UNSOLVED THERAPEUTIC PROBLEMS IN HEMOPHILIA

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Mortality in Haemophilia- A United Kingdom Survey

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To decide whether progress is being made in the treatment of any disease one has to know the natural history of the disease, the amount of suffering and incapacity it produces, and also the mortality, the numbers of deaths due to the disease, and the age at which they occur. The mortality for all of us is eventually 100 percent, so we must know the excess mortality in any age group, compared to the expected death rate of a normal population, amongst sufferers of the disease. There is relatively little documentation on the mortality from haemophilia so we decided to look at this in a retrospective survey in the United Kingdom and obtained data from two sources. First, we obtained from the offices of the Registrars General of England and Wales and Scotland for the years 1955-72 copies of all Death Certificates where the diagnosis of haemophilia had been included. These death certificates do not imply that haemophilia was the main or contributory cause of death. This source of information may underestimate the number of haemophilic deaths, since a sudden death due, for instance to a cerebrovascular catastrophe, may not be associated with underlying haemophilia if the medical attendant is not familiar with the patient. However it is unlikely that this number represents a significant percentage. Also it is possible that a haemorrhagic death may occur in babies or young children without the diagnosis of haemophilia having been made. Second, by courtesy of Dr. Biggs, I have included the causes of deaths in the 1969-74 survey of the Haemophilia Centres of the United Kingdom.

The first reference to inheritance and mortality in haemophilia comes from the Babylonian Talmud of the fifth century A.D. In this book of Rabbinical Law the male children of women whose sisters had had sons who died from excessive haemorrhage were exempt from circumcision. This law suggested a good understanding of the sex-linked inheritance of the disease. The scene then shifts some 1200 years to Charleston, Virginia, where in 1792, a newspaper records the death of Isaac Zoll, aged 19 years, who died from considerable bleeding

from a slight cut. Five brothers had also bled to death from the most minor trauma; it should be noted that the father had had two wives and that all the children who bled were from the first wife.

The first reliable documentation came from the careful and extensive review of Grandidier who in 1855 summarized the symptoms and mortality of a large haemophilic population in Germany at a time when no replacement therapy was available. Of the 142 deaths, the vast majority, 114, occurred before the age of 14 (Figure 1). This document makes grim reading and explains why haemophilia was comparatively rare then, although it is becoming increasingly common today.

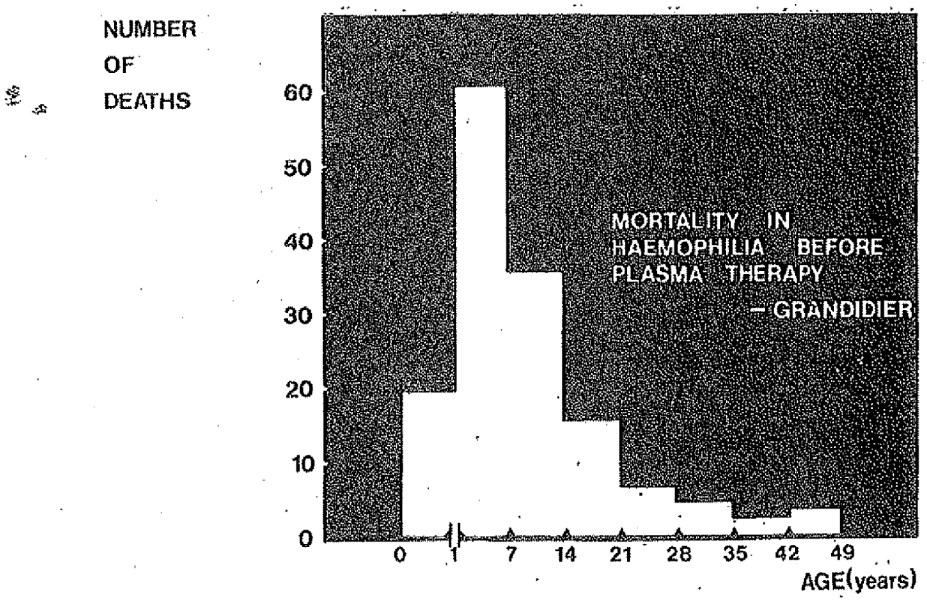

FIGURE 1. Age at Death of 142 Haemophiliacs, Compiled by Grandidier, 1855

We wish to look now at our first survey, which is the mortality of haemophiliacs in the United Kingdom based on the Registrar General's figures, for 18 years from 1955-72 (Figure 2). During this time there were 269 recorded deaths, 258 in haemophilia A and 11 in haemophilia B (Christmas disease) patients. Slightly surprising is the fact that the mortality in haemophilia showed no tendency to reduction over this period, even with the advent of cryoprecipitate from 1966 onwards. As we mentioned previously, it is necessary to analyse this mortality according to age (Figure 3). On this basis, a more optimistic picture is emerging in that now there are appreciably fewer patients dying under the age of 40 years. Even so, 49 of the series of 269 (30%) died at an age less than 21 years, so there is no cause for complacency.

