that in the general population to such an extent as to enable one to say positively that the marriage of first cousins has any effect in the production of insanity or idiocy, although it might still be shown, by more accurate methods of research, that it is so. With respect to deaf mutes, the proportion of offspring of first-cousin marriages is precisely the same as the proportion of such marriages for the large towns and the country, and therefore there is no evidence whatever of any ill results accruing to the offspring from the cousinship of their parents.

III. Marriages between Cousins in relation to Infertility and a High Death-rate amongst the Offspring

Professor Mantegazza states in a paper on consanguineous marriages[5] that he may conclude with tolerable safety, from his collection of 512 cases of consanguineous marriage, that consanguinity tends to cause sterility; for he found that between 8 and 9 per cent. of the recorded marriages were sterile. It is not clear, however, how he is entitled to draw this conclusion, unless he knows what is the proportion of sterile marriages in the general population, and he admits that he has no statistics on this point. M. Boudin, who wrote at an earlier date, is of the same opinion, and considers, further, that even where sterility does not afflict the consanguineous marriage itself, it is apt to affect the offspring.[6] Dr Balley is also of opinion that the ill-effects of such marriages are liable to appear in the second generation.[7]

It appears to me that these points may be settled pretty satisfactorily by a comparison between the fertility of the marriages of first cousins and of the marriages of their offspring, as recorded in the pedigrees in ''Burke's Landed Gentry'' and the ''Peerage,'' with the fertility of marriages between persons not akin.

I had already got a large number of marriages marked as being between first cousins, and accordingly proceeded to count the number of children arising therefrom. The marriages made within the twenty years immediately preceding the publication of those works were excluded; so that only complete families were counted. It soon became evident that the lists of the daughters were very incomplete, and that the daughters were perhaps sometimes omitted altogether; the sons dying in infancy are also frequently omitted (especially in the ''Landed Gentry''); and when such occurred I excluded them. I think that the lists of the sons surviving infancy are, however, pretty complete, and any incompleteness will clearly affect the record of marriages between persons not akin as much as it does the first-cousin marriages. The comparison to be made must, therefore, be only between the numbers of sons. I shall use the words *sterile* or *infertile* to mean the absence of children surviving infancy. The number of daughters recorded will be given, so as to show the extent of incompleteness.

In this manner 116 families, offspring of first cousins, were collected. In all but 12 of them the marriages were between children of brothers. In 11 of the 116 it is merely stated that there was issue of the marriage, and in 8 others there is no information as to whether there was issue or not. I found in a subsequent inquiry, by cross references to other pedigrees, that where there was no information there was nevertheless often a family; so that the absence of information is no indication of sterility, and indeed is perhaps some slight indication of fertility, because the family is omitted in order to economize space, and d.s.p. (*decessit sine prole*) is frequently added where there *was* no issue. In this case, however, cross references were of no avail, because the family would be recorded in the pedigree under consideration or not at all. The absence of information is here then a slightly

greater indication of sterility than in my later inquiry, where it is no indication at all.

The cases where issue was recorded may clearly be disregarded in making the comparison, since they might be matched by similar cases amongst the non-consanguineous marriages.

Subtracting, then, the 11 recorded cases of issue and the 8 cases of no information, we are left with 97 families; these gave 202 sons and 153 daughters. It is probable that about 212 daughters should have been recorded. Now 202 sons to 97 marriages is at the rate of 2.07 sons to each marriage; or, supposing the 8 cases of doubt to have been all sterile, we get 105 marriages as giving 202 sons, that is, at the rate of 1.92 sons to each marriage.

Thus the average number of sons who survive infancy, arising from a marriage of first-cousins amongst the gentry of England, is between 1.92 and 2.07.

The next step was to collect the non-consanguineous marriages. In order to secure myself from bias, I opened my book by chance and counted all the marriages in the pedigree which fell under my eye. I then did the same in another place, and so on. In this way 217 families arising from persons not akin were collected, and found to give 416 sons and 340 daughters. Here, as before, the daughters are deficient, and about 437 daughters ought probably to have been given. Now 416 sons to 217 marriages is at the rate of 1.91 sons to each marriage. Thus the average number of sons who survive infancy, arising from non-consanguineous marriages, is 1.91.

The balance of fertility is therefore slightly on the side of the cousins, but the small difference is probably due to chance.

In order to feel greater confidence in this result, a second method of analysis was carried out. If cousin marriages tend to cause sterility, they probably tend to cause partial sterility. Now amongst the 97 cousin marriages, 14 were sterile (in the sense defined), and amongst the 217 non-consanguineous marriages 33 were sterile. Thus we have 83 fertile cousin-marriages and 184 fertile non-consanguineous marriages; the former gave 202 sons, the latter 416 sons. It will be observed that this course entitles me to disregard the 8 cases of ''no information'' before referred to, for if they were sterile they are to be subtracted *ex hypothesi*, and if there was issue, they could be matched by similar cases amongst the non-consanguineous. Thus fertile first-cousin marriages produce sons at the rate of 2.43 sons to each marriage, and fertile non-consanguineous marriages produce sons at the rate of 2.26 sons to each marriage.

Therefore the analysis leads to a similar slight balance in favour of the fertility of the first cousins, just as did the former one.

I offer the following suggestion as a possible explanation of the greater fertility of the cousins, although mere chance is the more probable cause of the difference. Marriages between first cousins will be more apt to take place where there is a large group of persons who bear that relationship to one another. In such families fertility will be hereditary; hence it is possible that the comparison is to some extent being effected between abnormally fertile families and those in which fertility is only normal.

The next point to investigate is as to whether the offspring of first-cousin marriages are themselves affected by sterility.

To test this, recourse was again had to the ''Peerage'' and ''Landed Gentry,'' and 136 marriages of the offspring of first cousins were collected. Concerning 29 of these no information could be obtained, and, for the reasons before assigned; these may be set aside. Of the 107 remaining marriages, it is recorded that 14 had issue. Subtracting these, we are left with 93 marriages, and these gave 180 sons and 157 daughters. It should be mentioned that some few of the marriages were recent, so that the families would be not quite complete in these cases. Now 93 marriages giving 180 sons is at the rate of 1.93 sons to each marriage.

Again, 16 of these marriages were sterile, so that 77 fertile marriages gave 180 sons, that is at the rate of 2.34 sons to each marriage. If these two numbers, viz. 1.93 and 2.34, be compared with the corresponding numbers, viz., 1.91 and 2.26, for the non-consanguineous marriages, it is clear that there is again no evidence of want of fertility in the offspring of first-cousin marriages.

The results with respect to fertility may be summed up in the following Table:

Parentage	Average number of Sons to each Marriage	Percentage of Sterile Marriages[1]	Average Number of Sons to each Fertile Marriage
Not consanguineous	1.91	15.9	2.26
Parents first cousins	Between 2.07 and 1.92	Between 14.7 and 20.9	2.43
One parent the offspring of a marriage between first cousins...	1.93	17.2	2.34

[1]Sterility means absence of children surviving infancy.

The comparison may be best effected by means of the numbers in the last column. The figures in the second column are not of much value, since in some cases it was difficult to decide whether the entry should be made as being a case of ''no information'' or of sterility.

The comparison of the figures in the first and last columns shows, without much room for doubt, that the alleged infertility of consanguineous marriages, whether direct or indirect, cannot be substantiated.

I now pass on to the question of the youthful death-rate.

It has been stated by M. Boudin and others that the offspring of consanguineous marriages suffer from an excessively high rate of infant mortality. I have tried to put this to the proof as follows:

I recurred to the families in the ''Peerage'' which were offspring of first cousins, and marked every case where it is recorded that a son or daughter died in infancy or youth. Where the age of the child was mentioned, ten years was taken as the standard of youth.

''Burke's Landed Gentry'' was of no avail in this inquiry, because I found that children dying in infancy were never, or very rarely, mentioned therein.

From the ''Peerage'' I could only obtain 37 fertile first-cousin marriages; in two of these there were no children surviving youth. The 37 gave 86 sons, who survived infancy, 15 children (boys and girls) who died in infancy or youth, and 4 more as to whom the period of death was doubtful. Besides this, it is stated of one family, that ''all died young except one daughter.'' Now in the previous part of this paper it is shown that the average number of sons to a fertile first-cousin marriage is nearly 2½; so that it may not be unreasonable to credit this family with 4 infants who died.

On this supposition we should have 37 fertile marriages of first cousins giving 86 sons, who survived, and between 23 and 19 boys and girls who died early. Reducing these numbers to percentages, I find that –

One hundred fertile marriages of first cousins would give from 51 to 62 children who die young, and that for every 100 son, offspring of first cousins, who survive youth, there are from 22 to 27 boys and girls (their brothers and sisters) who die early.

These numbers cannot be used as giving the actual infant death rate, on account of the imperfections in the pedigrees in the ''Peerage,'' but they may be used in a comparison with other statistics deduced from the same source.

Now 89 fertile non-consanguineous marriages (collected by chance from the ''Peerage'') gave 197 sons, and 44 sons and daughters who died young. Reducing these numbers to percentages as before, I find-

That 100 fertile non-consanguineous marriages would give 49 children who die young, and that for every 100 sons, offspring of fertile non-consanguineous marriages, who survive infancy, there are 22 boys and girls (their brothers or sisters) who die early.

The numbers to be compared are therefore 51 or 62 with 49, and 22 or 27 with 22.

These are merely two diferent ways of consulting the facts, and it appears that both methods give some evidence of a slightly lowered vitality amongst the offspring of first cousins.

