Section of Laryngology

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Oxygenation in Radiotherapy of Malignant Disease of the Upper Air Passages [*Abridged*]

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The Oxygen Effect in Radiotherapy

The relationship between the sensitivity of all living cells, normal and malignant, to damage by X-rays and the amount of oxygen dissolved around them at the exact time of irradiation has been fully established by radiobiologists, notably Dr L H Gray and his colleagues. If a cell is deprived of oxygen its radiosensitivity may be reduced by a factor of nearly 3, but its sensitivity will be increased only very slightly in the presence of excess oxygen (Gray *et al.* 1953, Gray 1959 *a*, *b*, 1961, for summaries).

There is unequivocal evidence that solid growing mouse and rat tumours contain a proportion of cells which are anoxic (Hollcroft *et al.* 1952, Gray *et al.* 1953, Dittrich & Stuhlmann 1954, Goldfeder 1958, Du Sault *et al.* 1959, Thomlinson 1961, 1963, Du Sault 1963), and there is an accumulating body of clinical experience which indicates that a similar situation exists in many human tumours (Hultborn & Forssberg 1954, Churchill-Davidson *et al.* 1955, 1957, Churchill-Davidson 1960, 1961, Madigan 1962, van den Brenk *et al.* 1964).

Although these anoxic cells form only a very small proportion of the total number of cells in tumours, 1% being an average estimate (Thomlinson 1961, Powers & Tolmach 1963), they are likely to make all the difference between success and failure to sterilize a tumour by radiotherapy because, with their radiosensitivity reduced by a factor of nearly 3, they may survive the largest radiation dose it is possible to give in clinical practice and cause recurrence of the growth (*see* Fowler *et al.* 1963, from data of Hewitt & Wilson 1959).

How can this 'oxygen effect' be overcome? From the curve relating radiosensitivity to oxygen tension (Fig 1) it will be seen that there are two possible methods: (1) Try to improve the oxygenation of the tumour by providing more oxygen. (2) To deprive the whole tumour area of oxygen by cutting off its blood supply and then giving 3 times the normal radiation dose.

The second or 'anoxic method' is likely to be the most certain in effect, but can only be applied in limb tumours in which it is easy to cut off the blood supply by applying a tourniquet. It cannot be used in the treatment of tumours in other parts of the body as this involves making the whole patient anoxic and the reserves of oxygen in the tissues, especially the oxygen attached to myohæmoglobin, are such that cerebral damage occurs long before these are exhausted (Lindop 1962, Nunn 1962). Even for limb tumours, the anoxic method may be dangerous except for tumours of the distal part of the limb, because the tourniquet will not cut off the blood supply going down the

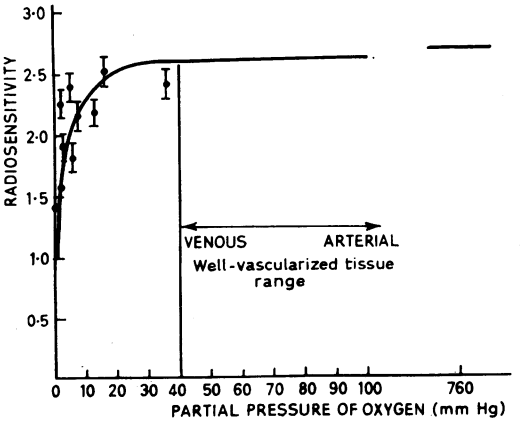

Fig 1 *Curve relating the radiosensitivity of the mouse Ehrlich ascites tumour cells to the oxygen tension around them at the time of irradiation. It represents the type of relationship for all living cells and indicates the region of the curve occupied by cells in well-vascularized tissue. (Adapted from Gray 1959a, by kind permission)*

inside of the femur or humerus. It is clear that the anoxic method is likely to be of limited use, at any rate for the present, especially as tumours of the distal parts of the limbs are comparatively rare.

How, therefore, can we try to improve the oxygenation of tumours? The most obvious way is for the patient to breathe oxygen and, owing to the circulatory conditions in tumours, it seems likely that a sufficient increase will be obtained only if oxygen at high pressure is breathed. A newer method is arterial infusion of hydrogen peroxide before and during irradiation (Mallams *et al.* 1962, Corgill 1962). Although this method has its hazards and can only be undertaken in a limited number of tumour sites, I understand that marked increases in tumour oxygen tension may be obtained and it seems that, when the complications have been overcome, it may well prove a most valuable method in the treatment of many ear, nose and throat tumours.

At St Thomas's Hospital, since 1954, we have been irradiating patients while they have been breathing high pressure oxygen. The oxygen pressures used are 4 atmospheres absolute (45 lb/sq. in. gauge pressure) for an anæsthetized patient, and 3 atmospheres absolute (30 lb/sq. in. gauge pressure) for a conscious patient. Almost all patients are now treated while conscious and are given a maximum irradiation dose of 3,500 – 4,000 rads in 6 treatments over eighteen or nineteen days.

