**CANCER OF THE STOMACH** **MEDICAL APPENDIX**

**(including adenocarcinoma, lymphoma and sarcoma)**

## DEFINITION

1. Cancer is a term which embraces a large number of different diseases, the common feature of which is a malignant tumour. This is a growth (neoplasm) which is not circumscribed but which infiltrates the surrounding tissues and metastasises (spreads to other sites on the body), thereby producing secondary deposits. Any tissue in the body may be affected.

2. Cancers are classified according to the tissue of origin. **Carcinoma** arises from epithelial tissue and **sarcoma** from connective tissue. The suffix **blastoma** implies a tumour of embryonic origin.

3. Cancer of the stomach is a malignant tumour of the stomach. The most common type is **adenocarcinoma**. Other malignant tumours of the stomach include **lymphoma** and **sarcoma**, including fibrosarcoma, neurogenic sarcoma, liposarcoma and leiomyosarcoma.

4. Cancer of the stomach occurs most frequently in the antrum of the stomach. Several histological classifications have been proposed. Of these, the most widely accepted defines two types of adenocarcinoma, the **gastric** or **intestinal** type and the **diffuse** type. These two are quite different in morphology and have different prognoses. The gastric or intestinal type is polypoid and often accompanied by metaplasia of surrounding areas. The diffuse type comprises scattered or small groups of cells. This is the type which when associated with submucosal spread results in linitis plastica.

## CLINICAL MANIFESTATIONS

5. The symptoms of cancer of the stomach may be indistinguishable from those of benign peptic ulcer disease. The commonest symptom is epigastric pain, which is often relieved by food or alkalis. At presentation many patients with cancer of the stomach have advanced disease with anorexia, vomiting and weight loss. Dysphagia may occur. Haematemesis and perforation are relatively rare complications but anaemia from insidious blood loss is common. 50% of patients have a palpable epigastric mass and splenomegaly may occur if the portal or splenic vein is occluded.

6. Patients may present with problems related to metastases. Locally enlarged lymph nodes may be found clinically or on X-ray. Haematogenous spread may produce jaundice or ascites and metastases occur to bone, lung and brain.

7. Cancer of the stomach is associated with a number of extra-abdominal signs which may precede the diagnosis. These include recurrent thrombophlebitis. Acanthosis nigrans is a pigmented verrucous lesion affecting the flexor areas of the body. Dermatomyositis may be found. Characteristic neurological presentations include neuromyopathy and profound acute organic brain syndrome.

### Characteristics of neoplasia

8. Tumours arise when tissue growth becomes insensitive to normal control mechanisms. Usually cells multiply in response to a reduction in tissue cell density, the process ceasing when normal tissue architecture is restored. Tumours arise from a common ancestral cell which - years before clinical disease becomes apparent - begins to reproduce inappropriately. Malignant transformation results from mutation in the cell's genetic material.

9. These genetic mutations change the amount or the activity of the protein product. Two particular gene classes play major roles in triggering cancer. Normally **proto-oncogenes** encourage cell growth and reproduction: **tumour suppressor genes** oppose it. Mutated proto-oncogenes become **carcinogenic oncogenes** driving excess cell multiplication. Inactivated tumour suppressor genes contribute to cancer by depriving the cell of its braking system. For cancer to develop mutations need to occur in several of the original cell's growth control genes.

10. Cells insensitive to growth control generate, within tissues, subpopulations of cells whose subsequent progress depends on selection pressure, favouring the emergence of cells with the greatest growth potential. It is this process which determines the histology of a tumour and its clinical course. Tumour cells usually retain the characteristics of their tissue of origin. However, tissue differentiation involves the synthesis of molecules not essential to cell survival and so loss of the parent tissue markers may confer growth advantage. Dedifferentiation in a tumour implies high growth rate and high malignancy. Tumours can also metastasise (migrate via the lymph or blood stream) to other parts of the body, producing **metastatic** deposits.

## AETIOLOGY

### General risk factors for all cancers

11. Much is now understood about the origins and mechanisms of cancer in general, but the precise causes of individual tumours often remain unknown.

