TUMOR ANGIOGENESIS
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Tumor Growth in Cornea

1. Tumor growth in the cornea. Gimbrone has shown an interesting experiment with the cornea of the rabbit. A Brown-Pearce tumor implanted within 3 mm. of the limbus grows slowly until it is vascularized in about 3 days and then it grows rapidly as a big lump extending through all layers of the cornea. In this particular case, after awhile it regressed due to some immune phenomena and the vessels regress also.

   But tumor implanted in the center of the cornea grows very slowly for a long period of time (1 days). Its growth is by diffusion only as it is nourished by dialysis of the fluid in the anterior chamber just beneath the cornea. It spreads as a 2 cell monolayer in the cornea but will not pile up any more than will a bacterial colony since the thickness of the tumor layer is limited by the distance of diffusion of nutrients and wastes and oxygen.

   After the edge of the growing monolayer slowly creeps past the 3 mm. mark from the limbus then vessels begin to come out and eventually this tumor becomes vascularized and then picks up its rate of growth.

2. Theoretically the substitution of silicone oil for the dialysis fluid would prevent the diffusion phenomenon and the tumor would not spread slowly.

3. This is an absolutely beautiful experiment and a single paper describing it (after we repeat it with V-2 carcinoma) should go either to the Journal of the National Cancer Institute or the Proc.of the National Acad. of Sciences. In the conclusion of this paper, this experiment showed the following:

   1. It shows that a rapidly growing tumor can be slowed markedly by "diffusion-limited" growth.

   2. It shows that the limits of simple diffusion of nutrients and wastes in the cornea are not more than (?) 1 mm., i.e., the thickness of the cornea since the tumor layer never becomes thicker than 3 or 4 cells.

   3. However, the vascularized tumor increases in all dimensions going to all layers of the cornea.

   4. Another point is that the vascularized tumor has a growth rate many times (__ x) that of the tumor limited to diffusion growth.

   5. This experiment also shows that by using the cornea, one is able to separate out in time and space the events which must occur in all solid tumor growth in-vivo. That is, an early slow growing diffusion phase in which there are no capillary hook-ups and a later fast growing perfusion phase in which the capillaries allow for rapid growth.

   6. This also shows that in the unvascularized tumor in the cornea growth of tumor is arrested in one dimension that is the up and down because of diffusion limitations. However, in the lateral dimension, there is continuous growth because of the dialysis from the anterior chamber. One could postulate that in a solid matrix in which diffusion limitations were uniform in all directions, that there would be a point at which growth would stop since

the surrounding normal tissues would be competing for the same diffusion area. Therefore, an equilibrium would be reached in the non-vascularized tumor in which growth and death of the cells in the nodule would be equal.

7. Finally this experiment shows the diffusion time and distance over which T.A.F. is effective. It appears that beyond 3 mm. T.A.F. gradients are so low or concentrations are so low that capillary endothelial cells do not respond. This is of interest because one sees only local blood vessel invasion in the tumors and does not see distant vascularization or remote vascularization.