Thirty-seven cases form, however, far too small a total on which to base satisfactory statistics. The numbers thus collected are far scantier than those collected by others, but as far as I am aware this is the only occasion in which the method of collection has been one in which the unconscious bias of the collector could not operate. In all these inquiries I was ignorant as to whither the figures were tending until I came to add up the totals.

This last inquiry is, I fear, worth but little, but so far as it goes it tends to invalidate the alleged excessively high death-rate amongst the offspring of cousins, whilst there remains a shade of evidence that the death-rate is higher than amongst the families of non-consanguineous parents.

IV. Conclusion

In my paper as read before the Statistical Society, the writings on this subject of some previous authors were reviewed. I may mention that Dr. Arthur Mitchell, of Edinburgh, conducted an extensive inquiry, and came to the conclusion that, under favourable conditions of life, the apparent ill-effects were frequently almost nil, whilst if the children were ill fed, badly housed and clothed, the evil might become very marked. This is in striking accordance with some unpublished experiments of my father, Mr. Charles Darwin, on the in-and-in breeding of plants; for he has found that in-bred plants, when allowed enough space and good soil, frequently show little or no deterioration, whilst when placed in competition with another plant, they frequently perish or are much stunted.

It will be observed that my investigation, so far as it is worth anything, tends to invalidate this opinion; but perhaps the apparent invalidation is due to the fact, that a large majority of Englishmen live under what are on the whole very favourable circumstances. Some authors (notably M. Boudin) express the most alarming opinions as to the evils of consanguineous marriage and support the opinion with large arrays of figures. Almost on all sides is found a general consent, as to the ill-effects of cousin marriages, which must certainly have far greater weight than my purely negative results. But it strikes me that in no case has the investigation been free from flaws, for in no case has it been really determined what is the proportion of consanguineous marriages in the whole population. The very various estimates which different people have given me of the frequency of cousin-marriages (from 10 per cent. down to 1 in 1,000, if my memory serves me right), lead me to believe that general

impressions on this point are almost valueless. Every observer is biassed by the frequency or rarity of such marriages amongst his immediate surroundings.

My own opinion is that the evil has been often much exaggerated, but that there are nevertheless grounds for asserting that various maladies take an easy hold of the offspring of consanguineous marriages.

My paper is far from giving anything like a satisfactory solution of the question; but it does, I think, show that the assertion that it has already been set at rest, cannot be substantiated.

The subject still demands attention, and I hope that my endeavour may lead more competent investigators to take it up from some other side.

1 Darwin GH. Marriages between first cousins in England and their effects. Fortnightly Review 1875;24:22–41.
This article is a part of a paper read before the Statistical Society of London, on the 16th of March last. The Society has courteously permitted its publication in this Review simultaneously with its appearance in their Journal for this month. The reader will find in the Journal further details, and a discussion of some of the previous writings on the subject of consanguineous marriages.
2 Compare this with 1.25 deduced from *Pall Mall Gazette*.
3 The circulars were ready stamped for return, which would induce many to return them by saving trouble.
4 I may mention that Mr. Clement Wedgwood made very careful inquiries for me concerning 149 marriages of skilled artisans in the Potteries, and did not find a single case of first-cousin marriages, and only three where there was any kind of relationship between the husband and wife. He was further assured, that such marriages never take place amongst them.
5 ''Studj sui Matrimonj Consanguinei.'' Milan 1868.
6 ''Annales d'Hygiène Publique,'' tom xviii. Pp 5–82.
7 ''Comptes Rendus.'' Tom. lvi. P. 135.

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Commentary: A Darwin family concern

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'I'm not quite sure that it's a good thing for cousins to marry', remarks Dr Crofts in Trollope's *The Small House of Allington*, published in 1863. 'They do, you know, very often', he is reminded, 'and it suits some family arrangements'.[1] To be sure, the doctor had a personal interest in the matter. A young woman he hoped to marry had just become engaged to her cousin. However, Dr Crofts was talking as a responsible medical man. The British medical press was raising questions about the risks to offspring of cousin marriages,[2,3] and a bright young doctor would have been familiar with the professional debates. (And in the end he gets his girl.)

Charles Darwin had picked up on these concerns very early. He was worried about heredity and also about the consequences of cousin marriage. Shortly before his own marriage to his first cousin, Emma Wedgwood, he had consulted a new book, Alexander Walker's *Intermarriage: Or the Mode in Which, and the Causes Why, Beauty, Health, and Intellect Result from Certain Unions, and Deformity, Disease and Insanity from Others* (1838). It touched a sensitive nerve. His Darwin grandmother, the wife of Erasmus Darwin, was addicted to gin and suffered from bouts of madness. Charles Darwin's own mother, unwell throughout his childhood, had died from an agonizing stomach ailment, probably peritonitis, at the age of 52 years. Charles was 8 years old when she died, and as an adult he was obsessively concerned with his own ill-health, particularly the recurrent stomach complaints that recalled his mother's fatal illness. Both his mother and Emma were Wedgwoods, and the Wedgwoods were notorious for their ill-health.[4] Whenever one of his children fell ill, Charles was inclined to see the same symptoms in himself, and to worry that it exposed a family propensity.

Or were the frequent illnesses of his children, and the health problems of the Wedgwoods, perhaps the consequence of cousin marriages?[5] This was a growing concern in scientific circles in Britain in the 1860s.

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'In many families, marriages between cousins are discouraged and checked', Francis Galton noted in 1865.[6] Charles Darwin's son George published an early paper recommending that cousin marriage should be avoided.[7]

The first thorough study of the subject in the UK was published in 1865, by Arthur Mitchell, Deputy Commissioner in Lunacy for Scotland. Scotland was an obvious choice. It was widely believed that marriage between close relatives was rampant in remote Scottish regions, particularly the Highlands and Islands. Mitchell noted that popular opinion in Scotland condemned 'blood-alliances' as 'productive of evil'.[8] And indeed national statistics showed that ~14% of 'idiots' in Scotland were children of kin. In 44% of families with more than one mentally handicapped child, the parents were blood relatives. Six per cent of the parents of deaf mutes were close relatives. Nonetheless, Mitchell was not convinced that this was the whole story. Fewer than 2% of marriages in Scotland were between first and second cousins. The rate was indeed higher in some isolated regions, but the evidence for bad effects was uncertain. In one small town on the north-east coast of Scotland, 9% of marriages were with first cousins and 13% with second cousins. Mitchell acknowledged that the children of these cousin marriages were often unprepossessing, but then many fishing families in the region were 'below par in intellect'.[8] A more telling case was Berneray–Lewis (now Great Bernera, off the Isle of Lewis). Here, 11% of marriages were with first and second cousins, yet Mitchell remarked that 'instead of finding the island [Berneray-Lewis] peopled with idiots, madmen, cripples and mutes, not one such person is said to exist in it'.[8]

Perhaps environmental factors—'occupation, social habits, etc.'—influenced the outcome. One 'shrewd old woman' remarked to him—'But I'll tell ye what, Doctor, bairns that's hungert i' their youth aye gang wrang. That's far waur nor sib marriages'.[8] Mitchell concluded that close-kin marriage tended to reinforce 'evil influences'.

Darwin was fascinated. Between 1868 and 1877, he published three monographs on cross-fertilization in animals and plants.[9–11] In the first of these books, *The Variation of Animals and Plants under Domestication*, he proposed that 'the existence of a great law of nature is almost proved; namely, that the crossing of animals and plants which are not closely related to each other is highly beneficial or even necessary, and that interbreeding [i.e., inbreeding] prolonged during many generations is highly injurious'.[9]

Darwin thought this was probably true of human beings, although he was reluctant at first to press the issue. ('Before turning on to Birds, I ought to refer to man, though I am unwilling to enter on this subject, as it is surrounded by natural prejudices'.)[9] However, he was bound to consider the implications for his own family. His scientific project and his personal concerns could hardly be separated. 'The philosophical difficulties and practical consequences of cousin marriages troubled him for years afterwards', Janet Browne observes.[5] 'There was no other theme in Darwin's science that more clearly reflected the personal origins of his intellectual achievement. He could scarcely have arrived at pangenesis without this attention to his marriage, his children's ill health, and his own sickness'.

He began to canvass his correspondents. William Farr—the senior statistician in the Registrar General's office—suggested to him that the 1871 census should include a question on cousin marriage.[12] Darwin began to lobby for it. His neighbour and ally, John Lubbock, had just been elected to parliament. In the summer of 1870, Darwin asked him to put Farr's proposal to the House. He even drafted arguments for Lubbock to use.

> In England and many parts of Europe the marriages of cousins are objected to from their supposed injurious consequences; but this belief rests on no direct evidence. It is therefore manifestly desirable that the belief should either be proved false, or should be confirmed, so that in this latter case the marriages of cousins might be discouraged. If the census recorded cousin marriages it could be established whether they were less fertile than the average. Later it might also be possible to find out whether or not consanguineous marriages lead to deafness, and dumbness, blindness, &c.[13]

Lubbock put it to the House that 'consanguineous marriages were injurious throughout the whole vegetable and animal kingdoms'. It was obviously 'desirable to ascertain whether that was ... the case with the whole human race'.[14] The response was unenthusiastic. One member remarked that Parliament was already busy every year debating the legality of marriage with the deceased wife's sister: 'if there were to be legislation about the marriage of first cousins also, the whole time of the House would be taken up in deciding who was to be allowed to marry anybody else'.[14] According to George Darwin, the proposition was rejected, 'amidst the scornful laughter of the House, on the ground that the idle curiosity of philosophers was not to be satisfied'.[15] Yet 45 members voted for Lubbock's motion in committee. Ninety-two voted against, but Lubbock remarked in his summing up that virtually everyone who spoke shared his concern.[14]

Farr now proposed to Darwin that an 'inquiry might be undertaken through private channels'.[16] Darwin agreed. He entrusted the study to his eldest son, George. George Darwin was not only an amateur genealogist but was also an accomplished mathematician. And influenced by the eugenic theories of his cousin Francis Galton, he had advocated controls

on marriage between unsuitable partners. He recommended that the mentally ill should be kept from marrying, and suggested that there might be good scientific reasons to prevent the marriage of first cousins.[17] Clearly, he was primed for his father's commission.