### Age

12. Some risk of cancer occurs at every age, but the risk for particular types varies at different ages. Most commonly there is a progressive increase in incidence from childhood to old age, (cancers of the skin, lung, gastrointestinal and genitourinary tracts, multiple myeloma and chronic lymphatic leukaemia). The rate of increase is typically proportional to the 4th or 5th power of age. Less commonly, there may be a peak in early life, with decline thereafter to zero, eg retinoblastoma or nephroblastoma.

### Gender

13. The incidence of cancer in relation to gender is not straightforward and it is changing - probably due to lifestyle and occupational changes. At the beginning of the last century overall cancer was more common in women due to the frequency of cancer of the cervix and the rarity, in both men and women, of cancer of the lung. Now, in developed countries, cancer is more common in men.

## Latent period

14. There is a delay between initial exposure to carcinogen and clinical disease. With short intense exposures, eg to ionising radiation at Hiroshima, solid tumours increase in incidence for 15-20 years. Incidence may then continue to rise, level off or decline depending on the tumour type. For acute leukaemia there is a peak incidence at about 5 years and very few cases appear after 30 years. Short intense exposure to carcinogens is exceptional and where exposure is chronic and prolonged, eg due to occupation, smoking or sunlight, cancer incidence increases with exposure duration. Precisely how this operates and how subsequent risk is affected by removal from the exposure is unknown.

15. Clinical cancer is the end result of a multistage process involving initiating and promoting agents. If the carcinogen is an initiating agent, eg asbestos, rather than a substance influencing a later stage nearer clinical manifestation, eg cigarette smoking, cancer incidence in the population may continue to rise, albeit more slowly, for a considerable time after exposure to the carcinogen has ceased.

## Risk factors in the individual case of all cancers

16. The main factors that determine whether a particular individual develops cancer relate to constitution and exposure to environmental factors.

## Genetics

17. The close connection between certain chromosomal abnormalities associated with recognised clinical syndromes and subsequent tumour development, eg polyposis coli and cancer of the large bowel, and xeroderma pigmentosum and skin tumours, confirms that an individual's genetic make-up has an effect on his susceptibility to cancer.

18. Many studies have looked at cancer rates in the families of individuals with the disease. There appears to be no material tendency for cancer in general to cluster in families and no genes have been identified that increase the risk of cancer in all tissues. However, all common cancers do cluster in families to some extent - the risk of a sibling of a patient developing a tumour at the same site is twice normal. This might be due to genetic susceptibility, but could equally well reflect lifestyle, eg diet, hygiene or a common legacy of infections in early life.

## Environmental factors

19. Our knowledge of the environmental causes of cancer relies on animal laboratory investigation and human epidemiology, with the two approaches complementing each other. Since there are features common to most cancers, there are factors which can cause cancer at all or many sites. Present evidence confirms the importance of life-style factors in cancer causation.

**Tobacco smoke**

20. Cigarette smoking is thought to cause 30% of all cancer deaths and has been conclusively linked to cancer of the lung, upper respiratory tract, oesophagus, bladder, stomach, liver, kidney and chronic myeloid leukaemia. It may also cause cancer of the colon and the rectum. Relevant factors include number of cigarettes smoked, tar content, age at smoking onset and duration of habit.

**Diet**

21. There is good evidence that some common cancers would be less common if diet were modified. Animal fat consumption, particularly red meat, high salt intake and ingestion of very hot beverages and food have all been linked to specific cancers. Similarly what is **not** in the diet may be important. Low consumption of vegetables and fruit, in the presence of high calorie intake, is associated with several different tumour types, eg childhood obesity and cancer of the breast and prostate, adult obesity and endometrial cancer. Consumption of alcohol (particularly along with cigarettes) increases the risk of cancer of the upper respiratory and digestive tracts. There is evidence that as little as two drinks a day may contribute to breast, colon and rectal cancer. In total, diet is considered to account for 30% of all cancer mortality in developed countries, alcohol for a further 3%, and salt for 1%.

**Radiation**

22. Radiation is difficult to avoid and in total, radiation of all types causes 2% of all cancer deaths. Most of these deaths result from natural sources particularly sunlight, UVB.

- **UVB radiation** causes 90% of all skin cancers, including basal cell cancers, malignant melanoma and squamous cell carcinoma.