The problems involved are both technical and physiological. The patient must be totally enclosed in a pressure chamber. As it may not even be possible to see the patient during treatment, means of making observations at a distance have to be devised. Great care has to be taken to avoid static or other electrical sparking which in the presence of oxygen might cause a fire or explosion. The physiological problems can be divided into two groups: those associated with raised barometric pressure and those associated with raised oxygen tension.

In the first group the most important problem is extensive rupture of the tympanic membranes or hæmorrhage into the middle ears. In our experience, about one person in three has difficulty in opening his eustachian tubes, excluding those with upper respiratory infections; we therefore perform bilateral myringotomies on all our patients by inserting small segments of hypodermic needles which remain *in situ* until the three-week course of treatment has been completed; no anæsthesia is required for this procedure. Pressure differentials in the paranasal sinuses and the gastro-intestinal tract may cause pain on decompression but this has seldom occurred in our patients. More gas is dissolved in the body fluids and during decompression bubbles may form (the bends or caisson disease); fortunately this is not a problem when oxygen is breathed owing to its being rapidly metabolized. The increased viscosity of gases makes breathing harder and causes impairment in the elimination of carbon dioxide, though this is not severe enough to be important. Too rapid compression or decompression will cause marked and very unpleasant temperature changes: we pressurize conscious patients to 3 atmospheres absolute in approximately fifteen minutes and decompress them in four to five minutes; anæsthetized patients are compressed rather faster.

In the second group the chief problem is oxygen convulsions, which are probably due to a direct toxic effect of oxygen on the central nervous system (Bert 1878, Dickens 1946, Donald 1947, Lambertsen *et al.* 1953*a*). The higher the oxygen pressure the shorter the time before symptoms occur. Barbiturate anæsthesia markedly increases the period a subject may be maintained at a given pressure (Marks 1944, unpublished, Taylor 1954, personal communication); this is why we are able to treat anæsthetized patients at 4 atmospheres absolute compared with 3 if they are conscious. We do not yet know which is the better method. In more than 800 exposures, of which over 400 have been without anæsthesia, 3 conscious patients and 1 anæsthetized patient have convulsed; no harm has resulted to any of them. Other effects are of little importance. Lung damage may occur in small animals (Smith 1899, Johnson & Bean 1957) but there is no evidence that it occurs in man except after extremely prolonged exposures. Rises in P_{CO_2} and blood pressure, bradycardia and electrocardiographic changes have all been reported (Donald 1947 Whitehorn & Bean 1952, Lambertsen *et al.* 1953*b*, Taylor 1958) but, with the exception of the rise in blood pressure, appear to be of little practical importance; moderate rises in blood pressure have been the rule in most of our conscious patients and, as rises in systolic blood pressure of up to 60 mmHg have occurred, we do not pressurize very hypertensive patients until their pressure has been reduced by a period of bed rest, &c.

All the best techniques of conventional radiotherapy – multiple fields, wedge and compensating filters, rotation, &c. – can be used with equal accuracy in the chamber.

All patients with head and neck tumours have a plaster cast made. This helps them to keep still and allows tungsten blocks to be mounted to protect the cervical spinal cord, which is liable to be damaged by irradiation. After pressurization, the patient is maintained at full pressure for fifteen minutes before irradiation is started because polarographic measurements of oxygen tension in tumours have shown that it may take

at least this length of time for the tumour to saturate with oxygen (Evans & Naylor 1963).

Results of Treatment

A preliminary trial, in which half the tumour was irradiated in air and the other half irradiated while the patient breathed high-pressure oxygen, showed recognizably more histological damage in the half irradiated in oxygen (Churchill-Davidson *et al.* 1955); in 1955, therefore, we started a trial giving potentially curative treatment to whole tumours. As we hoped to demonstrate an improved radiation response quickly and as we did not know what complications to expect, we selected for treatment only those patients whose tumours were so locally advanced that they were considered to have no chance of cure by conventional radiotherapy. All patients treated to date have been selected in this way.

We last analysed the results on April 1, 1963, by which time 160 patients had been treated. As would be expected when patients with such advanced disease were selected, 38 (24%) of them had developed metastases outside the treated area and no less than 10 (6%) had developed a second primary tumour. Although not uniform, the overall response to treatment has been definitely better than would have been expected from conventional radiotherapy and in 15–20% of cases it has been dramatically better.

Moderate-size tumours with a reasonably good blood supply, which had not caused excessive damage to the normal surrounding structures, have shown the greatest 'oxygen effect'. Especially good results have been obtained in treating tumours of the tongue, floor of mouth, tonsil, nasopharynx, larynx and, rather surprisingly in view of the high distant-metastasis rate, bronchus. The one tumour site in which the response has been disappointing has been the brain. The response of secondary squamous carcinoma in lymph glands, notoriously resistant to conventional radiotherapy, is very markedly improved.

