To ensure its sustained growth, a tumour may secrete chemical compounds which cause neighbouring capillaries to form sprouts which then migrate towards it, furnishing the tumour with an increased supply of nutrients. In this paper a mathematical model is presented which describes the migration of capillary sprouts in response to a chemoattractant field set up by a tumour-released angiogenic factor, sometimes termed a tumour angiogenesis factor (TAF). The resulting model admits travelling wave solutions which correspond either to successful neovascularization of the tumour or failure of the tumour to secure a vascular network, and which exhibit many of the characteristic features of angiogenesis. For example, the increasing speed of the vascular front, and the evolution of an increasingly developed vascular network behind the leading capillary tip front (the brush-border effect) are both discernible from the numerical simulations. Through the development and analysis of a simplified caricature model, valuable insight is gained into how the balance between chemotaxis, tip proliferation and tip death affects the tumour's ability to induce a vascular response from neighbouring blood vessels. In particular, it is possible to define the success of angiogenesis in terms of known parameters, thereby providing a potential framework for assessing the viability of tumour neovascularization in terms of measurable quantities.

1. Introduction. Unless furnished with an adequate blood supply and a means of disposing of waste products by a mechanism other than diffusion, a solid tumour cannot grow beyond a few millimetres in diameter and remains in an avascular state. Avascular nodules can be cultivated in the laboratory (Folkman, 1976) or can be found in vivo (carcinomas in situ being a good example) and typically consist of a central necrotic core surrounded by a thin outer layer of live, proliferating cells. Mathematical models describing this avascular growth can be found in, for example, Greenspan (1976), Chaplain (1990), Adam and Maggelakis (1990), and references therein.

Transition from this dormant avascular state to the vascular state, wherein the tumour possesses the ability to invade surrounding tissue and metastasize
to distant parts of the body, depends upon its ability to induce new blood vessels from the surrounding tissue to sprout towards and then gradually penetrate the tumour, thus providing it with an adequate blood supply and microcirculation. In order to accomplish this neovascularization, it is now a well-established fact that tumours secrete a number of diffusible chemical compounds into the surrounding tissue and extracellular matrix. Much work has been carried out into the nature of such factors and their effect on endothelial cells since initial research began in the early 1970s with Folkman, culminating in the purification of several tumour angiogenic factors, the cloning of their genes from libraries of complementary DNA (cDNA) and the determination of their amino acid sequences (Strydom et al., 1985; Folkman and Klagsbrun, 1987; Deshpande and Shetna, 1989). Throughout the rest of this paper, we use TAF as a generic term for the various growth factors and other chemicals which elicit a response from neighbouring blood vessels. The extensive literature on the subject is testimony to its importance in our understanding of the mechanisms by which solid tumours develop and grow (see, for example, the reviews of Folkman and Klagsbrun (1987) and Paweletz and Knierim (1989)). Various experimental techniques and model systems have been developed in order to study and identify the processes involved in angiogenesis and these include implanting a section or fragment of a solid tumour into the cornea of various test animals such as the rabbit (Gimbrone et al., 1974) or mouse (Muthukkaruppan et al., 1982), the dorsal air sac in the rat (Folkman, 1976), the hamster cheek pouch chamber (Eddy and Casarett, 1973), the chick embryo chorioallantoic membrane (CAM) (Ausprunk et al., 1974; Klagsbrun et al., 1976; Ishiwata et al., 1988) and capillary endothelial cells in tissue culture (Jaffe et al., 1973; Birdwell et al., 1977; Madri and Pratt, 1986). These model systems enable us to document the complete sequence of events which takes place during tumour-related angiogenesis.

In response to the angiogenic stimulus, or TAF, which has been secreted into the surrounding host tissue by the tumour cells, the endothelial cells of neighbouring capillaries firstly release proteolytic and collagenolytic enzymes that degrade and disintegrate their basal lamina and the intercellular matrix through which they must move. They then migrate towards the solid tumour, the source of the angiogenic stimulus. Solid sprouts are formed as the endothelial cells elongate and align with one another. The proliferation of endothelial cells a short distance behind the sprout tip contributes to the number of migrating cells. Thus solid strands of endothelial cells are formed in the extracellular matrix, lumina develop within these strands, and mitosis continues, increasing the sprout length. Anastomosis—the process whereby reconnections and fusions form a closed network—occurs between neighbouring sprouts, with the formation of loops which network the blood circulation. Pericytes appear at the base of the loops and the endothelial cells form a basal