Charles Darwin laid out the research design. George was to compare the incidence of close-kin marriage in the general population with that among the parents of patients in asylums. If it turned out that marriages between close relatives produced a disproportionate number of 'diseased' children, this would 'settle the question as to the injuriousness of such marriages'.[18]

The first step was to find out how common it was in England for first cousins to marry. Apparently nobody knew the answer. George Darwin was given estimates that ranged from 10 to 1% in a 1000. 'Every observer', he concluded, 'is biassed by the frequency or rarity of such marriages amongst his immediate surroundings'.[15] He would have to discover the facts for himself. Expert in the new statistical techniques that were being developed by Farr and Francis Galton, George decided to attempt a scientific survey—one of the very first statistical studies of a social problem in the UK. After making ingenious use of public records and mail questionnaires, he concluded that ~4.5% of marriages in the aristocracy were with first cousins; 3.5% in the landed gentry and the upper middle classes; ~2.25% in the rural population; and among all classes in London, ~1.l5%.

The next step was to gather statistics from mental asylums. Charles Darwin wrote on George's behalf to the heads of the leading institutions. Several provided detailed responses. These indicated that only 3–4% of patients were the offspring of marriages between first cousins. 'For Heavens sake', Charles urged his son, 'put a sentence in some conspicuous place that your results seem to indicate that consanguineous marriage, as far as insanity is concerned, cannot be injurious in any very high degree'.[18] George complied. 'It will be seen [he concluded] that the percentage of offspring of first-cousin marriages [in mental asylums] is so nearly that of such marriages in the general population, that one can only draw the negative conclusion that, as far as insanity and idiocy go, no evil has been shown to accrue from consanguineous marriages'.[15]

Other studies suggested that the offspring of cousin marriages were more likely to suffer from blindness, deafness or infertility. George accepted that these conditions were highly hereditary, but saw no convincing evidence that they were caused by cousin marriage. In fact, first-cousin marriages were, if anything, more fertile than others. Presumably a man was more likely to marry a cousin if he had many to choose from. First-cousin marriage would therefore be more common among people who came from large—and so presumably fertile—families.[15]

Only one small piece of evidence gave George pause. Among men who had rowed for Oxford or Cambridge, men who were obviously the fittest of the fit, sons of first cousin parents appeared slightly less frequently than might have been expected (2.4% as opposed to 3–3.5% among their peers).[19]

George Darwin was well aware that his conclusions flew in the face of a common and ancient prejudice. He conceded that marriages between cousins might be quite all right for the rich but bad for the poor.

> I may mention that Dr Arthur Mitchell, of Edinburgh, conducted an extensive inquiry, and came to the conclusion that, under favourable conditions of life, the apparent ill-effects were frequently almost nil, whilst if the children were ill fed, badly housed and clothed, the evil might become very marked. This is in striking accordance with some unpublished experiments of my father, Mr Charles Darwin, on the in-and inbreeding of plants; for he has found that in-bred plants, when allowed enough space and good soil, frequently show little or no deterioration, whilst when placed in competition with another plant, they frequently perish or are much stunted.[15]

In short, cousin marriage caused no harm in the best families. Charles Darwin endorsed these conclusions.[9] In later editions of *Variation*, he modified his original rule, weakening the claim: 'it is a great law of nature, that all organic beings profit from an *occasional* cross with individuals not closely related to them in blood'[9] (emphasis added). On the other hand, the experience of animal breeders indicated that 'the advantage of close interbreeding [i.e., inbreeding], as far as the retention of character is concerned, is indisputable, and often outweighs the evil of a slight loss of constitutional vigour'.[9]

Francis Galton wrote enthusiastically to George Darwin that he had 'exploded most effectually a popular scare'. He added that his cousin could make a fortune from his discovery.

> Thus: there are, say, 200,000 annual marriages in the kingdom, of which 2,000 and more are between first cousins. You have only to print in proportion, and in various appropriate scales of cheapness or luxury: WORDS of Scientific COMFORT and ENCOURAGEMENT To– COUSINS who are LOVERS then each lover and each of the two sets of parents would be sure to buy a copy; i.e. an annual sale of 8,000 copies!! (Cousins who fall in love and don't marry would also buy copies, as well as those who think that they might fall in love.) [20]

Galton's protégé, Karl Pearson, made a follow-up study in 1908. He was less systematic than George Darwin, relying on correspondence from readers of

the *British Medical Journal*. These selected respondents reported a very high incidence of first-cousin marriages in their families. A smaller proportion of marriages were with more distant cousins, but Pearson remarked that second and third cousins in these families were also often related in more than one line. He lumped them all together and concluded that 'consanguineous marriages in the professional classes probably occur in less than 8% and more than 5% of cases'. Yet, only 1.3% of patients in the Great Ormond Street Hospital for Children were the children of cousins. Pearson concluded that 'the diseases of children are not largely due to any consanguinity between their parents'.[21]

Endorsed by the Darwinian establishment, George Darwin's conclusions reassured many people whose family trees featured marriages between cousins. Englishmen could also rest more easy when they considered that Queen Victoria was married to a first cousin, and that several of her descendants had also married cousins. And Darwin's conclusions seemed only common sense to landowners in the House of Lords, who knew that the inbreeding of good stock was sound policy.

Conflict of interest: None declared.

References

[1] Trollope A. *The Small House of Allington*. London: George Smith, 1864.

[2] Gardner J. On the intermarriage of relations as the cause of degeneracy of offspring. *Br Med J* 1861;**1:**290.

[3] Child G. On marriages of consanguinity. *British and Foreign Medico-Chirurgical Review* 1862;**29:**461–71.

[4] Browne J. *Charles Darwin: Voyaging*. London: Jonathan Cape, 1995.

[5] Browne J. *Charles Darwin: The Power of Place*. London: Jonathan Cape, 2002.

[6] Galton F. Hereditary talent and character. *Macmillan's Magazine* 1865;**12:**319.

[7] Darwin GH. On the intermarriage of relations as the cause of degeneracy of offspring. *Contemp Rev* 1873;**22:**412–26.

[8] Mitchell A. On the influence which consanguinity in the parentage exercises on the offspring. *Edinburgh Medical Jl* 1864–5;10:781–94, 894–913, 1074–85.

[9] Darwin C. *The Variation of Animals and Plants Under Domestication*. London: John Murray, 1868.

[10] Darwin C. *The Effects of Cross and Self Fertilization in the Vegetable Kingdom*. London: John Murray, 1876.

[11] Darwin C. *The Various Contrivances by which Orchids are Fertilized by Insects*. London: John Murray, 1877.

[12] Farr W (to Darwin). *The Darwin Correspondence*. Cambridge University Library, 1868; http://www.darwinproject.ac.uk/.

[13] Darwin C. (to Lubbock J.). *Darwin Correspondence*. Cambridge University Library, 1870 (reproduced in Darwin F. (ed.), *The Life and Letters of Charles Darwin*, London: John Murray, 1887); http://www.darwinproject.ac.uk/.

[14] 44 Hansard, 34d ser., cciii, col. 1870:817–1010.

[15] Darwin GH. Marriages between first cousins in England and their effects. *Jl Statistical Soc* 1875;**xxxviii:**153.

[16] Farr W. (to Darwin C.). *Darwin Correspondence*, Cambridge University Library, 1870; http://www.darwinproject.ac.uk/.

[17] Darwin GH. On the beneficial restrictions to liberty of marriage. *Contemp Rev* 1873;**22:**412–26, 424.

[18] Darwin (to Darwin GH). *Darwin Correspondence*. Cambridge University Library, 1874; http://www.darwinproject.ac.uk/.

[19] Darwin GH. Note on the marriages of first cousins. *Jl Statistical Soc* 1875;**xxxviii:**344–48.

[20] Pearson K. *The Life, Letters and Labours of Francis Galton*. Cambridge: Cambridge University Press, pp. 1914–30.

[21] Pearson K. Cousin marriages. *The British Medical Jl* 1908;**1:** 1395.

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Commentary: Of the same blood

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All human beings are related, and some are more closely related than others. In medical and demographic literature, consanguineous marriage is usually defined as marriage between a man and a woman who are related as second cousins or closer.[1] First-cousin marriage is supposed to be the most prevalent form globally. Effects on disease and death have been demonstrated primarily among children of

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parents who are related as first cousins or closer, whereas it is not clear that similar effects are seen among children of parents who are second cousins or more distant relatives. Recent studies on the frequency of consanguinity have shown that it is not rare and declining in human populations, but prevalent and perhaps increasing globally. To date, studies on the effects of consanguinity at a population level have not been successful in establishing consensus about the kinds and sizes of these effects. However, as other causes of disease and death are declining in many regions of the world where consanguinity is prevalent, the relative importance of consanguinity as a risk factor for disease and death increases.[2–4] A project to determine the global burden of disease due to consanguinity has been established under the leadership of Alan H Bittles, and the results of this project will be important for evaluating the public health impact of consanguinity worldwide (Alan H Bittles, personal communication).