- **Electromagnetic radiation** as a cause of cancer has been the subject of several recent studies. The results are confusing and inconsistent and reported associations may not be causal. It is of two main types:

  i. **Extremely low frequency fields**, eg power lines and household appliances. Basic science confirms that these radiations are of too low frequency to initiate cancer causing genetic mutation as they are of insufficient energy to ionise molecules.

  ii. **Radiofrequency electromagnetic radiation**, eg cellular telephones, microwaves and living creatures. Although more energetic than i., they are still unable to cause molecular ionisation.

  In conclusion, at this date there is no good scientific evidence that electromagnetic radiation causes cancer. Any possible association remains hypothesis.

- **Ionising radiation**

  Ionising radiation can penetrate animal tissues and damage DNA and theoretically has the power to produce cancer in most tissues. The actual risk due to exposure to ionising radiation may, however, be different. It is often overestimated and not evidence based. Amongst Japanese residents of Hiroshima and Nagasaki who survived more than a year after detonation, only 1% have died of tumours.

  Studies of humans exposed to high dosage of ionising radiation, eg the Japanese atomic bomb survivors or individuals medically irradiated for tumours, have shown an increased incidence of cancer due to that exposure. There is, however, no firm evidence from human low dose epidemiological studies which unequivocally demonstrates an increase in cancer incidence. This may be due to the very large size of study population which would be needed to demonstrate an increased incidence.

  For radiation protection purposes it is, therefore, accepted that there is no threshold level below which no carcinogenic effect is produced and the risk of a cancer developing is extrapolated on a dose-proportional basis from high to low doses and dose rates.

  All humans are constantly exposed to ionising radiation from both the natural environment and man-made products. The natural sources include cosmic radiation from space, radiation from the ground and from inhaled and ingested materials. Air travel and mining both increase exposure to background radiation. Radiation originating in the body comes mainly from potassium, while lungs are exposed through radon in inhaled air. Man-made radiation comes from medical uses, past atomic tests, man-made products and radioactive waste.

  Natural radiation differs depending on location. In the UK the average annual dose is less than 2,000 microsieverts. There is, however, a considerable range; it may rise to 8,000 microsieverts in some areas and to 100,000 in some homes. The UK average annual dose from man-made sources in total is less than 300 microsieverts and again there may be variation.

  From 1952 to 1958 the UK carried out 21 atmospheric nuclear tests in the Pacific Ocean. The locations were chosen because of their isolation and low natural radiation level. On average, the Christmas Island annual background radiation is less than 700 microsieverts.

**Radiation dose**

23. The effects of ionising radiation depend on the exposure size of the accumulated dose. A discussion of radiation dose is at Annex A.

## Therapeutic drugs

24. About 20 agents, not all of which are in current use, are known to cause cancer. Potential carcinogens may still be used if the hazard is judged to be less than the chance of saving a life, eg certain cancer drugs. Close scrutiny is kept on drug hazards and the position of oestrogens in hormone replacement therapy (HRT) - known to cause endometrial cancer, and of the oral contraceptive pills, which have been associated with carcinoma of the cervix, breast and hepatoma, is closely monitored. Together, prescribed drugs are held responsible for less than 1% of all fatal cancers.

## Occupation

25. Historically, study of occupational exposure has identified many important carcinogens. Material or process modification and, latterly, health and safety statute have removed many potential hazards in the developed world. However, the long latent period of cancer means that a considerable time will be required for the effects of industrial carcinogens to be eliminated and, equally, that new hazards may remain unsuspected for a long time. At present overall, occupation is considered responsible for 2-3% of all fatal cancers in developed countries. Particularly important occupational carcinogens are asbestos dust exposure, exposure to combustion products of fossil fuels and ionising radiation.

## Pollution

26. Investigation of the relation between environmental pollution - air, soil and water - and cancer is difficult because of the widespread nature of pollution and similar risk to people over a wide geographical area. It is generally accepted that, in the UK at the beginning of the last century, air pollution via combustion may have contributed to a few per cent of lung cancers. Over the last 30 years, with increasing statute on pollution reduction, this has become much less common. Advances in chemical analysis have allowed recent interest in pollution of soil and water as possible cancer risks.

27. Another complicating factor in accurately attributing risk of cancer to individual external agents is **interaction**. Some carcinogenic agents act together to produce effects much greater than the sum of the separate individual effects, eg smoking and asbestos in relation to cancer of the lung, smoking and alcohol in relation to carcinoma of the oesophagus, and aflatoxin and hepatitis B infection in cancer of the liver.

