FAMILIAL CARCINOMA OF THE PROSTATE IN A SIBSHIP WITH OTHER TUMOURS AND AN AGGREGATION OF PAGET'S DISEASE OF BONE

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INTRODUCTION

IT has long been recognised that some families have a high incidence of malignancy. Where a dominant inheritance is observed, e.g., with retinoblastoma, genetic factors clearly operate. In other families though the incidence of malignancy is high in one sibship, no cases are found in the preceding or succeeding generations. In this case either the disease is due to inheritance of a recessive gene from each parent, or else to some common environmental agent. Possibly both are necessary. Further, in a cancer sibship the cancers may be of different kinds. This makes it all the more necessary to consider chance association or different environmental agents. Nevertheless, in the literature there are various reports of families with an unusually high incidence of neoplasia in which the pattern of malignancy differs from individual to individual but the overall family pattern would suggest that there might be some genetic basis. Warthin1 2 reported such a family with an unusually high incidence of gastro-intestinal and uterine cancer. This family has been further reviewed on two occasions.3 4 In 1936 there were 174 members who were 25 years of age or over. In these there were 43 cases of primary carcinomas in 41 individuals and with two exceptions all involved the gastro-intestinal tract or endometrium. By 1970 there were more than 650 blood relatives, 95 of whom had developed a malignant neoplasm (13 had more than one primary neoplasm). Gastrointestinal and endometrial carcinomas were again predominant, though leukaemia (two cases) lymphosarcoma (two cases) and plasmocytoma (one case) had appeared.

Several other “cancer families” have been reported in the United States5 6 7 and Savage8 has reported a family in the United Kingdom. The possible import-
ance of HLA type in these families is suggested by the American report in which 20 of 21 members of "Cancer Family M" had HLA haplotype, HL-A2-HL-A12 (relative odds = 6.30).

Familial carcinoma of the prostate has been reported. We have observed such a grouping in a Belfast family.

FAMILY HISTORY

The family history has been obtained partly from the hospital notes and partly from members of the family. All members of the family were born and lived in North Belfast. The figure gives the family tree and indicates those members of the family suffering from malignant tumours. The table lists the cancers, simple tumours, and other documented diseases in the sibship. The mother died in 1936 and is said to have had bone disease, probably from the children’s description.

PEDIGREE OF FAMILY K

Paget’s disease. There are no medical records in this case. The father died aged 58. Necropsy showed renal arteriosclerosis with scarring, left ventricular hypertrophy and pulmonary oedema. No malignancy was found in the prostate.
| Sex    | Age at Death | Site of Malignancy | How Confirmed | Other Diseases                                      |
|--------|--------------|--------------------|---------------|-----------------------------------------------------|
| Female | 77           |                    |               | Paget’s disease of bone.                             |
|        |              |                    |               | Ischaemic heart disease.                             |
|        |              |                    |               | Non-functioning left kidney.                         |
|        |              |                    |               | Duplex right renal pelvis.                           |
| Male   | 67           |                    |               | Paget’s disease of bone.                             |
| Male   | 53           | Prostate           | Death Certificate |                                                   |
| Male   | 70           |                    |               | Diverticulitis of colon.                            |
| Male   | 50           | Prostate           | Histology     | Multiple subcutaneous lipomata.                     |
| Male   | 62           | Prostate           | Histology     |                                                    |
| Male   |              | Rectum.            | Histology     | Paget’s disease of bone.                             |
| Male   |              |                    |               | Rosacea.                                            |
| Male   |              |                    |               | Polycythaemia vera progressing to myelosclerosis.   |
| Male   |              | Prostate           | Histology     | Paget’s disease of bone.                             |
| Female | 56           |                    |               | Multiple sclerosis.                                  |

or elsewhere. Of the four siblings with carcinoma of the prostate, three have died, the mean age at death being 55 years. The fourth affected sibling is 62 years old, is on stilboestrol therapy and is reasonably well, having had a prostatectomy. He also suffers from Paget’s disease of bone. One sibling with Paget’s disease is alive and otherwise well. Two other siblings with Paget’s disease have died, apparently from myocardial infarction though necropsy was not carried out. The sibling with primary polycythaemia and adenocarcinoma of the rectum is still alive. The polycythaemia has progressed to myelosclerosis. He has no evidence of recurrence of the rectal tumour. In the third generation, one male died aged two years, from pneumonia. There are eleven third generation living members (aged 40-50), four of whom are males. All are apparently well.
DISCUSSION