The global prevalence of consanguineous marriage

Historically, there has been a diversity of rules concerning marriage between close relatives, changing over time, and varying between different societies and social classes. There are indications that the ancient Egyptians in certain periods encouraged mating between brothers and sisters. Cleopatra VII was the child of a brother and a sister. She married her two younger brothers, but had no children with them. Later, she gave birth to children in her relations with Marcus Antonius and Julius Caesar.[5]

It is now clear that consanguineous marriage is common in many parts of the world. The most thorough overview of the global prevalence of consanguineous marriage has been compiled by the British–Australian geneticist and professor Alan H Bittles. He has conducted extensive research on the prevalence and medical consequences of consanguineous marriage during the last three decades, and is the leading international authority within the field. The overview is accessible at Bittles' web site http://www.consang.net [6] and in several of his publications.[1,7–9]

According to current studies, consanguineous marriage is most common in North Africa, the Middle East, Western Asia and South India. In these areas, 20–50% of all marriages are between consanguineous partners. In South America, North India and Central Asia, the proportion is 1–10%. In other words, more than half of the world's population live in areas where consanguineous marriage is widespread.

In Japan, consanguineous marriage used to be common, but the tradition declined as the country was industrialized and became prosperous after World War II.[1] It was also common in China until recently, but first cousin marriage was prohibited by law in 1981.[1] In Europe, Russia, North America and Australia, consanguineous marriage is rare in the population as a whole, but it is practiced within ethnic and religious minorities.[1] There is a lack of data, particularly from Southeast Asia and sub-Saharan Africa, but surveys have shown that consanguineous marriage is common in Indonesia and in several sub-Saharan countries.

Consanguineous marriage cannot be linked to any specific religion or religious rules. It is practiced among people of various religions, and the attitudes towards consanguineous marriages vary among followers of the same religion.[1] At present, it is supposed to be most common in societies where Islam is the dominant religion.[6] In India, the Aryan Hindus of North India have customs prohibiting consanguineous marriage in five generations on the woman's side of the family, and seven generations on the man's side. The Dravidian Hindus of South India, on the other hand, practice consanguineous marriage extensively, both first-cousin and uncle–niece marriages.[8] Within Christianity, customs have varied. The Catholic Church has a ban on first-cousin marriage, but exceptions can be granted upon request.[9,10] Orthodox churches prohibit both first-cousin and second-cousin marriage.[9,10] Protestant churches have no such restrictions.[8,11] Likewise, Judaism and Buddhism have no bans on first-cousin or second-cousin marriages.[8,11]

Incestuous marriages, i.e. marriage between siblings, or between parents and children, are prohibited in most societies and religions. Very few countries have laws against first cousins or more distant relatives getting married. First-cousin marriage is prohibited in 30 American states,[8] and in China, as previously mentioned. It is legal in all other countries. No countries prohibit second-cousin marriage.

There are many possible reasons why so many societies prefer marriages within the family.[1] In poor countries, the family is often the main—sometimes the only—provider of welfare and security. The choice of spouse is not only a matter of personal preference, but also a matter of securing the welfare and property of the family. In most countries where consanguineous marriage is common, it is most prevalent among those with low income and little education, and among people living in rural areas.[1] This pattern is not without exceptions, because consanguineous marriage is also practiced by rich families to preserve properties and estates. Consanguinity was common among European royalty and aristocracy up until the middle of the 1900s, and the two first Norwegian kings after independence from Sweden in 1905, Haakon VII and Olav V, were both married to first cousins, the British Queen Maud and the Swedish Crown Princess Märtha, respectively. As described by Adam Kuper[12] in a commentary in this issue of the *IJE*, George Howard Darwin (1845–1912) published a study in 1875 on '*Marriages between first cousins in*

England and their effects',[13] where he made an immense effort to make up for the evidence lost when a proposal to insert the words 'Were your father and mother first cousins or not?' in an upcoming census was defeated in the House of Commons. George Darwin describes in a personal tone, with great detail and honesty, how he suffers the ordeals of complex data collection, only to achieve data that are at best indicative of what he could have had if the information had been collected routinely from the total population.

Rediscovering consanguinity

Studies on consanguinity have to a large extent aimed at identifying patterns of inheritance and single mutations in families where rare diseases occur, whereas there has been limited interest in the gross effects of consanguinity on a population level. Although some countries, such as Pakistan, have included questions about consanguinity in demographic surveys and censuses, there is, to the author's best knowledge, no country in the world other than Norway that performs routine registration of close biological relations between parents.[1]

A small group of people has been important for the rediscovery of the high prevalence and effects of consanguinity, and for introducing epidemiological perspectives into the field. In 1987, Khoury and collaborators published a review of studies on the effects of consanguinity on mortality before the age of 20 years, using relative and attributable risks to assess the role of consanguinity.[10] Khoury then concluded, in line with textbooks and common perceptions at the time, that consanguinity was rare and had little effect both on an individual level and on public health. The belief that frequencies of consanguinity were low and declining was challenged a few years later when Allen Bittles and his collaborators published a groundbreaking article in '*Science*', where they estimated that between 20 and 50% of all marriages in many regions of Africa and Asia are consanguineous.[7] In the same year, Khlat and Khoury reviewed reports that the proportions of consanguineous marriages in Arab countries ranged between 22 and 54%.[14] After 1991, several reports on high frequencies of consanguinity have been published. For example, data from the 1990/91 Pakistan Demographic and Health Survey showed that at a national level 49.4% of all marriages were between first cousins, 10.8% were between second cousins and 1.4% were categorized as between other cousins.[15] One reason why the high global prevalence of consanguinity was discovered in the 1990s may be that it is common in some immigrant populations of Western Europe, as shown in British and Norwegian studies.[16–18] Sarah Bundey and collaborators estimated the coefficients of inbreeding for babies in Birmingham using ancestral information for four generations, showing that 69% of the Pakistani children had parents who were closely related, and 40% had parents who were more closely related than first cousins.[16] Data from the Medical Birth Registry and Statistics Norway show that among parents with Pakistani origin, ~44% were related as first cousins or closer and the total prevalence of parental consanguinity was 55% up until 2001, after which the proportion of couples who are first cousins has declined to about 29% and the total prevalence to 40%, thus showing a decline in the frequency of consanguineous marriage over time and generations since the 1980s.[3,18]

Genetic effects of consanguinity

Careful examination of inbred families is a widely used method for identifying recessive diseases, but studies on consanguinity can be used to evaluate the effect of increased homozygosity in any disease. The probability of homozygosity for any allele increases, including alleles that are deleterious and may cause disease and death. Consequently, offspring of consanguineous parents are at an increased risk both for monogenic autosomal recessive disorders and for conditions with multifactorial inheritance. Theoretically, the increase in risk is proportional to the degree of inbreeding (expressed as the coefficient of inbreeding, F). For conditions with recessive inheritance the relative increase may be considerable, whereas for multifactorial inheritance, the risk to offspring of consanguineous parents is moderately increased 'relative' to the risk to offspring of unrelated parents.

The theoretical model for conditions with an underlying continuous liability and a threshold for disease is outlined by Falconer.[19] The model assumes that genetic action is additive, and that the phenotype reflects the summed effect of a number of genetic and environmental risks, each with small or moderate influence. Under these circumstances, the liability is assumed to be normally distributed in the general population. Consanguinity increases the population variance of traits that are determined by several genes and continuously distributed in the population, whereas there may be no, or only slight, depression of the mean. The depression of the mean is due to dominance deviations, which are interactions between alleles at a locus or epistasis, resulting in non-additivity.[19] Increased variance and depression of the mean due to consanguinity have been demonstrated for birth weight.[11] When the model is extended to offspring of consanguineously related parents, the distribution of the liability for disease will still be normal and the threshold for disease will be the same. However, a larger proportion of the population develops the disease due to the greater variance in the population.[20] This phenomenon is illustrated in Figure 1.

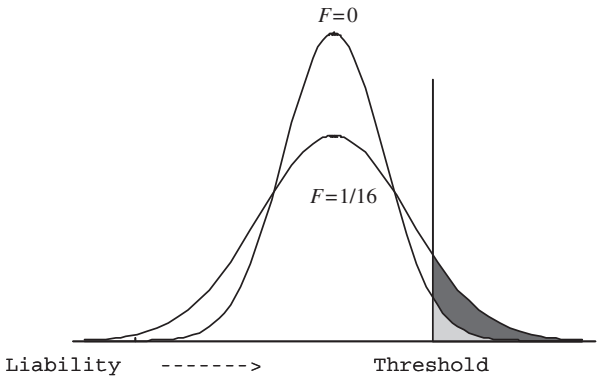

Figure 1 Distribution of genetic liability with random mating and with first-cousin mating (coefficient of inbreeding $F = 1/16$). The areas at the right of the threshold indicate the increase in frequency of a threshold character. Adapted from Vogel and Motulsky 1997, chapter 6 'Formal Genetics of Humans: Multifactorial Inheritance and Common Diseases', page 214, figure 6.20. Springer-Verlag Berlin Heidelberg with kind permission of Springer Science plus Business Media[20]

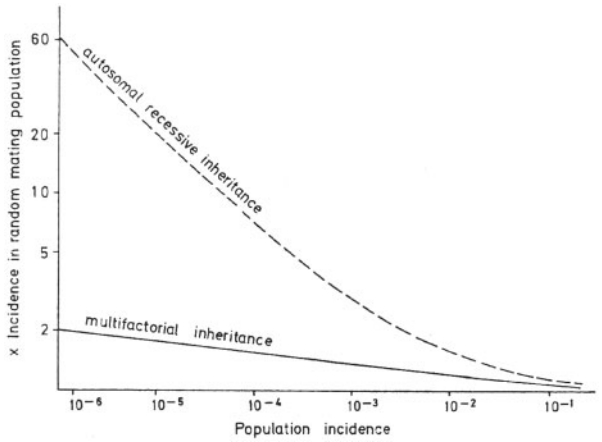

Figure 2 Increased risk of autosomal recessive and multifactorial characters among children from first-cousin matings compared with the population risk. Adapted from Vogel and Motulsky 1997 chapter 6 'Formal Genetics of Humans: Multifactorial Inheritance and Common Diseases', page 214, figure 6.21. Springer-Verlag Berlin Heidelberg

The 'relative risk' of recessive and multifactorial conditions for inbred children 'decreases' as the risk for these conditions increases in the general population (Figure 2). However, the 'absolute' difference in risk between the inbred and the non-inbred groups may be constant, despite changes in the risk for the non-inbred population. A constant risk difference between offspring of first-cousin parents and unrelated parents has been demonstrated for death before the age of 10 years in a meta-analysis of data from populations with different mortality rates in the reference group.[21]

Conditions that have a monogenic 'autosomal dominant inheritance' may also be more prevalent among offspring of consanguineous parents.[22] Homozygosity of dominant genes may be associated with an earlier age at onset, higher penetrance and more serious development of the disease compared with the heterozygous state.