Table 2
Tumour sterilization in irradiated area

	High-pressure oxygen series	*Air series*
Sterilization of the primary – all sites:		
Total cases available for assessment	146	65
Clinical assessment	75 (51%)	12 (18%)
Proven histologically to date	37 (25%)	2 (3%)
Sterilization of glands – secondary squamous from head and neck tumours:		
Total cases available for assessment	56	25
Clinical assessment	39 (70%)	6 (24%)
Proven histologically to date	18 (32%)	2 (8%)

Three patients have survived over seven years without recurrence, a further 3 patients over six years, 1 patient over five years, 2 patients over four years, 4 patients over three years, 4 patients over two years and 23 patients over 1 year. Moreover, the rates of sterilization of the growth in the irradiated area are much higher than the number of long-term survivors would suggest. Of the 160 cases treated 146 allowed assessment of the result in the primary area. In 75 (51%) there was clinically no residual growth and this had been histologically proven in 37 (25%).

Fifty-six of 65 patients with secondary squamous carcinoma in glands from head and neck tumours allowed assessment. In 39 (70%) there was clinically no residual growth and this had been histologically proven in 18 (32%).

Equally encouraging results have been obtained by van den Brenk, who has treated more than 250 patients over the last two years (van den Brenk *et al.* 1964). Although neither of us has been able to run a fully randomized control series, we have both treated a number of comparable patients to similar irradiation dosage in air at atmospheric pressure (Tables 1 and 2).

Table 1
Number of patients surviving without apparent recurrence in treated area

	Time of survival							
		Years						
	6 months	*1*	*2*	*3*	*4*	*5*	*6*	*7*
High-pressure oxygen series	80/139 (57%)	40/127 (31%)	17/106 (16%)	13/88 (15%)	9/69 (13%)	7/58 (12%)	6/46 (13%)	3/21 (14%)
Air series	20/62 (32%)	8/54 (15%)	4/37 (11%)	0/21 (0%)	0/15 (0%)	0/10 (0%)	–	–

Note: Ten patients have been excluded from the high-pressure oxygen series: 5 with carcinoma of breast who had mastectomies performed after irradiation; 4 with laryngeal neoplasms who died from coronary thrombosis (2 cases) and staphylococcal enteritis (2 cases) within three months of treatment and in whom the irradiated area was found to be histologically clear; and one with a carcinoma of nasopharynx, who was clinically clear of disease when lost to follow-up three months after treatment.
One patient has been excluded from the air series. Her carcinoma of parotid gland failed to regress completely after treatment and a radiogold implant was subsequently carried out

Complications

(1) *Laryngeal cartilage necrosis* has occurred in 21% of patients in whom the larynx has had to be irradiated. The onset is usually six to nine months after treatment. We do not know whether it has been due to a direct effect on the cartilage cells or to damage to their blood supply or to a combination of both; cartilage in other sites has not been affected and there is no doubt that the necrosis has been, at least partially, due to the use of oxygen as no necrosis has occurred in 35 patients treated to similar dosage in air. Fortunately a small dose reduction appears to have eliminated this complication without reducing the tumour sterilization rate; we have had no case of cartilage necrosis for the last eighteen months.

(2) *Failure in complete healing of tissue defects:* It is not surprising that, in spite of the tumour being sterilized, it has been difficult to get tissue defects, caused by some of the more massive tumours, to heal; the stroma will be damaged by the irradiation and the blood supply much reduced. If tumours above a certain size are to be treated, it may well prove necessary to carry out reconstructive surgery to bring the tissue edges together immediately or very soon after the course of radiotherapy has been completed (van den Brenk 1963, personal communication). An alternative method may be to give the patient high-pressure oxygen to breathe for several hours daily for some weeks after treatment as has been used to obtain healing of benign ischæmic ulcers on the legs (Illingworth *et al.* 1961).

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The Effect of Intra-arterial Hydrogen Peroxide

Hydrogen peroxide perfusions are still experimental but hydrogen peroxide has been used in the past in attempts to treat phosgene poisoning, to oxygenate a placenta of a premature fœtus and to introduce oxygen into necrosing malignant glands prior to radiotherapy.

The technique of Mallams, Finney & Balla (1962) involved perfusing 0·12% hydrogen peroxide and using about 250 ml in about thirty minutes. Radiotherapy was given during the last few minutes of the perfusion.

Among the results of some basic experimental work at the Middlesex Hospital on this type of perfusion it was found that when blood and hydrogen peroxide are mixed there is an increase in oxygenation which is exactly the same as the theoretical calculated increase – which means that all the added oxygen oxygenates hæmoglobin. All the blood is fully oxygenated and then the mixture bubbles. All the oxygen is accounted for and so nothing else can be oxygenated. Examination of the mixtures do not show any methæmoglobin formation. In terms of ml of oxygen per 100 ml of blood this type of perfusion in the external carotid artery produces an increase of 2 ml of oxygen per 100 ml of blood; therefore venous blood would be raised half way to arterial