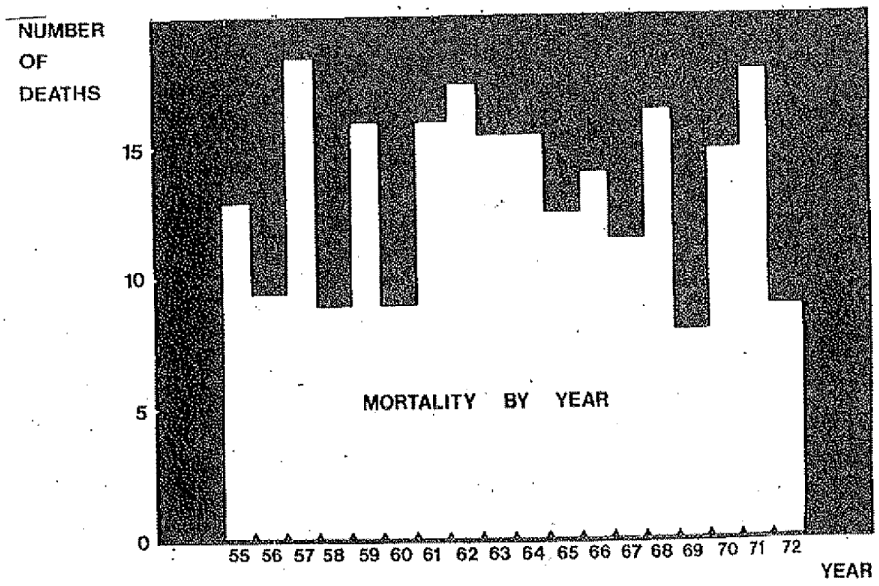

FIGURE 2. Annual Number of Recorded Deaths in Haemophiliacs. Data from Registrar-Generals' Reports, United Kingdom, 1955-1972

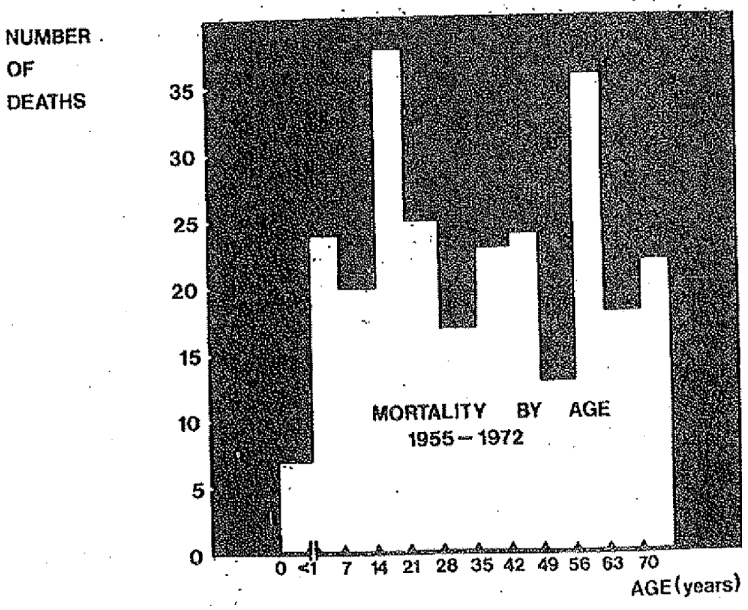

FIGURE 3. Age at Death of Haemophiliacs, 1955-1972. Registrar-Generals' Reports, United Kingdom

This relatively high mortality was broken down into causes of death divided into three time periods - 1955-1960, 1961-1966 and 1967-1972. As seen in Figure 4, we grouped the causes of death into main categories: 1) intra-cerebral, 2) intra-abdominal (retroperitoneal or perirenal bleeding, intra-mural haematomas of intestine), 3) gastrointestinal (haematemesis and melaena, peptic ulcer) and 4) miscellaneous group which included the non-haemorrhagic deaths. The disturbing point is the steady progression of deaths due to intra-cerebral haemorrhage, from 23 in the first period of 5 years to 42 in the past 5 years. It is difficult to be precise over the exact cause of these deaths as post-mortem data is not given in the Death Certificate, but the majority of cerebral deaths appeared to be due to cerebral haemorrhage, or less often, subdural haematoma. Deaths from intra-abdominal bleeding have declined. The reason is that bleeding occurs usually over several days and can be stopped by replacement therapy. In earlier studies it was noted that gastrointestinal haemorrhage was one of the commonest causes of death (Wilkinson et al., 1961), and in the Manchester study it accounted for one third of the total deaths (Nour Eldin, 1961). Similarly, in Pittsburgh, one half of the total of 14 recorded deaths were due to retroperitoneal haemorrhage (Lewis, 1970). In contrast, cerebral haemorrhages are often too sudden or catastrophic to be affected by replacement therapy. The fourth category of deaths, the "other causes" include infections myocardial infaracts and cancers. The number of deaths directly due to jaundice or hepatitis was surprisingly low at 3 out of 269. There were 7 deaths in patients with inhibitors although these may well have been under-reported. Although there were only 3 recorded deaths from drug overdosage or suicide, it appears to us that the problem of addiction to pain-killing drugs has been increasing recently.