There are few studies on the potential positive biological effects of consanguinity among humans. Plant and animal breeding is a well-known method for producing traits that are advantageous for specific purposes or under specific environmental conditions. Theoretically, there will be similar effects in inbred human populations that should be possible to demonstrate with appropriate data. Some studies, including a recent intriguing study from Iceland,[23] have demonstrated positive associations between consanguinity and fertility. However, most of these studies have serious problems accounting for possible residual confounding due to socio-economic and cultural factors.

Effects of consanguinity on disease and death

The biological basis for the influence of parental consanguinity on birth defects and early death is well established through case reports, experimental studies on animals and plants and studies of familial aggregation of specific recessive diseases. In spite of the extraordinarily strong evidence, it has been challenging to establish the effects of consanguinity on mortality and morbidity in human populations.[9,10,14,15] In addition to the general dearth of data, both on consanguinity and relevant outcomes, these difficulties are primarily due to insufficient information on socio-economic factors, rarity of the condition under study, small samples, problems with definitions and ascertainment of the outcomes, aggregation of different types of consanguineous marriages diluting the effect of inbreeding and refined categorization of consanguineous types leading to loss of statistical power.

Generally, the effects of consanguinity on infant death seem to be the most consistent result in studies of human inbreeding, whereas the results for stillbirth and birth defects tend to vary from no effect to small effects when measured as relative risks. In a registry-based Norwegian study, the number of first-cousin marriages was sufficiently large and the analyses adjusted for the effects of socio-economic factors, maternal age, parity and other possible confounders in multivariate analyses.[2,3] The Norwegian data show, for the first time, a significant effect of consanguinity on stillbirth, and also indicates an effect of consanguinity on mortality throughout childhood and young adulthood, in addition to the expected effects on infant death and birth defects.[3]

Almost all studies of the effects of consanguinity on populations focus on early death and congenital disorders. So far, very few have addressed adult diseases although there is clearly a large potential for such studies in populations where consanguinity is prevalent, provided that it is possible to obtain reliable data in an ethically and culturally sustainable way.

How should we measure effects of consanguinity?

Does the effect of consanguinity differ under different circumstances? This question was addressed by Khoury and others who found indications of smaller effects due to consanguinity in populations with high vs low mortality rates.[10] In his analysis, the measures of association were relative risks, and public health impact was measured as population-attributable risks. The results were interpreted as possible support for the theory of 'washing out' of deleterious recessive genes over generations of inbreeding. By definition, relative risks are dependent on the occurrence of the condition in the control group representing the general or the non-consanguineous population, and will, therefore, necessarily be lower when baseline rates are higher. Consequently, analysis of the effects of consanguinity (or any other exposure for that sake) should not rely solely on the comparison of relative risks. An analysis of excess risks of pre-reproductive death for offspring of first cousin parents revealed that the absolute effect of consanguinity on stillbirth (from ~24 weeks of gestation) and childhood mortality (children followed up to a median of 10 years) was constant (4.4%) across a wide range of population risks of pre-reproductive death.[21] A limitation of Bittles' and Neel's study was that there was no adjustment for socio-economic differences between the consanguineous and non-consanguineous groups within each population. This may have inflated the estimates of the excess risk for children with consanguineous parents, particularly in populations with large mortality differences between socio-economic groups. In some Norwegian studies of consanguinity we have used a multivariate model that adjusts for other variables and estimates the adjusted excess risk.[17,24] Hence, adjusted excess risks may replace relative risks (or odds ratios) as measures of association, allowing for comparisons between populations with different background risks. A comparison of data from Pakistan, The Middle East, Britain and Norway showed that the excess risks for infant death among children of first-cousin parents were similar (excess risks were 18, 15, 12 and 12 per 1000 live births, respectively), whereas the relative risks pointed in the opposite direction and varied according to the overall mortality in the population (relative risks were approximately 1.3, 1.5, 2 and 2, respectively), evidently with lower relative risks in the population (Pakistan) with high infant mortality rates in the non-consanguineous group.[2,15,25–28] The proportion of infant deaths that could be contributed to consanguinity in Pakistan was ~15% (with an overall infant mortality rate of 99/1000), whereas the corresponding proportion in Norway was 41% (among immigrants from Pakistan with an infant mortality rate of 14/1000). This illustrates that relative risks, excess risks and population-attributable risks should all be considered when the effects of consanguinity are assessed.

New opportunities

There are at least three good reasons for increasing the scientific focus on consanguinity. First, cousin marriages are very common in the world today; secondly, the evidence for the detrimental biological effects of consanguinity is strong but not well documented and evaluated in large human populations; and thirdly, new genetic technologies provide opportunities for studies in consanguineous populations aiming at discovering genetic factors in human traits and disease in general. For example, homozygosity mapping is a technique which is used to identify recessive mutations in consanguineous families.[29] Morrow and co-workers used this technique to identify autism genes in consanguineous families, demonstrating the usefulness of such families in genetic studies of common complex diseases.[30]

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References

[1] Bittles AH. The role and significance of consanguinity as a demographic variable. *Popul Dev Rev* 1994;**20:**561–84.

[2] Stoltenberg C. Birth defects, stillbirth and infant death. Epidemiological studies of the effects of consanguinity and parental education. Births in Norway 1967–1995. Thesis: Faculty of Medicine. The University of Oslo. *Nor J Epidemiol* 1998;**8 (Suppl 2):**1–120.

[3] Surén P, Grjibovski A, Stoltenberg C. Consanguinity in Norway. *Report* 2007;**2:**1–64.

[4] Pedersen J. Determinants of infant and child mortality in the West Bank and Gaza Strip. *J Biosoc Sci* 2000;**32:** 527–46.

[5] Jorde LB. Inbreeding in human populations. In: Dulbecco R (ed.). *Encyclopedia of Human Biology*. San Diego: Academic Press, 1991, pp. 431–41.

[6] Bittles AH. Consanguinity/Endogamy Resource. http://www.consang.net (14 August 2009, date last accessed).

[7] Bittles AH, Mason WM, Greene J, Rao NA. Reproductive behavior and health in consanguineous marriages. *Science* 1991;**252:**789–94.

[8] Bittles AH. Consanguinity and its relevance to clinical genetics. *Clin Genet* 2001;**60:**89–98.

[9] Bittles AH. Empirical estimates of the global prevalence of consanguineous marriage in contemporary societies. Paper number 0074. *Centre for Human Genetics, Edith Cowan University, Perth, Australia and Morrison Institute for Population and Resource Studies*. California, USA: Stanford University, 1998.

[10] Khoury MJ, Cohen BH, Chase GA, Diamond EL. An epidemiologic approach to the evaluation of the effect of inbreeding on prereproductive mortality. *Am J Epidemiol* 1987;**125:**251–62.

[11] Magnus P, Berg K, Bjerkedal T. Association of parental consanguinity with decreased birth weight and increased rate of early death and congenital malformations. *Clin Genet* 1985;**28:**335–42.

[12] Kuper A. Commentary: A Darwin family concern. *Int J Epidemiol* 2009;**38:**1439–42.

[13] Darwin GH. Marriages between first cousins in England and their effects. *Fortnightly Review* 1875;**24:**22–41. Reprinted *Int J Epidemiol* 2009;**38**:1429–39.

[14] Khlat M, Khoury M. Inbreeding and diseases: demographic, genetic, and epidemiologic perspectives. *Epidemiol Rev* 1991;**13:**28–41.

[15] Grant JC, Bittles AH. The comparative role of consanguinity in infant and childhood mortality. *Ann Hum Genet* 1997;**61:**143–49.

[16] Bundey S, Alam H, Kaur A, Mir S, Lancashire RJ. Race, consanguinity and social features in Birmingham babies: a basis for prospective study. *J Epidemiol Comm Health* 1990;**44:**130–35.

[17] Stoltenberg C, Magnus P, Skrondal A, Lie RT. Consanguinity and recurrence risk of stillbirth and infant death. *Am J Publ Health* 1999;**89:**517–23.

[18] Grjibovski A, Magnus P, Stoltenberg C. Decrease in consanguinity among parents of children born in Norway to women of Pakistani origin: a registry-based study. *Scand J Publ Health* 2009;**37:**232–38.

[19] Falconer DS. *Introduction to Quantitative Genetics*. 2nd edn. London: Longman, 1981.

[20] Vogel F, Motulsky AG. *Human Genetics*. 3rd edn. Berlin: Springer, 1997.

[21] Bittles AH, Neel JV. The costs of human inbreeding and their implications for variations at the DNA level. *Nature Genetics* 1994;**8:**117–21.

