In June 2001 I was introduced to the work of the Dutch academic Piet Jongbloet [1,2] by a colleague. The hypothesis he advances is that conception occurring a significant time after ovulation is more likely to result in offspring with birth defects, owing to deterioration of the ovum (gametopathy). From this, he deduces that such disorders will be more common among practitioners of natural family planning, who are more open to conception at this time, and thus more common among Catholic populations generally. The model is stretched so far as to explain higher rates of drug addiction and imprisonment among the Catholic population of the United Kingdom. Though the presentation my colleague gave suggested that the gametopathy theory was widely accepted, a fairly exhaustive search of the literature found that almost all studies of ovum degradation were *in vitro* and carried out in connection with assisted reproductive technology. In relation to the gametopathy:natural family planning link, I found two groups beside Jongbloet himself publishing in support of the hypothesis [3,4] and two against [5-7].

This is a quick attempt to summarise the reading and thinking I did in 2001-2002 on gametopathy/birth defects and the possible link to particular contraceptive practices common in particular religious groups. To indicate the conclusion in advance, it seems impossible to tell whether rhythm-linked gametopathy effects are significant in the aetiology of Down Syndrome and anencephaly. I have no reason to fault the particular case studies quoted by Jongbloet [1,2] , but the very high incidences of Down Syndrome reported suggest a genetic predisposition to the disorder that may or may not have any relevance to the general population. The sample sizes are also probably too small, especially when incidences are binned by age. Accordingly, I concentrated my searches on large-scale epidemiological studies, paralleling the anencephaly data presented in Jongbloet's 1978 paper [2]. Examining all the evidence I could find for both Down Syndrome and anencephaly:

- There is a possible correlation between catholicity and the incidence of these diseases which may be independent of ethnic origin (see Figures 1 and 2)
- There is a less tenuous correlation with ethnic origin – Western European and Middle Eastern incidences tend to be higher than Indian, East Asian, and African. The correlation between ethnic origin and anencephaly is stronger than between ethnic origin and Down Syndrome, and a histological marker has been suggested [8] which seems to reasonably fit distribution in Old World populations. (again, see Figures 1 and 2)
- The correlation with maternal age is extremely strong for Down Syndrome, far outweighing other factors. On the contrary, there is no correlation between the incidence of neural tube defects (anencephaly + spina bifida) and maternal age, suggesting that different mechanisms are responsible. (see Figure 3)