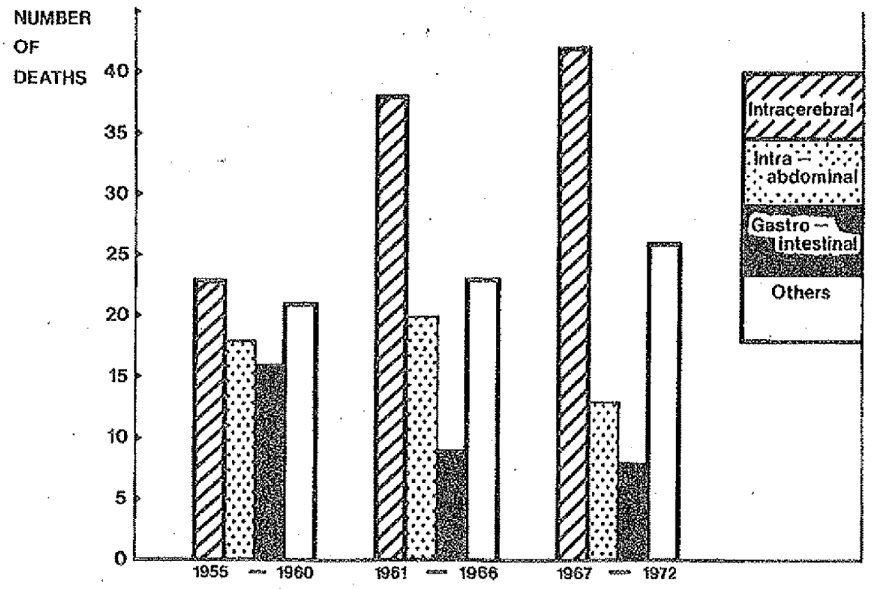

FIGURE 4. Major Causes of Mortality in Haemophiliacs, 1955-1972. Registrar-Generals' Reports, United Kingdom

Further information about mortality can be obtained by considering the longevity and age distribution of living patients with the same disease. In Figure 5 is shown an analysis of the age distribution of known haemophiliacs in the U.S.A. compared to the U.S. normal male population (N.H.L.I. Blood Resource studies, 1972). The proportion of young haemophiliacs is greater than their expected distribution in the community with a relative deficiency in the middle age or elderly groups. These figures reflect partly the lack of adequate effective therapy a decade or more ago and hopefully this youthful population will be more likely to grow into middle and old age than did their predecessors.

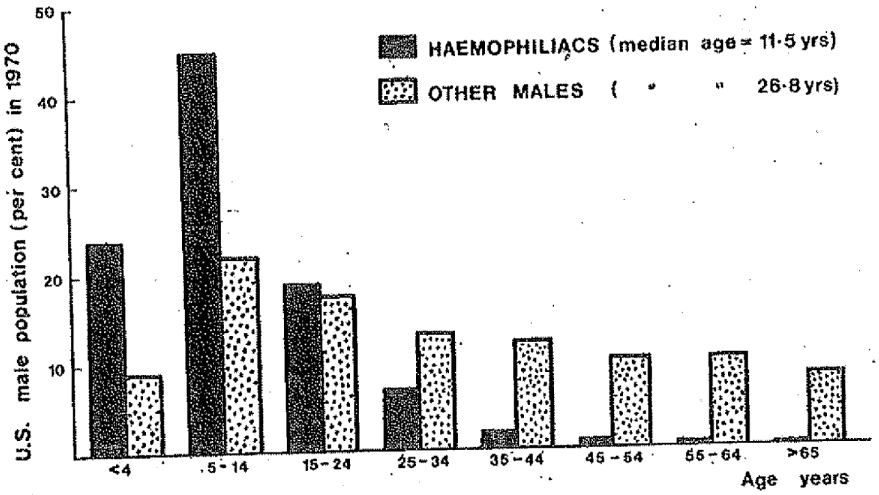

FIGURE 5. Age Distribution of Haemophiliacs Compared to the Normal Male Population. (N.H.L.I. Blood Resource Studies, 1972)

This type of data can be analysed differently to show how the proportion of haemophiliacs in our community decreases with increasing age. The dotted line in Figure 6 represents the age-related incidence of haemophilia in our community in the West of Scotland, compared to the overall incidence in the United Kingdom of just over 1 per 10,000. On the horizontal axis is shown the year of birth of our patients, the youngest patients being on the left and the eldest on the right. A relatively high incidence of young people dwindles off rapidly after the age of 35 years at a rate higher than that for the normal population.