[22] Zlotogora J. Dominance and homozygosity. *Am J Med Genet* 1997;**68:**412–16.

[23] Helgason A, Pálsson S, Gudbjartsson DF, Kristjánsson T, Stefánsson K. An association between the kinship and fertility of human couples. *Science* 2008;**319:**813–16.

[24] Stoltenberg C, Magnus P, Skrondal A, Lie RT. Consanguinity and recurrence risk of birth defects: a population-based study. *Am J Med Genet* 1999;**82:**423–28.

[25] Bundey S, Alam H, Kaur A, Mir S, Lancashire RJ. Why do UK-born Pakistani babies have high perinatal and neonatal mortality rates? *Paediatr Perinat Epidemiol* 1991;**5:**101–14.

[26] Bundey S, Alam H. A five-year prospective study of the health of children in different ethnic groups, with particular reference to the effect of inbreeding. *Eur J Hum Genet* 1993;**1:**206–19.

[27] Stoltenberg C, Magnus P, Lie RT, Daltveit AK, Irgens LM. Influence of consanguinity and maternal education on risk of stillbirth and infant death in Norway, 1967–1993. *Am J Epidemiol* 1998;**148:**452–58.

[28] Pedersen J. The influence of consanguineous marriage on infant and child mortality among Palestinians in the West Bank and Gaza, Jordan, Lebanon and Syria. *Community Genet* 2002;**5:**178–81.

[29] Lander ES, Botstein D. Homozygosity mapping: a way to map human recessive traits with the DNA of inbred children. *Science* 1987;**236:**1567–70.

[30] Morrow EM, Yoo SY, Flavell SW *et al*. Identifying autism loci and genes by tracing recent shared ancestry. *Science* 2008;**321:**218–23.

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Commentary: The background and outcomes of the first-cousin marriage controversy in Great Britain

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Introduction

During the early years of Christianity there were major social and legal differences in attitude towards consanguineous marriage in the Eastern and Western Roman empires, reflecting pre-existing divisions between the Classical Greek and Roman worlds. In Athens and Sparta first-cousin, uncle–niece and half-sib marriages were permissible,[1–3] with half-sib marriage, and even full-sib marriage continuing within the ruling Ptolemaic dynasty and the settler population of Lower Egypt between the first and the third centuries AD.[4] By comparison, in Rome there was strong disapproval of first-cousin marriage,[3] and the marriage between the Emperor Claudius (41–54 AD) and his niece Agrippina was regarded as especially scandalous. The genetic relationships involved in these consanguineous unions are summarized in Table 1, accompanied by the equivalent coefficients of relationship (r) indicating the proportion of genes shared by each parent, and coefficients of inbreeding (F), a measure of the proportion of loci at which the offspring of a consanguineous union would be expected to inherit identical gene copies from both parents.

Not surprisingly, given the period in human history, none of the early judgements on the degrees of permitted and prohibited marriages between biological relatives appears to have had an especially rational scientific basis. However, by the middle of the fifth century the Church had adopted the Roman doctrine on consanguineous marriage, with the initial impact in England recounted by the Venerable Bede writing in the early eighth century.[5] According to Bede, on his installation as the first Archbishop of Canterbury, Primate Augustine had requested advice from Pope Gregory I on Church regulations with respect to first-cousin marriages. The reply from the Pope in 591, citing *Leviticus* **18**:6, was that 'Sacred law forbad a man to uncover the nakedness of his near kin'. Furthermore, depending on the translation consulted, the Pope advised either that 'unions between consanguineous spouses do not result in children'[5] or 'the offspring of such marriages cannot thrive'.[6] The Papal decision to cite the rather vague but apparently all-embracing ban on consanguineous unions in *Leviticus* **18**:6 is noteworthy, since in *Leviticus* **18**:7–18 quite explicit guidelines are provided on the partners a man may or may not take as a wife, with first-cousin unions, and indeed uncle–niece relationships, acceptable.

Church permission to marry a biological relative could be sought and granted on payment of a dispensation fee with two different systems used to calculate degrees of consanguinity: the Roman system counted the distance between relatives by summing the number of links from each related individual to a common ancestor, whereas the Germanic system counted the number of links between one partner in the relationship and their common ancestor.[1,6,7] Under a canon issued by Pope Alexander II in 1076, the Germanic system was selected as the formal method of consanguinity classification by the Church. This created considerable initial confusion since, for example, a first-cousin relationship ($F = 0.0625$) is classified as the fourth degree of consanguinity under the Roman system but the second degree according to the Germanic method.[1] Some semblance of order was restored by Pope Innocent III at the IV Lateran Council in 1215 with the decision that the restrictions on consanguineous marriage applied to third-cousin relationships or closer ($F \geqslant 0.0039$).[7] This level of regulation was confirmed by the post-Reformation Council of Trent (1545–63) and remained in force until 1917 when the requirement for consanguinity dispensation was reduced to couples related as second cousins or closer ($F \geqslant 0.0156$) and in 1983 to first cousins or closer. Somewhat surprisingly, multiple pathways of consanguinity, which often occur in small endogamous communities, were ignored in the latter revision.[7]

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Table 1 Human genetic relationships

Biological relationship	Coefficient of relatedness (r)	Coefficient of inbreeding (F)
Incest[a]	0.5	0.25
Half-sib		
Uncle–niece	0.25	0.125
Double first cousin		
First cousin	0.125	0.0625
First cousin once removed	0.0625	0.0313
Double second cousin		
Second cousin	0.0313	0.0156
Second cousin once removed	0.0156	0.0078
Double third cousin		
Third cousin	0.0078	0.0039

[a]Defined as a father–daughter, mother–son or brother–sister relationship.

As part of his criticism on the practices of the Roman Catholic Church, Martin Luther had condemned the requirement for consanguinity dispensation payments, since according to Divine Rule as revealed in *Leviticus* **18**:7–18, there should be no impediment to marriage between first cousins. Accordingly, first-cousin marriages were accepted by the various Protestant denominations founded in much of northern Europe. Although, ironically, a ban on first-cousin marriage was maintained by the state Lutheran Church in Sweden until 1680, and royal dispensation to marry a first cousin was required until 1844.[8]

The situation in England was somewhat different, although it also centred on the permissible relationships between spouses, but with *Leviticus* **18**:7–18 once again cited. On the death of his elder brother Arthur in 1491, Henry VIII had obtained Papal dispensation to marry his brother's widow Catherine of Aragon.[6] As the marriage failed to produce a male heir Henry petitioned the Pope for a divorce on the grounds that his marriage to Catherine, his sister-in-law, was invalid under the *Levitical* statutes. Despite support from English and Continental legal experts his petition was rejected, so in 1533 Henry established the Church of England with himself, as monarch of England, the head of the Church.[6] Having embarked on this major religious realignment, and wishing to marry Catherine Howard, a cousin of his executed second wife Anne Boleyn, in 1540 Henry issued a statute that legalized marriage between all first cousins, consanguineous and affinal. In 1560, during the reign of the Protestant Elizabeth I, the consanguinity and affinity regulations were formally codified by Archbishop Parker as *The Tables of Kindred and Affinity of the Church of England*, with subsequent revisions in 1563 and 1940.[6]

The 19th century controversies on affinal and consanguineous marriage

A late 19th century compilation of books and papers on cousin marriage published in Europe from the 16th to the start of the 19th century suggests limited interest in consanguinity,[9] and during the early 1800s attention in England was concentrated on affinal rather than consanguineous marriage, i.e. unions between individuals related through marriage rather than genetic relationships. Lord Chancellor Lyndhurst had introduced a bill into the House of Lords to place a restriction on the time period during which marriages within the prohibited degrees of affinity could be annulled, and a revised form of the Lyndhurst Bill passed by Parliament declared valid all such marriages contracted before 31 August 1835.[10] A clause was, however, added that made affinal marriages solemnized after that date void. Opposition to the impact of this clause on widowers who wished to marry their deceased wife's sister resulted in the introduction of the Wife's Sister Bill to Parliament in 1842, but formal approval of this seemingly innocuous piece of legislation was not obtained until 1907, with the Bill unsuccessfully brought before Parliament on numerous occasions during the intervening years.[10]

In the interim, despite the widespread acceptance of first-cousin unions in England, as evidenced in the popular literature of the first half of the 19th century,[11] increased concerns were being expressed on the adverse health effects of first-cousin marriage. The initial reports from France on an increased prevalence of deaf–mutism among the progeny of first cousins[12] were investigated by Sir William Wilde, who, as Assistant Census Commissioner, included a question on consanguineous marriage and deaf–mutism in the Post-Famine 1851 Census of Ireland. According to the Irish Censal data, 4747 individuals with deaf–mutism were enumerated, a prevalence of 1/1380, and in 3.6% of cases the parents were related as first, second or third cousins.[13]

The controversy surrounding first-cousin marriage rapidly escalated, especially in the USA after an article delivered in 1855 to the Ninth Meeting of the American Association for the Advancement of Science by the Rev. Charles Brooks, an Episcopalian clergyman who in a diatribe against first-cousin marriage declared that 'The improvement of society and prosperity of thousands of families depend on its solution; and, in a degree, the safety and elevation of society'.[14] This claim appeared to be justified by an extensive study into the outcomes of consanguineous unions by Dr Samuel Bemiss of Louisville, Kentucky, based on information provided by medical colleagues into the mean number of offspring and the rates of early deaths that resulted from consanguineous unions ranging from incest ($F = 0.25$) to third

cousins ($F = 0.0039$) versus deaths among non-consanguineous progeny.[15] The data showed a significant positive relationship between early deaths and the degree of consanguinity. But they also indicated that although tuberculosis had been diagnosed as the cause of death in 8.7% of non-consanguineous progeny, it was responsible for 22.7% of deaths among consanguineous offspring, a finding strongly suggestive of a significant difference in the living conditions of the two groups.