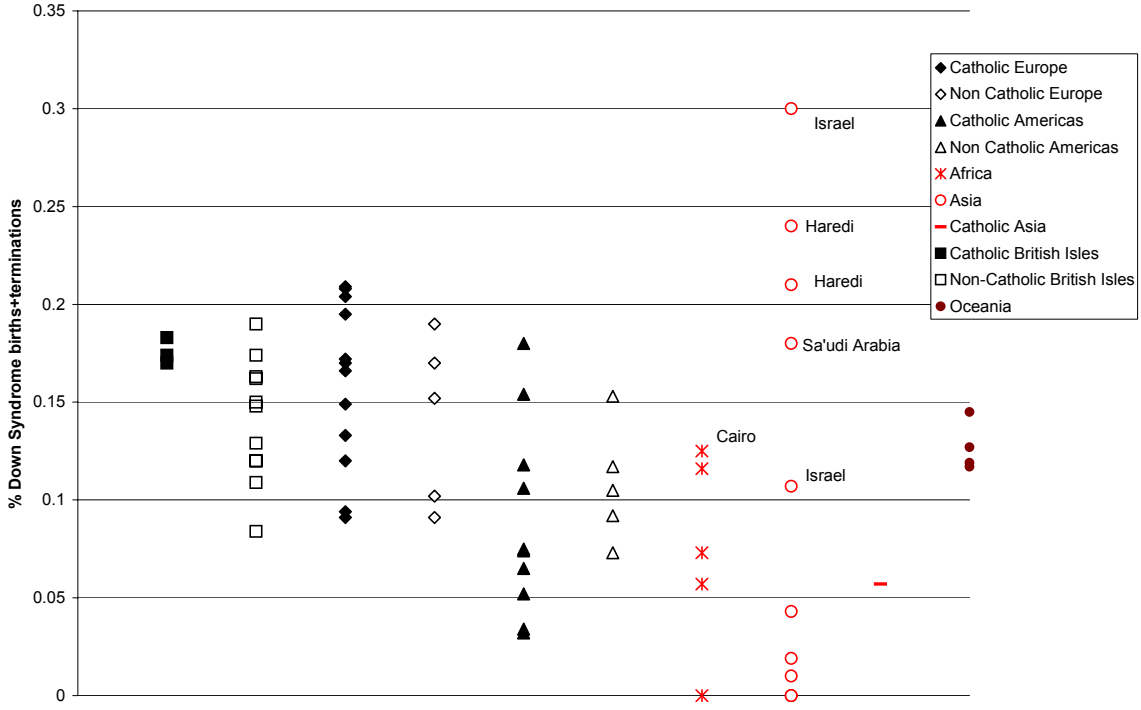

Figure 1: Incidence of Down Syndrome at a number of centres. Age –adjusted WHO data from 24 centres [9] and more recent data from a number of sources detailed in the appendix. A number of cities (Belfast, Boston, New York) have been placed in both catholic and non-catholic data sets, and African-Americans

have been placed in both the Africa and non-catholic Americas data sets. Locations in Marxist Europe have been assigned according to their traditional religious affiliation.

Note from Figure 1 that there are possibly higher rates in Catholic vs. Non-Catholic countries in the British Isles, Europe, America, and Asia; although the majority of the data sets have not been adjusted for age, the same trend is seen on the basis of fewer data points from the subset of age-adjusted data reported by the World Health Organisation[9]. Interestingly, all the high Asian rates reported are in the Middle East, among communities within the Judaeo-Christian-Islamic tradition, which may relate either to genetics or sexual behaviour. The highest African rate is also Middle Eastern. Interestingly, the incidence in India is the lowest reported anywhere [9]. There has been some suggestion that diagnosis is more likely in western countries [10] which might generate artificially low rates elsewhere in the world.

Heavyweight statistics and some new studies are probably required, and it is probably impossible for valid cross-cultural studies to be done since the introduction of prenatal testing – i.e., I would hope to see a very large difference between Catholic and Non-Catholic populations on the basis of differential termination rates, and chromosomal information on aborted infants would not be available from countries where abortion is illegal.

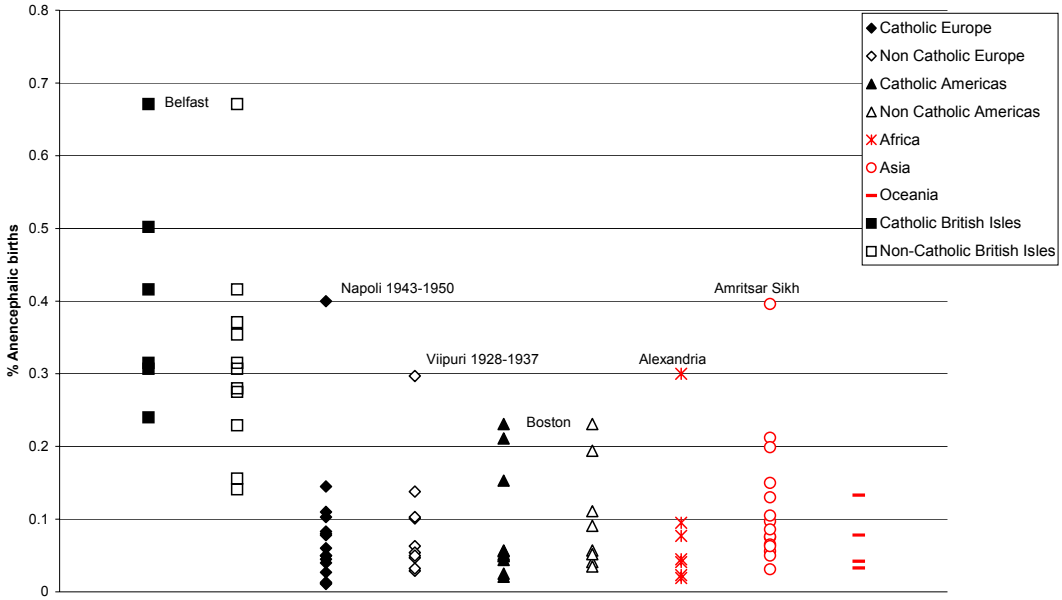

Figure 2: Incidence of Anencephaly based on WHO data [9] and more recent data from a number of sources detailed in the appendix.