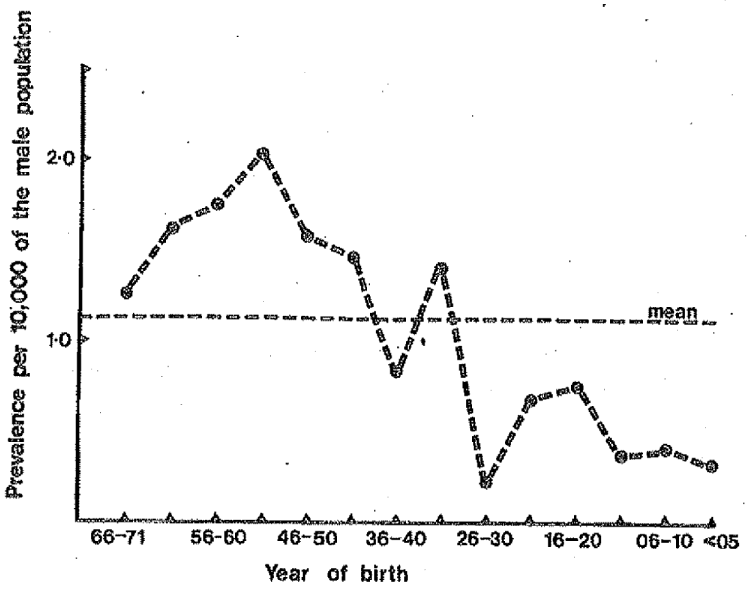

FIGURE 6. Age Distribution of Haemophiliacs Registered in the West of Scotland Compared with the Overall Incidence of Haemophilia in the Community

Finally, we show by courtesy of Dr. Biggs and the British Haemophilia Directors, the results of the United Kingdom Survey (British Journal of Haematology, in press) for the years 1969-74 (Table 1). Some of this data will overlap with the Registrar Generals' figures shown already. A total of 62 deaths were recorded. Of the 62 deaths, 29 or almost half were directly the result of haemophilia. Sixteen deaths were due to cerebrovascular haemorrhage and 7 due to other types of haemorrhage or operations. A further 20 deaths were the result of causes not related to haemophilia, including cardiovascular disease and cancer. Therefore, the overall chances of dying from haemophilia are about two-fold greater than the normal population. However, as shown in Table 2, a considerable number of the excess deaths due to haemophilia still take place at an early age. This table shows the age at death of patients having haemophilia. In the haemophiliacs less than 40 years there were 22 of the 57 deaths. Of the haemophilia B patients, an even higher proportion of deaths (6 of the 9) occurred at less than 40 years. Also, the deaths of patients with antibodies (10 of the 57) is some two-fold higher than their reported 10% incidence of the total population confirming that they do confer an increasing likelihood of earlier mortality.

TABLE 1. The Causes of Death of Haemophilia A Patients
United Kingdom Survey 1969-1974

	Number of Cases	
Intracranial bleeding	16	
Other types of bleeding	3	
Operations and complications	4	29
Jaundice	5	
Reaction to plasma infusion	1	
Cardiovascular disease	9	
Cancer	7	20
Miscellaneous (not haemorrhagic)	4	
No information	13	13
Total	62	

TABLE 2. Age at Death of Patients Having Haemophilia
United Kingdom Survey 1969-1974

	Haemophilia A 2,456 cases		Haemophilia B 373 cases
Age	All cases	Patients with antibodies	
0-19	10	2	3
20-39	14	2	3
40-59	22	4	2
60	16	3	1
Total	62	11	9
Average age at death	42.3	46.3	33.6

In summary, this data from the two sources contains both good and bad news. Clearly, the picture is optimistic in relation to the figures of Grandidier but bad in that an unacceptable preponderance of young people still die from haemophilia. Hopefully the recent advances in knowledge of hepatitis will reduce the mortality from liver disease. The clinical progress in the field of treatment of inhibitors is still not sufficient to provide a cure. Perhaps,

most attention should be drawn to the area of cerebrovascular and central nervous system haemorrhage, for these form the largest single cause of mortality in haemophiliacs. In particular, any form of trauma to the head should receive prompt and generous treatment irrespective of the initial clinical signs in an attempt to avert the development of the massive intra-cerebral or subdural haematoma.

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