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SIX CASES OF CARCINOMA OF THE OESOPHAGUS OCCURRING IN ONE FAMILY

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The great majority of cases of cancer met with in routine practice seem to occur sporadically and to have no obvious environmental or hereditary basis. This is true of carcinoma of the oesophagus, because, although factors such as sex, occupation, habits, and economic status may predispose to the neoplasm, the fundamental causes are unknown and all that can be said is that the disease is likely to be the result of a complex interaction between inherited and environmental factors. In the family to be described, in which there were six deaths in two generations from carcinoma of the oesophagus, it seems probable that a genetic factor was primarily responsible. The pedigree is reported in the hope that an investigation of similar families may throw light on the circumstances in which the disease may be inherited.

It is appreciated that data such as this may be very misleading, because a high familial incidence of cancer can be due to chance and will occur in any large series (Gorer, 1953). Nevertheless, it seems worth while investigating fully a family such as this, particularly as the oesophagus is a relatively rare site for carcinoma. The Registrar-General gives the following figures for 1952:

	Male	Female
All malignant neoplasms ..	45,429	42,213
Digestive organs and peritoneum ..	20,175	18,403
Oesophagus	1,475	850

The family concentration is thus the more remarkable, and, as the evidence is in favour of an inherited rather

than a fortuitous or environmental origin, it seems relevant to try to find out why particular members were affected and others remained free. Linkage studies may be of use for this purpose, and an investigation of the ABO blood groups has been carried out in as many as possible of the patients and their relatives. In this we were prompted by the recent finding of the statistically significant association between blood group A and carcinoma of the stomach (Aird *et al.*, 1953). In any future study involving a forward survey of similar families a complete investigation of the blood groups and other inherited traits would be well worth carrying out. This matter is referred to again later.

Comments

1. It will be seen from the pedigree that in generation II, three out of six, and in III, three out of eight siblings were affected by the disease. These figures are not significantly different from the 1:1 ratio that would be expected if the carcinoma were due to a single dominant gene present in the heterozygous state in I 1 or I 2 but failing to find expression in that generation. An alternative explanation is that the gene arose as a mutation early in the development of the gonads of I 1 or I 2. The fact that three individuals (II 7, III 1, and III 7) died at a rather early age does not materially affect the above hypothesis.

2. The pedigree also shows that in each generation those who were affected died at approximately the same age: in addition, those in the second cancer generation (III) contracted the disease much earlier.

3. In three of the cases (II 11, III 8, and III 13) the site of the cancer is known with certainty to have been at the lower end of the oesophagus. In one (III 10) the growth was in the upper third (but did not originate in the hypopharynx). In one (II 5), the symptoms suggest that it was in the mid- or lower zone, and in one (II 1) the site is not known. In the three cases (II 11, III 10, and III 13) in which the histology is known the growth was a squamous-cell carcinoma.

Cancer of the mid- and lower oesophagus is much more prevalent in men than in women (8:1, Price, 1950) and the disease is commoner among commercial travellers, barmen, and waiters than among those engaged in other trades: to explain this it has been suggested that the oesophagitis produced by alcohol and tobacco in association with a poor diet may be a predisposing factor.

An attempt has been made to assess the habits and environment of the present family. None of them was engaged in any alcoholic trade and in none was there any history of excessive smoking or alcoholism. An idea of the circumstances in which generation II lived has been obtained by visiting the house in which they were brought up and which is still occupied by II 12, III 28, and III 29, and IV 18. No adverse features were noted, the food being good, the house clean, and the economic status of the family very satisfactory. Thus the usually stressed exogenous factors are not apparent in the first cancer generation. It will be seen that this consisted entirely of women, and the proportion affected is explained on the genetic theory.

The transmitter (II 1) of the disease to the next generation married a man who died of pulmonary tuberculosis, and their environment and social status were very poor and the house in which they lived and reared their family is condemned. Their two affected daughters (III 10 and 13) continued to live there after they were married and until they died. Whether the decline in economic status of this branch of the family had anything to do with the continuance of the cancer is speculative, but it is known that the poorer classes show a greater proportionate death rate from oesophageal cancer than do the higher-income groups (Clemmesen, 1951). The offspring (III 16) of the

Key to Pedigree

(NOTE: Those individuals about whom no information has been obtained have been omitted from the key.)

- I 1. Born 1856. Died in 1926, aged 70, of rheumatic endocarditis. No blood relation to her husband.
- I 2. Born 1852. Died in 1915, aged 63, of cardiac disease and renal coma.
- II 1. Born 1882. Died in 1935, aged 53, of cancer of the oesophagus. No post-mortem examination. Blood group not known.
- II 2. Died, aged 63, of pulmonary tuberculosis.
- II 3. Died about 1932? from rheumatoid arthritis.
- II 5. Born 1885. Died in 1934, aged 49, of cancer of the oesophagus, following gastrostomy. Blood group not stated in hospital records. No post-mortem examination.
- II 6. Born 1879. Died in 1923, aged 44, from chronic bronchitis and myocardial degeneration. Occupation window cleaner.
- II 7. Born 1889. Died in 1913, aged 24, of toxæmia of pregnancy.
- II 9. Alive and well, aged about 62.
- II 11. Born 1894. Died in 1951, aged 57, of carcinoma of the oesophagus. Post-mortem examination showed squamous-cell carcinoma 6 cm. long starting 5 cm. above the cardia. No secondaries noted. Blood group A.
- II 12. Aged 63, suffers from bronchitis, otherwise well. Blood group A. Rhesus positive. No consanguinity with wife. His mother died of cancer, type unknown.
- III 1. Died in childhood. No other details known.
- III 3. Born 1903. Alive and well apart from "rheumatism." Blood group B, rhesus positive.
- III 5. Born 1905. Hypertensive, B.P. 200/110. Blood group O.
- III 6. Born 1891. Died in 1949, aged 58, from emphysema.
- III 7. Born 1908. Died in 1933, aged 25, from cerebral haemorrhage.
- III 8. Born 1910. Died in 1947, aged 37, of carcinoma of the oesophagus. Type of growth not known but oesophagoscopy showed ulcerating carcinoma 34 cm. from upper front teeth. X-ray examination showed obstruction to be in the lower third of the oesophagus. No post-mortem examination. Blood group B.
- III 9. Alive and well.
- III 10. Born 1913. Died in 1945, aged 32, of carcinoma of the oesophagus. Oesophagoscopy showed growth to be 15 cm. from incisor teeth and x-ray examination demonstrated obstruction to be at level of second and third dorsal vertebrae. Snippet showed rather poorly