A strong correlation with ethnicity is evident in Figure 2. All the highest figures in the British Isles are in Ireland and Scotland, and Wales is also significantly higher than England, while England is significantly higher than the rest of Europe and the highest French rates are reportedly in the northwest of the country, with a more celtic population [8]. In this reference Feingold postulates correlations with particular histological markers which appear reasonable for the Old World anencephaly distribution. Rates are considerably lower in english-speaking North America and Oceania where the population is less thoroughly anglo-celtic, but environmental factors may also be important. Finally, a strong caveat has been published concerning shortcomings in the design of many of the studies contributing to surveys of anencephaly [11], suggesting that it may not be valid to compare data from geographically separated studies at all[1].

[1] Despite extensive research, little progress has been made in elucidating the etiologies of anencephalus and spina bifida. International and national distributions of disease occurrence have often been used as a basis for generating etiological hypotheses (e.g., potato blight, tea consumption, and zinc deficiency hypotheses). However, few of the epidemiological studies of neural tube defects (NTDs) have been conducted with scientific rigour in design, and most are of dubious validity, often with low precision in the estimates. This paper shows that the accepted geographic patterns of NTDs may be attributable to variations in the validity of studies used to describe these patterns. The nonuniformity in the duration and diligence of case ascertainment, the lack of a standardized nomenclature and classification, and the definition of the denominator remain principal problems in evaluating the epidemiology of NTDs. For example, the distinction between incidence and prevalence is not always made, and there is no consistency in the placement of the gestational boundary between late fetal deaths and spontaneous abortions. Findings are

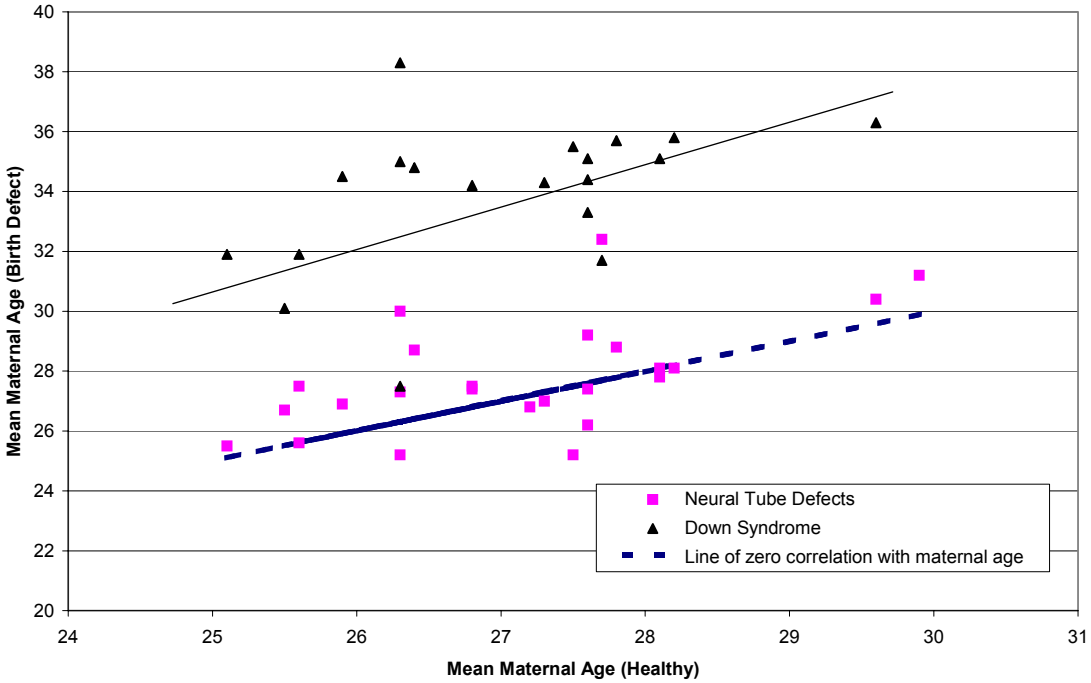

Figure 3: Average age of mothers of healthy children and Down Syndrome/Neural Tube Defect children, from WHO data [9]. Unfortunately anencephaly and spina bifida data are not separated in the reference, though these are roughly parallel in incidence (see Table 3, appendix).