## Specific risk factors for gastric cancer

28. Gastric cancer is responsible for more deaths world-wide than any other type. The incidence is declining in Europe, North America and Australia, but remains high in Japan, China, South America and Eastern Europe. The decline is due to reduction in tumours of the body or distal part of the stomach. Cancers of the gastroesophageal junction are increasing in incidence in Europe and North America, and appear to have a different aetiology. In the UK, recent cancer registry statistics confirm that it represents 5.0% of all cancers and 5.8% of cancer deaths.

29. Both genetic and environmental factors are important in the aetiology of the condition. The disease is strongly age-related, is commoner in males and in those of blood group A. In the UK, it is most common in North Wales. There is a marked socio-economic gradient, with a much greater incidence in the less well off.

30. People from a high-incidence area retain the high disease risk on emigration to a low-incidence area. However, the next and succeeding generations have an incidence much closer to that of the new community.

31. Of the possible environmental influences, dietary factors have been extensively investigated. Salted and smoked fish, pickles, bacon, cooked cereals, alcohol and magnesium have all been postulated as causes of cancer of the stomach. None of these associations has been confirmed. There is evidence that fresh yellow vegetables may have a protective role.

32. Chemical factors may be important in the aetiology of cancer of the stomach. A possible relation of nitrosamines to gastric cancer has been proposed because nitrosamines are known carcinogens in animals. However it has not been confirmed that they cause cancer in humans and at present, the hypothesis remains speculative.

33. Cancer of the stomach is conclusively linked to radiation exposure, being confirmed by the report of the Radiation Effect Research Foundation follow-up study on survivors of the atomic bomb and the 1994 UNSCEAR report.

34. There is a weak association between smoking and cancer of the stomach.

35. There is an association between gastric ulcer and cancer of the stomach in that cancer may, rarely, develop in a chronic benign gastric ulcer. The risk of such a malignant change is less than 1%.

36. There is a causal association between gastric resection and cancer of the stomach, when mucosal metaplasia, subsequently leading to carcinoma, develops in areas close to the site of the anastomosis. This is thought to arise due to prolonged contact of the gastric mucosa with irritant bile.

37. Medical opinion once held the view that cancer of the stomach is more common in those with pernicious anaemia and it was considered that there was a causal connection. It is not now thought that there is any such connection. Cancer of the stomach develops more frequently in areas of gastric atrophy. Pernicious anaemia also arises from a lesion of the stomach characterised by gastric atrophy. Thus both conditions may have a common basis, but one does not cause the other.

38. Carcinoma of the stomach has not been shown to be caused by climatic extremes, trauma, physical or mental stress or lowered resistance arising from hardship or other diseases. There is no evidence that its progress is dependent on external factors other than medical treatment.

39. There has been much interest in the role of the organism Helicobacter pylori, in dyspeptic disease, including gastric cancer. Several studies have shown that populations at high risk of gastric cancer have a high prevalence of H pylori infection from childhood. The association does not hold, however, in all populations studied, eg in Africa there is a high prevalence of H pylori infection from childhood but a low prevalence of gastric cancer. H pylori infection similarly does not explain the male predominance. The reported association with H pylori is not shown in cancer of the cardia or gastroesophageal junction.

40. A model of gastric carcinogenesis has been proposed, suggesting a continuous progression of lesions of increasing severity over a period of 20 to 30 years. From normal gastric mucosa the stages are superficial gastric, chronic gastritis, hypochlorhydria, chronic atrophic gastritis, chronic atrophic gastritis with metaplasia, dysplasia and finally carcinoma. However, empirical evidence shows that this sequence of events is not inevitable; the progression of lesions may arrest at any stage and regression or even healing, may occur. The factors which influence the progression of lesions or their healing are unknown.

41. The above model is not proved but there is considerable corroborative evidence. 10% of patients with atrophic gastritis develop gastric cancer over 15 years and there is a high association between metaplasia and gastric cancer.

42. It is clear that present understanding of H pylori and gastric cancer is not complete. If H pylori is present but not treated any associated gastritis will not resolve. It has been observed that H pylori gastritis may progress to atrophic gastritis. If there is pangastritis or antral gastritis with atrophy of the antrum or corpus of the stomach, the risk of cancer of the stomach is increased by 18 times. Overall it would appear that H pylori can cause cancer but that this outcome is not inevitable. It may be that there is a requirement also for genetic predisposition or the presence of a carcinogenic co-factor.