Charles Darwin and the first-cousin marriage controversy in England

In 1839, the then 30-year-old Charles Darwin married his first cousin Emma Wedgwood aged 32 years, following the marriage of Charles' elder sister Caroline to Emma's brother Josiah Wedgwood III in 1837. Ten children were born during the course of the next 17 years and by all accounts the marriage was happy, with Charles and Emma sharing a close companionship. However, in his letters to friends, Darwin expressed a concern that the periodic bouts of debilitating ill-health from which he suffered might be transmitted to their children.[16] In fact, 3 of their 10 children died in childhood. Their third-born girl Mary of unknown cause within weeks of her birth in 1842, his favourite daughter Annie at 10 years of age in 1851, probably of tuberculosis, and in 1858 their last-born child Charles Waring, born when Emma was 48 years of age and whose death at 18 months is assumed associated with Down syndrome comorbidities.[16] The remaining seven offspring appear to have enjoyed good health, with a mean age at death of 77 years, and three of the sons, George, Francis and Horace, were elected Fellows of the Royal Society of London for their scientific work, and Leonard was a Member of Parliament from 1892 to 1895 and President of the Geographical Society from 1908 to 1911.

Darwin would have been aware of the heated discourse in England and elsewhere on the advisability of marriage between first cousins; for example, the letters in the columns of the *British Medical Journal*,[17,18] and in France 25 papers on different aspects of consanguinity were published in 1862 alone.[9] Especially after the death of his daughter Annie, Darwin appears to have become convinced that marriage to his first cousin may have been a mistake from a biological perspective. His concerns were first publicly expressed in the improbable context of the avoidance of self-fertilization in orchids.[19] On the basis of this observation, Darwin postulated the existence of a universal mechanism to reduce the harmful effects of close inbreeding, concluding in the final sentence of his book 'For may we not infer as probable ... that marriage between near relations is likewise in some way injurious, - that some unknown great good is derived from the union of individuals which have been kept distinct for many generations?' Coming from such a distinguished scientist, married to a first cousin and connected by birth and marriage to the Wedgwood industrial dynasty, Darwin's views were rapidly disseminated and vigorously debated by members of the medical and legal professions.[3,20,21]

To produce credible evidence on the topic of consanguinity, Darwin persuaded his friend and neighbour Sir John Lubbock, MP, to petition Parliament for the inclusion of a question on the prevalence of first-cousin marriage in the 1871 Census of Great Britain and Ireland. The proposal was voted down by the Parliamentary Committee vetting the content of the 1871 Census Bill,[22] evoking from Darwin the response 'When the principles of breeding and of inheritance are better understood, we shall not hear ignorant members of our legislature rejecting with scorn a plan for ascertaining by an easy method whether or not consanguineous marriages are injurious to health'.[23]

George Darwin and the prevalence and outcomes of first-cousin marriage in England

Charles and Emma Darwin's second son George had an obvious personal interest in his father's views on first-cousin marriage, and he also had been annoyed at the rejection of Lubbock's proposal to Parliament '... amidst the scornful laughter of the House ...'[24,25] As indicated in the reprinted *Fortnightly Review* article by George Darwin,[24] which closely matches a paper concurrently published in the *Journal of the Statistical* Society,[25] to circumvent the Parliamentary veto, Darwin devised a mathematical method of estimating the prevalence of first-cousin marriage based on the proportion of marriages between persons with the same surname. Using as his initial data source *The Registrar-General's Annual Report for 1853*, with an estimated 32 818 different surnames recorded for the 275 405 persons listed, Darwin observed that '... about one marriage in a thousand takes place in which the parties are of the same surname, and have been uninfluenced by any relationship between them ...' But rather than the expected 0.1% of same-surname (isonymous) marriages that might have been predicted on this random basis, when Darwin and a research assistant checked the marriage announcements printed in *The Pall Mall Gazette* for the years 1859–63 they found that 1.25% of the 18 528 marriages listed were between persons with the same surname. The questions that then arose were: (i) what proportion of the 1.25% of same-surname marriages were between first cousins?; and (ii) what proportion of first-cousin marriages were between couples who shared the same surname?[24,25]

To answer the first question for first-cousin marriage among 'the upper classes', Darwin sought guidance from two socially impeccable sources, *Burkes Landed Gentry* and the *English and Irish Peerage*, from which he calculated that 0.78% of same-surname marriages were between first cousins, and to solve the second question he distributed approximately 800 pre-stamped circulars to members of the 'upper middle and upper classes', with the request that they provide the names of any family members who had married their first cousins, and also those who had married someone with the same surname but who was not their first cousin.

Darwin acknowledged that the information provided may have been incomplete: 'I have been much surprised to find how very little people know of the marriages of their relations'. He also realized that there would be probable positive bias, since respondents may have been more likely to recall a first-cousin union but fail to respond if they had no same-surname or first-cousin marriages to report. Despite these problems, Darwin was able to calculate that same-surname first-cousin unions accounted for 57% of all same-surname marriages, whereas the ratio of same-surname first-cousin marriages to different-surname first-cousin marriages was 1:4. To translate these figures into city, urban and rural categories Darwin consulted the *General Registry of Marriages for 1872* and calculated that the highest percentage of first-cousin unions occurred in rural districts (2.25%), and the lowest in metropolitan London (1.5%). However, these levels of consanguinity fell far short of the first-cousin marriage rates he had calculated for the landed gentry (3.5%) and members of the aristocracy (4.5%).

The second part of Darwin's enquiry was to examine the possible adverse health consequences of first-cousin marriage, which he initially assessed by determining the comparative prevalence of first-cousin offspring among the inmates of 19 lunatic asylums in England, Scotland, Wales and Ireland.[24,25] Once again, quite serious problems were noted in the collection of reliable and unbiased data. Some regional variation also was indicated, with the 5.25% first-cousin parentage among inmates in Scottish institutions explained in terms of the often mountainous nature of the Caledonian terrain, which may have led to a higher proportion of consanguineous unions in geographically isolated communities. However, the overall prevalence of 3.9% first-cousin parentage among the asylum inmates for whom relevant information was available versus the 3.4% first-cousin unions in the general population suggested that the adverse effects of consanguinity on mental health had previously been over stated.

Commenting on the paper after its presentation to the Statistical Society, Francis Galton, a half-cousin of Charles Darwin, summarized the findings as having '... undoubtedly swept away, to some extent, an exaggerated opinion which was current as to the evil resulting from first-cousin marriages'.[25] In a subsequent private letter to Darwin dated 10 November 1875 Galton further stated that 'You have exploded most effectively a popular scare', and in jocular vein suggested that George Darwin could very profitably write a pamphlet on the theme 'WORDS of scientific COMFORT and ENCOURAGEMENT To COUSINS who are LOVERS', which given the probable numbers of actual and potential first-cousin couples in England at the time could attract annual sales of some 8000 copies.[26]

By that stage George Darwin had extended his studies to focus on more general health effects of first-cousin marriage by determining the prevalence of first-cousin parentage among the rowing eights of the Colleges of Oxford and Cambridge Universities, whom he described as '... a picked body of athletic men ...', but with coxes excluded.[27] Since 2.4–2.8% of these picked athletes were the offspring of first-cousins by comparison with the 3.0–3.5% first-cousin parentage of their social peers as calculated in Darwin's earlier studies,[25,26] he concluded that '... these numbers appear, to some extent, to justify the belief that offspring of first cousins are deficient physically ...'. Although this interpretation is dependent on acceptance of the superior physical status accorded by Darwin to Oxford and Cambridge boating men.

The aftermath

Given the findings of his son's studies, and perhaps influenced by their enthusiastic welcome by Francis Galton, Charles Darwin revised his previously negative opinion on the health outcomes of first-cousin marriage on the grounds that '... the widely different habits of life of men and women in civilised nations, especially amongst the upper classes, would tend to counter-balance any evil from marriages between healthy and somewhat closely related persons'.[28] This apparent triumph of nurture over nature, at least among the socio-economically advantaged, was further reflected in the omission of any reference to the inadvisability of marriage between close relatives in the second edition of his book on self-fertilization in orchids, and with the phrase 'And on the Good Effects on Intercrossing' removed from the book's title.[29] Given our present knowledge of genetics, and with the invaluable gift of hindsight, Charles Darwin's concerns on the harmful effects of first-cousin marriage were excessive, and his extrapolation from the ill-effects of self-fertilization in plants where the progeny would predictably be homozygous at 100% of gene loci ($F = 1$) to the outcomes of first-cousin marriage in humans ($F = 0.0625$) is difficult to justify.

Despite the results of George Darwin's studies and his father's recantation, first-cousin marriage rapidly

declined in prevalence in Great Britain from the levels calculated by George Darwin and supported by a survey of medical practitioners conducted by Karl Pearson covering the mid- to late 19th century.[30] By the beginning of the 20th century, just 0.9% of children in Great Ormonde Street Hospital, London, had first-cousin parents,[30] a survey of genealogists' families in the 1920s indicated 0.3% first-cousin marriage[31] and the most recent hospital-based data suggest 0.2% first-cousin unions among autochthonous UK residents in the English Midlands.[32]

The change has been much more extreme in the USA, where by the end of the 19th century 13 states had already introduced legislation to control or ban first-cousin marriage.[1] Currently, first-cousin marriage is illegal or a criminal offence in 31 of the 50 states,[33] and despite a unanimous legal recommendation in 1970 that all state laws prohibiting first-cousin marriage should be rescinded because of a lack of evidence of significant ill-effects,[34] legislation banning first-cousin marriages in Texas was passed in 2005.

