abnormalities and the risk of thrombosis are reversed in polycythaemic patients by therapeutic phlebotomy. The liver is the main site for clearing plasminogen activator,[14] and in the absence of antiplasmin this may account for the localisation of thrombus formation in the hepatic outflow. Thrombocytosis is a common feature in myeloproliferative disorders, and platelet IgG Fc receptors may be activated in vivo by the high concentrations of circulating immune complexes found in these disorders.[15 16] The raised concentrations of plasma β thromboglobulin and the high incidence of clinical thromboses are both reduced by prophylaxis with aspirin.[10 15]

There is also a high incidence of thrombosis in systemic lupus erythematosus and an associated reduction in endothelial cell synthesis of prostacyclin[17] and vasculitis. DNA antibodies are found in about a tenth of patients with myelofibrosis,[18] and a vasculitis affecting small vessels has also been described.[19] It remains to be established, however, whether these observations are important in the aetiology of thrombosis in chronic myeloproliferative disorders. Another feature that has been seen in a few patients with myelofibrosis is the paroxysmal nocturnal haemoglobinuria syndrome.[20] This is another clonal haemopoietic stem cell disorder, which is more often associated with aplastic anaemia and acute leukaemia. Patients with paroxysmal nocturnal haemoglobinuria have a high incidence of intra-abdominal thrombosis, which is probably caused by complement induced platelet activation.[21 22] Paroxysmal nocturnal haemoglobinuria-like abnormalities found by the sucrose and cold antibody lysis tests[20] and activation of complement[23] are also common in myelofibrosis, and thrombosis in chronic myeloproliferative disorders may therefore be linked to these abnormalities.

There are, therefore, several different explanations for the hepatic vein thrombosis seen in chronic myeloproliferative disorders. The development of thromboses in patients with occult disorders suggests that previously overlooked mechanisms may be important. Different mechanisms may be at work in different patients, and each may require different treatment strategies.

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Second malignant tumours in head and neck cancer

Commoner than elsewhere

Although advances in surgical repair, radiotherapy, and chemotherapy have improved control of cancer of the head and neck,[1 2] these improvements have hardly influenced survival.[3-5] One of the main reasons for this failure is the development of second malignant tumours, which occur more commonly in the head and neck than in any other site.[6-8] Among patients with head and neck cancer more are alleged to die from second tumours than from their original disease.[3 6] Despite recent interest in second tumours little is known about risk factors and in particular about the influence of treatment of the first primary tumour on development of a second.

Several workers have tried to assess the influence of TNM stage, sex, site, and behavioural characteristics on the development of second malignant tumours. The risk of a second primary tumour is thought to be independent of the stage of the first[7 9] and seems to be no greater in men than in women,[10] but whether it is influenced by the site of the primary tumour remains controversial.[7 9] The greatest risk, however, seems to be continued use of alcohol and tobacco, though opinion varies about which is more influential. Wynder *et al* found tobacco but not alcohol to be associated with an increased risk.[11] They also found, however, that stopping both smoking and drinking did not prevent further tumours from developing, although Moore showed a decreased incidence when smoking ceased.[12] Moore also noted a greater risk of second malignant tumours with continued smoking,[13] although Castigliano did not.[14] Others have found that smoking and drinking together seem to increase the risk of second malignant tumours.[7 9 15 16] Thus, although smoking and drinking may increase the risk, stopping smoking and drinking do not seem to remove it.

The increased interest in second malignant tumours has not been matched by an equally critical appraisal of the effect of treatment on the primary lesion. Most squamous carcinomas of the head and neck region are managed with surgery, radiotherapy, or a combination of both. Most studies have not clearly distinguished between the numbers of second tumours arising after surgical treatment of the primary tumour and after radiotherapy.[6 8 9 17-23] Those that have recorded them separately have made little or no attempt to correlate this with the extent of disease at the time of initial treatment,[7 10 11 24-28] although one study found that the risk of second malignant tumours was independent of the stage of the disease.[9]

Moreover, the length of follow up has varied widely among the studies. There are also great difficulties in comparing surgery and radiotherapy. Not all patients are screened for other primary tumours at the time of initial treatment, so a second tumour might be wrongly attributed. Furthermore, the longer patients survive the more likely they are to develop another tumour.[6 7]

The few studies that have tried to assess the effect of treatment suggest no significant difference between radiotherapy and surgery within five years after treating the primary tumour.[10 28] For example, over five years Parker and Enstrom found that 11 out of 678 surgically treated patients and 22 out of 1473 irradiated patients developed second primary tumours.[10] Beyond five years, however, the incidence of second malignant tumours seems to be higher in those who received radiotherapy.[7 11 24 26] For example, among 535 patients with laryngeal carcinoma followed up for five to 25 years, second primary tumours occurred in 3·9% of those treated by surgery and 9% of those treated with radiotherapy.[24] Such tumours do not, however, always occur in previously irradiated sites.

Recently we have shown that normal oral mucosa exposed to ionising radiation during the treatment of orofacial tumours displays abnormal DNA profiles.[29] Although these returned to the normal diploid state within six weeks after completing treatment, the potential for latent radiation damage remains.[30-32] This may explain why after five years the incidence of second malignant tumours seems to be greater in those who received radiotherapy. The fact that children and adolescents exposed to irradiation show a predisposition to neoplasia in the head and neck[33-36] invites suspicion that the same may be true for adults exposed to radiotherapy. Yet another factor is the potential interaction between radiation damage and continued use of tobacco or alcohol. These potential causal factors for oral cancer might act as promoters of any radiation induced damage and hence give rise to more mucosal abnormalities.

The tumour itself may exercise an effect on the regional mucosa. Slaughter *et al* first described the concept of field cancerisation,[37] and recent research using exfoliative cytology has identified evidence for field change within the normal oral mucosa of patients with oral cancer even in those who do not smoke or drink alcohol.[38] If that is so then radiotherapy has a greater potential to treat the surrounding mucosa than surgical excision.

Difficult though it would be, an attempt should be made to establish the relative risk for second malignant tumours of one form of treatment over another. At the very least TNM classification, age, smoking and drinking habits, method of treatment, and development of further tumours within five and 10 years should be recorded.

The promise shown by certain retinoids in preventing neoplastic change[39] seems to be confirmed by recent reports,[1 2] but their inability to affect local, regional, or distant recurrence is disappointing and should prompt further study into the effect of all treatment strategies.

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