It might be argued that gametopathy arising from practice of the rhythm method should manifest itself in a shift to a smaller difference in average age between mothers of Down syndrome children and mothers of normal children. Data points significantly below the upper line in Figure 3, corresponding to this situation, are from Madrid, Melbourne, Medellin, Mexico City, and Czechoslovakia. Points significantly above the line, however, indicating older than average Down syndrome mothers, are Sao Paulo, Zagreb, Bogota (!) and Melbourne (!!). Similarly, Ljubljana, Zagreb, and Manila show the strongest deviation toward younger mothers of children with neutral tube defects.

From Figure 3 it seems likely that while pre-ovulatory aging may be important in the aetiology of Down Syndrome, it has little or no significance for anencephaly. The link with gametopathy must therefore be considered weaker for anencephaly and it is perhaps significant that Jongbloet does not reproduce the anencephaly results of Penrose [2,12] in his more recent publication[1].

compared from studies conducted at different times, without due regard to the effect of secular trends, and using studies that have varying levels of case ascertainment. In etiological research, it is important to perform studies that are accurate and precise, but the literature used to define the spatial distribution of NTDs has often been accepted without due regard to the effect of these factors.

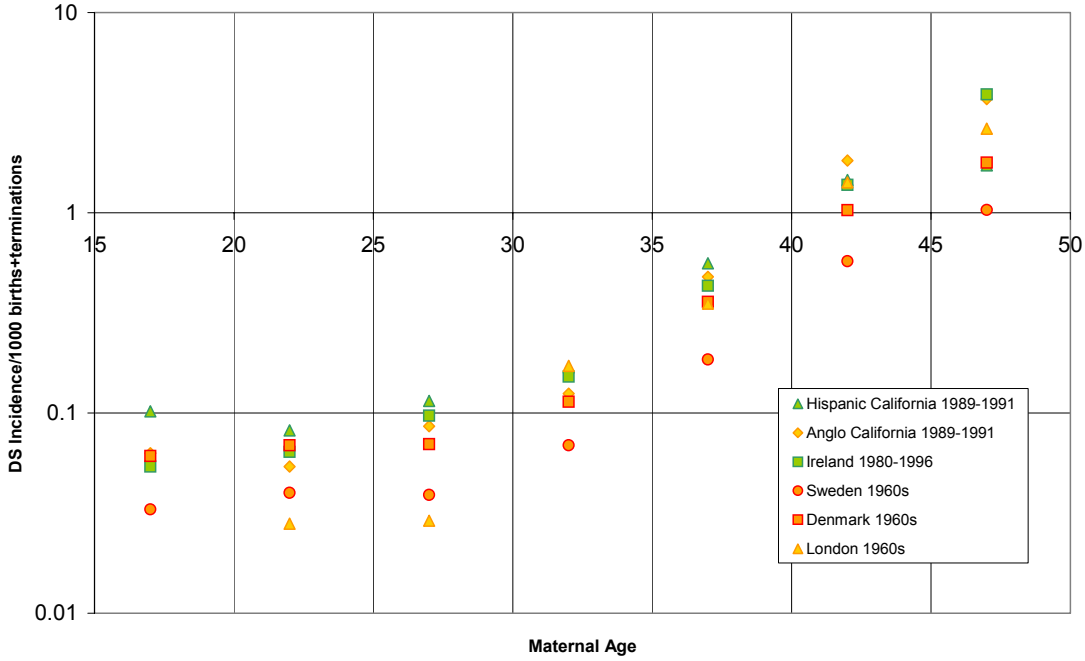

Figure 4: Incidence of Down syndrome by age in European and European-Amerindian populations