Consanguineous marriage in the 21st century

George Darwin's influence on studies into the distribution and prevalence of cousin marriage continues, with the isonymic (same-surname) method he devised used to estimate random and non-random inbreeding in historical communities and in present-day populations where pedigree or genomic information is unavailable. As detailed on the Global Consanguinity website http://www.consang.net, consanguineous marriage remains popular in many parts of Asia and Africa and it has been estimated that currently >10% of the global population are either married to a partner related as second cousin or closer ($F \geqslant 0.0156$) or are the progeny of such a union.[33]

Over the course of the last 50 years there has been large-scale migration from these regions to many Western countries. In the UK and several other European countries concern has been expressed on the adverse health effects of consanguineous marriage, driven in the UK by inflammatory claims from some Members of Parliament whose constituencies include sizeable communities of South Asian migrants, with calls for a ban on first-cousin marriage.[35] However well intentioned, in their tone and willingness to cite vague health 'statistics', the proponents of the move to prohibit first-cousin marriage curiously echo their counterparts of the 19th century. There is no doubt that in some families first-cousin marriage can facilitate the expression of rare recessive disease genes carried by both parents, causing major childhood illness.[36] However, a recent meta-analysis of 69 studies from 15 countries has indicated a mean 3.5% increase in prereproductive mortality at first-cousin level, which is lower than earlier estimates and indicates that a large majority of first-cousin progeny are no more likely to be seriously disadvantaged in health terms than the offspring of unrelated parents.[33]

As cogently warned in the 19th century by Dr Arthur Mitchell, Deputy Commissioner in Lunacy for Scotland and a contemporary of Charles and George Darwin, 'Startling illustrations of calamitous sequences to cousin-marriages have been detailed, and pointed at with a finger of warning, *the relation of cause and effect being assumed* (author's italics)'.[37] This unfortunate tendency continues, with a readiness to blame any and all types of adverse pregnancy, birth and childhood health outcomes on consanguinity, despite the lack of any obvious let alone proven causal relationship, adequate control for socio-demographic variables, or allowance for the influence of other important population genetic factors, in particular clan, tribe, caste and *biraderi* endogamy according to the population studied.[33,38,39]

Thus in the UK Bangladeshi community, which has a rate of sensorineural childhood deafness of 3.86/1000 versus 1.65/1000 in the general UK population, consanguineous marriage has been widely and uncritically assumed to be the causative factor. A study of Bangladeshi patients confirmed both a high prevalence of first-cousin (24.8%) and other forms of consanguineous marriage (8.6%) among the parents of affected persons, and in 60% of cases the deafness was genetic in origin with a recessive mutation in the *GJB2* (Connexin 26) gene identified in 17% of patients.[40] However, the rate of deafness was 2.73/1000 in children born to the two-thirds of Bangladeshi families who had not contracted a cousin marriage, suggesting that mutant genes causing the disorder are common in the Bangladeshi gene pool, and indicating other major non-genetic causes including congenital cytomegalovirus infection.[40]

Conclusion

The study by George Darwin provided valuable evidence that fears regarding the ill-effects of first-cousin marriage were exaggerated. Especially in high-income countries there is the capacity to provide health education at individual, family and community levels, with genetic counselling, premarital diagnosis and prenatal diagnosis for genetic disorders widely available where requested. Rather than seeking to ban a form of marriage that has been legal in England for >450 years, i.e. some 15–20 generations, ensuring access to these viable and non-discriminatory options is the logical way to proceed and more likely both to receive community acceptance and be successful in maintaining and improving health.

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References

[1] Ottenheimer M. *Forbidden Relatives: the American Myth of Cousin Marriage*. Urbana: University of Illinois Press, 1996.

[2] Ager SL. Familiarity breeds: incest and the Ptolemaic dynasty. *J Hellenistic Stud* 2005;**125:**1–34.

[3] Adam W. Consanguinity in marriage, Part 1. *Fortnig Rev* 1865;**3:**710–30.

[4] Scheidel W. Brother–sister marriage in Roman Egypt. *J Biosoc Sci* 1997;**29:**361–71.

[5] Bede (c731). Cited in *The Ecclesiastical History of the English People*. London: Penguin Books, 1990.

[6] Goody J. *The Development of the Family and Marriage in Europe*. Cambridge: Cambridge University Press, 1985.

[7] Cavalli-Sforza LL, Moroni A, Zei G. *Consanguinity, Inbreeding and Genetic Drift in Italy*. Princeton: Princeton University Press, 2004.

[8] Bittles AH, Egerbladh I. The influence of past endogamy and consanguinity on genetic disorders in northern Sweden. *Ann Hum Gen* 2005;**69:**549–58.

[9] Huth AH. *An Index to Books and Papers on Marriage between Near Kin*. London: Index Society, 1879.

[10] Anderson NF. The ''Marriage with Deceased Wife's Sister Bill'' controversy: incest anxiety and the defense of family purity in Victorian England. *J British Stud* 1982;**21:**67–86.

[11] Anderson NF. Cousin marriage in Victorian England. *J Fam His* 1986;**11:**285–301.

[12] Menière P. Recherches sur l'origiène de la surdi-mutité, 3rd series. *Gazette Médicale de Paris* 1846;**12:**223–26, **13**:243–46.

[13] Wilde WR. *On the Physical, Moral and Social Condition of the Deaf and Dumb*. London: John Churchill, 1854.

[14] Brooks C. Laws of reproduction, considered with particular reference to inter-marriage of first cousins. *Proceedings of the 9th Meeting American Association for the Advancement of Science*. Cambridge: Joseph Lovering, 1856, pp. 236–46.

[15] Bemiss SM. Report on the influence of marriages of consanguinity upon offspring. *Trans Am Med Ass* 1858; **11:**319–425.

[16] Keynes R. *Annie's Box: Charles Darwin, his Daughter and Human Evolution*. London: Fourth Estate, 2001.

[17] Crossman E. Intermarriage of relations as a cause of degeneracy of the offspring. *BMJ* 1861;**1:**401–2.

[18] Gardner J. On the intermarriage of relations, as a cause of degeneracy of the offspring. *BMJ* 1861;**1:**290–91.

[19] Darwin C. *On the Various Contrivances by which British and Foreign Orchids are Fertilized by Insects, and on the Good Effects of Intercrossing*. 1st edn. London: John Murray, 1862, p. 360.

[20] Childs GW. Marriages of consanguinity. *Westmin Rev NS* 1863;**24:**88–104.

[21] Adam W. Consanguinity in marriage, Part 2. *Fortnig Rev* 1865;**3:**74–88.

[22] HMSO. *British Parliamentary papers, Parliamentary Debates* Third series. Vol. 203. London: Her Majesty's Stationery Office, 1870, pp. 817–18, 1006–10.

[23] Darwin C. *The Descent of Man and Selection in Relation to Sex Vol. 2*. London: John Murray, 1871, p. 403.

[24] Darwin GH. Marriages between first cousins in England and Wales and their effects. *Fortnigh Rev* 1875;**24:**22–41. Reprinted in Int J Epidemiol 2009;**38**:1429–39.

[25] Darwin GH. Marriages between first cousins in England and Wales and their effects. *J Stat Soc* 1875;**38:**153–84.

[26] Pearson K. *The Life, Letters and Labours of Francis Galton Vol. 2*. Cambridge: Cambridge University Press, 1924, p. 188.

[27] Darwin GH. Noteon the marriages of first cousins. *J Stat Soc* 1875;**38:**344–48.

[28] Darwin C. *The Effects of Cross and Self Fertilisation in the Vegetable Kingdom*. London: John Murray, 1876, pp. 460–61.

[29] Darwin C. *On the Various Contrivances by which Orchids are Fertilized by Insects 2nd edn*. London: John Murray, 1877.

[30] Pearson K. Cousin marriages. *BMJ* 1908;**1:**1395.

[31] Smith MT. Estimates of cousin marriage and mean inbreeding in the United Kingdom from 'birth briefs'. *J Biosoc Sci* 2001;**33:**55–66.

[32] Bundey S, Alam H, Kaur A, Mir S, Lancashire RJ. Race consanguinity and social features in Birmingham babies: a basis for prospective study. *J Epidemio Comm Health* 1990;**44:**130–35.

[33] Bittles AH, Black ML. Consanguinity, human evolution and complex diseases. *Proc Natl Acad Sci USA*. 2009; doi/10.1073/pnas.0906079106 [Epub 23 September 2009].

[34] National Conference of Commissioners. *Handbook on Uniform State Laws and Proceedings of the Annual Conference Meeting in its Seventy-ninth Year*. Baltimore: Port City Press, 1970.

[35] Dyer O. MP is criticized for saying that marriage of first cousins is a health risk. *BMJ* 2005;**331:**1292.

[36] Bittles AH. Consanguinity and its relevance to clinical genetics. *Clin Gen* 2001;**60:**89–98.

[37] Mitchell A. On the influence which consanguinity in the parentage exercises upon the offspring. *Edinburgh Med J* 1864–65;**10:**781–94.

[38] Bittles AH. Endogamy, consanguinity and community disease profiles. *Comm Gen* 2005;**8:**17–20.

[39] Bittles AH. A community genetics perspective on consanguineous marriage. *Comm Gen* 2008;**11:**324–30.

[40] Bajaj Y, Sirimanna T, Albert DM *et al*. Causes of deafness in British Bangladeshi children: a prevalence twice that of the UK population cannot be accounted for by consanguinity alone. *Clin Otolaryngo* 2009;**34:**113–19.