MODEL OF DIFFUSION OF OXYGEN TO SPHEROIDS GROWN IN STATIONARY MEDIUM — I. COMPLETE SPHERICAL SYMMETRY

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The use of spheroids as a tumor model has become commonplace since it was discovered that many cell lines can form spheroids when grown on a surface to which the cells cannot attach. This culture system complicates experiments which depend on oxygen supply because the oxygen concentration in the vicinity of a stationary spheroid has not been well defined. We present in this paper solutions to the oxygen diffusion equation for simple geometries: a spheroid in an infinite stationary medium and in a finite spherical stationary medium. Comparison of these solutions provides an estimate of the oxygen supply to a spheroid in a Petri dish. We show that typical spheroids can be expected to cause a substantial depletion of the oxygen in the nearby medium. Any disturbance of the medium or the spheroids will temporarily increase the oxygen supply. We provide a method for estimating the rate of return to equilibrium in the finite cases. These results indicate that the oxygen supply to stationary spheroids can be altered temporarily by small movements or changes in temperature which cause convection currents, or permanently by changes in the depth of the medium.

1. Introduction. Multicellular structures termed spheroids which grow by cell proliferation from aggregates of a few cells to diameters of up to a few millimeters have been used extensively as in vitro tumor models (Sutherland et al., 1971; Sutherland and Durand, 1976; Folkman and Greenspan, 1975; Carlsson, 1977; Yuhas et al., 1977). When spheroids are grown in suspension the oxygen concentration profile can be determined readily since the growth medium at the surface of the spheroids is renewed continuously by the sedimentation of the spheroids through the medium. The calculated oxygen concentration profile has been used to infer that the maximum distance that
oxygen can penetrate corresponds to the thickness of the rim of viable cells under certain growth conditions (Franko and Sutherland, 1979).

Spheroids are more commonly grown in stationary medium, probably because the cells of most cell lines cannot adhere to each other well enough to permit the spheroids to remain intact in stirred medium. Petri dishes or multiwell chambers are used. The spheroids are covered with a few millimeters of medium, and rest either directly on the plastic or on a thin layer of agar or other gelatin-like substance which is permeable to oxygen. This arrangement requires oxygen to diffuse from the air above the medium, which requires a concentration gradient through the medium. Thus the calculation of the oxygen concentration profile within the spheroid also requires a solution for the concentration of oxygen in the medium near the spheroid. Any movement of the spheroid will disrupt the external concentration gradient, thereby altering the oxygen gradient within the spheroid. Hence it is of some importance to be able to estimate the return time to steady state. The objective of this paper is to show, using two hypothetical, less complex geometries, that typical spheroids can cause a substantial local depletion of oxygen.

In his book, Rashevsky (1960) gave a mathematical model for the concentration of oxygen in steady state both inside and outside a consuming sphere. In the case of complete symmetry he obtained complete solutions to his equations when no anoxic zone occurred within the sphere, and partial solutions when an anoxic zone did occur. These equations have been applied to estimate the critical size of a spherical structure at which a central anoxic zone develops (Blumenson and Bross, 1976), but they are not adequate to yield the oxygen concentration profile inside and outside a spheroid in a finite medium when the spheroid contains a large anoxic zone.

In this paper we present the complete solution in the completely spherical case of the concentration equations in both an infinite and a finite spherical medium. We also give a method for estimating the return time to steady state after a disturbance.

These boundary conditions correspond to spheroids grown suspended in a stationary medium. In a future paper a model simulating spheroids grown near an impermeable barrier will be described, in which case there is no longer complete symmetry.


2.1. Derivation of the steady-state models. In this section we consider four models representing the oxygen concentration gradient produced by growing spheroids suspended in both infinite and finite media, in the case of no anoxic zone as well as the case where an anoxic zone occurs.

Let \( u(r) \) be the concentration of oxygen outside the spheroid, and \( v(r) \)