Because of the very strong influence of maternal age on the incidence of Down Syndrome, it makes most sense to compare observations in which the effect of age is taken into account. All such data that I could find is given in the appendix. Figure 4 shows Irish and Californian data from about the same time (c.1990) with extra studies from non-catholic countries from the 1960s thrown in for comparison. There does seem to be a slightly higher incidence of Down Syndrome at younger maternal age in the catholic countries studied, but little difference at the higher maternal ages where most cases occur. It is important to keep in mind an alternative explanation, beside gametopathy, for any different, which is the effect of maternal stress on the offspring – the higher reported degree of birth defects in 'crisis' pregnancies [13,14] – which should be a factor in any reported higher rate of birth defects in Ireland, and most Latin American countries, where abortion is illegal.

The most significant apparent risk to the offspring in the data presented is the very strong and unambiguous link between Down Syndrome and maternal age. It would seem that main conclusion that can be drawn from this data should therefore be:

Marry young and have children early!

The hypothesis that post-ovulatory conception may be dangerous for the offspring under certain conditions is plausible, and is not disproved by the data. Clearly, the most foolproof way to avoid gametopathic conceptions would be total abstinence during the post-ovulatory period. Until further studies are done, this should be recommended for those who find 'artificial' methods of birth control repugnant and are at risk of Down syndrome due to genetic history.

Another recommendation would be exogamy, which is clearly not an option for already married couples! An effort should be made to recommend to young celtic and haredi individuals to seek out someone of Indian or Sub-Saharan African descent rather than marrying within their own community, for instance...

Appendix

Part One: Anencephaly

The map from Penrose [12] is based on data from a number of hospitals only, over different time periods and with different sample sizes. The data plotted, and additional data from non-European regions or larger geographical entities, are given below:

Table 1: Penrose anencephaly 1955

Location	Period	No. Births	No. Anecephalics	%
London	1938-1953	52 693	82	0.156
Birmingham	1940-1947	158 307	366	0.229
Liverpool	1923-1932	13 964	44	0.315
Belfast	1938-1955	30 855	207	0.671
Dublin	1953-1954	12 552	63	0.502
Copenhagen	1911-1949	167 940	170	0.101
Mälmo and Lund	1917-1949	105 812	67	0.063
Helsinki[2]	1935-1944	17 084	5	0.029
Viipuri[2]	1928-1937	11 425	34	0.297
Reykjavik	1949-1955	10 655	5	0.047
München	1929-1941	141 706	117	0.083
Zürich	1921-1944	49 539	27	0.054
Paris	1945-1955	144 611	65	0.045
Lyon	1945-1955	59 406	7	0.012
Napoli	1943-1951	8 994	36	0.400
Parma	1938-1947	8 228	12	0.145
Torino	1949-1955	7 991	1	0.013
Barcelona	?	12 969	10	0.078
Athens	1951-1955	34 978	21	0.060
All Scotland	1939-1945	655 892	1 672	0.280
All Scotland	1950-1954	456 829	1 254	0.275
All Holland	1950-1954	1 148 097	1 179	0.103
Belfast	1951-1955	42 555	158	0.371
London	1938-1953	50 023	69	0.138
Japan	1948-1953	65 431	49	0.075
Rhode Island	1936-1952	168 654	326	0.194
Boston	1930-1941	29 024	67	0.231
Rochester	1944-1950	8 716	5	0.057
London, Ont.	1940-1955	10 834	12	0.111
Montreal	1940-1955	19 839	42	0.211
Johannesburg (African)	1951-1955	32 186	6	0.019
Pretoria (A)	1953-1955	4 407	1	0.023
Johannesburg (European)	1952-1953	7 779	6	0.077
Pretoria (E)	1953-1955	8 413	8	0.095
Bombay	1946-1955	76 763	58	0.076
Singapore	1953	8 267	8	0.097
Hong Kong	1951-1953	32 176	18	0.056

[2] This marked east-west difference in Finland has persisted into more recent times :
(18) Granroth, G.; Hakama, M.; Saxen, L.; *BRITISH JOURNAL OF PREVENTIVE AND SOCIAL MEDICINE, 1977 Sep*, *31*, 164-170. .