- differentiated squamous-cell carcinoma. No post-mortem examination. Blood group not known.
- III 11. Born 1920. Alive and well.
- III 13. Born 1922. Died in 1951, aged 29, of carcinoma of the oesophagus. Post-mortem examination showed the entire lower third of the oesophagus to have been completely destroyed by necrotic malignant tissue. Malignant change extended into the stomach for about 2 cm. distal to the cardiac orifice. Secondary deposit in the upper pole of the left kidney. Histology of oesophagus showed squamous-cell epithelioma and that of the tumour deposit in the upper pole of the left kidney a keratinizing squamous epithelioma. Blood group not known.
- III 14. Alive and well.
- III 15. Born 1914. Alive and well.
- III 16. Born 1915. Alive and well. Blood group B, rhesus positive.
- III 17. Alive and well.
- III 19. Died in childhood.
- III 20-25. Alive and well.
- III 26. Born 1921. Alive and well. Blood group A, rhesus positive. Non-secretor.
- III 28. Born 1925. Alive and well. Blood group A, rhesus positive.
- III 29. Alive and well. Blood group O. Rhesus positive.
- IV 1 and 2. Alive and well.
- IV 3. Died at birth.
- IV 4 and 5. Alive and well.
- IV 6. Stillborn.
- IV 7. Died of meningitis in childhood.
- IV 8. Born 1932. Has elephantiasis of the legs. } Family history of this
- IV 9. Born 1933. Has elephantiasis of the legs. } on paternal side.
- IV 10. Born 1939. Alive and well.
- IV 11. Died in childhood.
- IV 12. Born 1941. Alive and well.
- IV 13. Born 1938. Alive and well. Blood group B, rhesus positive.
- IV 14. Born 1949. Alive and well.
- IV 16. Alive and well. Identical twin; born 1949. Blood group O, rhesus negative. Non-secretor.
- IV 17. Alive and well. Identical twin; born 1949.
- IV 18. Aged 4 months. Alive and well.

third affected sister (II 5) also lives in poor circumstances and has indifferent dietetic habits. As she is at risk genetically it will be especially interesting to see if she develops the disease.

4. The possibility that a gene responsible for the cancer might have been linked with one of the ABO blood groups has been investigated. It will be seen (a) that two of the patients with the cancer had different blood groups; II 11 was group A, and III 8 was group B; (b) that III 3, who, because of his age as compared with his affected siblings, may be no longer at risk, has a similar blood group (group B) to his brother who died of the disease.

These data are meagre, and all that can be said is that in this family the presumed gene determining the cancer has not been completely linked in transmission with one of the ABO genes.

The question of linkage when carrying out further family studies has been considered, and it is important that tests used should give clear-cut results. The following investigations appear suitable, and we are indebted to Professor L. S. Penrose for his advice on the matter: (a) the blood groups; (b) the ability to secrete blood antigen in the saliva; (c) the ability to taste phenyl thiourea; (d) fingerprints; (e) cephalic index; and (f) red-green colour vision and sex.

5. The hypothesis that the cancer is due to a single dominant gene is consistent with the facts and is by far the most likely explanation if further cases occur either in the third generation or in the offspring of II 5 or 11. Five individuals (III 15, 16, 26, 28, and IV 12) appear to be particularly at risk, and of these the first four need to be kept under close observation, since they are now of approximately the same age as their cousins were when they developed the disease. If the genetic theory is correct then there is less than a 20:1 chance that one or more of the five will not contract the disease.

The forward survey of the family will be of much interest in the light of the genetic and environmental information which has been obtained up to the present time.

A possible analogy with multiple polyposis of the colon and rectum suggests itself (Dukes, 1952), and perhaps what is inherited in this family is a precancerous condition of the oesophagus.

Summary

A pedigree showing six cases of carcinoma of the oesophagus in two generations is described. Reasons are given for thinking that in this family the disease may have been due to a single dominant gene. The possible part played by environmental factors is discussed. It is hoped that others will report any similar observations, since pooled information on families might be of great value in determining the factors responsible for the disease.

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Among the conclusions on the epidemiology of non-gonococcal urethritis reached at a recent symposium in Monaco, arranged by the International Union against the Venereal Diseases and Treponematoses, were the following: The prevalence of the disease is tending to approach, if not exceed, that of gonorrhoea. Its incidence is unaffected by race, geographical location, season of the year, or age and sexual habits of the patient. Although its incubation period has not been fixed definitely, it is longer than in gonorrhoea. Allergy seems to play no part in its causation, though ill-considered local treatment may do so. Examples of case-to-case infection have been observed.