## CONCLUSION

43. Cancer of the stomach is a malignant tumour of the stomach. Certain factors discussed above are known to be associated with an increased risk of developing the disease. The precise relation between the organism, Helicobacter pylori, and cancer of the stomach is not known. There is no evidence that the course of the condition is affected by environmental factors other than those involved in its treatment.

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March 2000

**Annex A**

## Radiation dose

1. The first definition of a unit of radiation dose was made in 1928 by the International Congress of Radiology. The roentgen (R) was defined as that quantity of radiation which produces in 1 cm of air one unit of charge of either sign, thus defining a unit of exposure. Units of **absorbed dose**, the actual energy absorbed in the tissue being irradiated are now used. The radiation absorbed dose or **rad** is now cited in SI (Systeme Internationale) units – joules per kg – of absorbing material. The fundamental unit, 1 joule/kg, is 1 gray (1 Gy), equivalent to 100 rads (R).

2. Different radiation types have greater or lesser effect per unit dose, so they are all expressed relative to the effects of X-rays, ie. a unit equivalent dose is used. To calculate the roentgen equivalent in man (**rem**), the absorbed radiation dose is multiplied by a radiation weighting factor, dependent on type and energy of the radiation. The current SI unit of equivalent dose is the **Sievert**. For X-rays and gamma rays the equivalent dose in sieverts and the absorbed radiation dose in grays are the same. The relationship between the different dose units is:-

   1 gray (Gy) = 1 joule/kg = 100 rads (R) = 100 rems (r) = 1 sievert (Sv) = 1,000 millisieverts (mSv) = 1,000,000 microsieverts (microSv). Typical doses of radiation include:

   Chest X-ray – 0.02 mSv
   Brain scan – 7 mSv
   Bone scan – 4 mSv
   Average annual UK dose from cosmic rays – 0.26 mSv
   Average annual UK dose from gamma rays – 0.35 mSv
   Average annual UK dose from natural background radiation – 2.2 mSv

3. **Effects of total body irradiation**

| **Equivalent dose (Sv)** | **Effect** |
|---|---|
| Sub lethal to man<br>0.0001 (0.1 mSv) | Around 2 weeks' natural background radiation, no detectable effect |
| 0.001 (1 mSv) | Around 6 months' natural background radiation, no detectable effect |
| 0.01 (10 mSv) | No detectable effect |
| 0.1 (100 mSv) | Minimal decrease in peripheral lymphocyte count, no clinical effect |
| 1 (1000 mSv) | Mild acute radiation sickness in some individuals (nausea, possible vomiting), no acute deaths, early decrease in peripheral lymphocyte count, decrease in all WBC and platelets at 2-3 weeks, increase in late risk of leukaemia, solid tumours |

| Equivalent dose (Sv) | Effect |
|---|---|
| Lethal to man<br>10 (10,000 mSv) | Severe acute radiation sickness, severe vomiting, diarrhoea, death within 30 days of all exposed individuals. Severe depression of blood cell and platelet production, damage to gastrointestinal mucosa. |
| 100 (100,000 mSv) | Immediate severe vomiting, disorientation, coma, death within hours |
| 1000 (1,000,000 mSv) | Death of some micro-organisms, some insects within hours |
| 10,000 (10,000,000 mSv) | Death of most bacteria, some viruses |
| 100,000 (100,000,000 mSv) | Death of all living organisms, denaturation of proteins |

**Radiation dose limits**

4. Since the days of Marie Curie it has been appreciated that ionising radiation exposure may be hazardous to health. Radiation dose limits were first recommended for ionising radiation exposure in 1928. The statutory limit on the amount of radiation to which the general public may be exposed in excess of natural background radiation and excluding medical exposure is set, from 1 January 2000, at 1 mSv per annum.

5. The most important source of man-made exposure is medical investigation which accounts for 90% of man-made exposure. Average natural background radiation is raised to 2.6 mSv by all man-made exposure. UK estimated exposure, excluding medical investigation, is 0.04 mSv. Other statutory limits include occupational dose limits. From 1 January 2000, these are 20 mSv per annum for classified workers and 6 mSv per annum for unclassified workers.

January 2000