Evidently this sibship has had familial carcinoma of the prostate. Judging by the paucity of published reports, this is rare. This rarity makes it possible that the concentration is a matter of chance, but it is somewhat against its being due to an environmental agent alone. We think it likely that this family concentration is due to these brothers inheriting a causative recessive gene from each parent. The parents were not known to be related. It may be, and it is quite likely, that a common environmental agent was also necessary to produce the cancers, in sibs genetically and immunologically vulnerable. Two of the brothers with carcinoma of the prostate were painters, one a grocer, and one a breadserver. We do not see any occupational risk in these employments. Because the parents are dead, we could not study them. The recessive gene evidently being very rare, we are not likely to see any manifestation in the next generation. Cousin marriage in any degree would be dangerous in this kinship, and the members should be warned against it. The next generation should be kept under surveillance, especially into middle age and old age.

It may be that the gene effect is on the immune system. HLA typing and other methods of studying the immune system became available only when so many of the siblings had died that no useful study was possible.

The existence of Paget’s disease of bone in the family may or may not be related. Concentration of Paget’s disease of bone in a family has been recorded in the past.13 Particular care must be taken in the male members of such a family as this to distinguish the osteosclerotic secondary deposits of prostatic carcinoma from Paget’s disease of bone. The presence of Paget’s disease in one brother was recorded by x-ray when he was 31. This is unusually early. We have not included as Paget’s disease in the figure or table two brothers in which the old clinical and x-ray reports recorded the possibility of the co-existence of both Paget’s disease and prostatic metastases but were indecisive.

What is the meaning of the occurrence of carcinoma of rectum and of myelosclerisisis (supervening on polycythaemia vera) in sib number 8? If either or both were caused by the recessive gene we have postulated, the expression has been very different. Perhaps different environmental agents were at work, or perhaps there were other modifying genes. Rectal examination of the prostate in this sib is impossible because of the proctectomy. A striking disability in him is a myopathy. There is severe muscle wasting and weakness. The serum creatine phosphate kinase has often been abnormally low. The serum iron has been low for a long time. The deficiency up to now has not been corrected so as to maintain a packed cell volume within normal limits.

Even more intriguing is the occurrence of multiple sclerosis in a sister. Another patient of ours, in another unrelated sibship with multiple cancers, has fibrosing alveolitis. There is evidence that the development of a disease may depend both on a genetically determined vulnerability to an environmental agent, and also on exposure to the particular environmental agent. An example is flax byssinosis.14 It is possible that a single genetic mechanism may make the subject vulnerable to more than one environmental agent. The disease developed in any one of the
sibship would then depend on the particular agent each one was exposed to. Variation must also be due to sex differences; females could not develop prostatic carcinoma.

Since the immune constitution is not likely to be modifiable, prevention will depend on identifying the environmental agent. If, as methods improve, genetic vulnerability can be determined, epidemiologists can study transmission in the vulnerable population, the only population worth studying. Even now susceptible kinships can be kept under surveillance. In oncology units enquiry should be made about other cases of cancer in the family. In this way affected kinships can be selected for surveillance. It is noteworthy that though Thiessen\textsuperscript{15} reported an excess of prostatic carcinoma in the male relatives (mainly fathers) of women with breast cancer, neither sister in this family had either breast or genital cancer. The daughters of the brothers with prostatic carcinoma perhaps should have special surveillance for breast carcinoma.

**SUMMARY**

Multiple familial malignancy is described in one sibship, all the members of which were born and lived in Belfast. Five of the eight males have had confirmed primary cancer. Four have had prostatic carcinoma. A fifth male has had a carcinoma of rectum and also myelosclerosis. One sister had multiple sclerosis. There is an aggregation of Paget's disease of bone in the family. It appears likely that a genetic influence in this family predisposes to prostatic carcinoma. The relation, if any, of this influence to the other diseases in the family remains uncertain.

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