of DNA synthesis and cell proliferation and that the function of nuclear receptor is concerned only with the regulation of the autophagic process. The latter view receives inferential support from observations on the growth behavior of human mammary and prostatic cancers. For example, whereas one tumour may display hormonal dependence, manifested as tumour regression induced by endocrine ablative therapy, another tumour may display hormonal responsiveness, manifested as tumour regression induced by endocrine additive therapy. However, since neither dependence nor responsiveness of mammary tumours is expressed in the absence of receptor proteins for steroid-hormones, it is likely that in both cases tumour regression hinges on the function of a common receptor-dependent mechanism.

With the present level of understanding, the control of proliferative growth by steroid-hormone is best visualized in terms of a model consisting of three regulatory elements assumed to be components of the cellular genome. It is proposed that, first, an initiator gene is responsible for switching on DNA synthesis and cell proliferation in the presence of an adequate concentration of steroid-hormone; second, a nullifier gene is responsible for switching off DNA synthesis and cell proliferation when the organ reaches a normal size, and accounts for negative feedback; and third, an autophage gene programs a cell for its own eventual destruction by capacitating the autophagic mechanism, perhaps through the formation of an inactive steroid–receptor complex. A fall in the concentration of hormone below levels required for the maintenance of a differentiated cell stimulates autolysis and removal of cells; it is conceivable that this effect depends on the function of a receptor molecule while is transformed from an inactive to an active state by declining hormonal concentration.

Whether endocrine therapy will result in carcinostatic or carcinocidal effects can probably be predicted by determining both the concentration of steroid-hormone and of receptor protein within the nucleus of the tumour cell. However, even on this basis some autonomous tumours will be indistinguishable from dependent tumours, and to improve the response rate to therapy, other methods which do not rely on either steroid-hormone or receptor measurements are needed to identify such resistant tumours.

A large number of autonomous tumours do not contain cytoplasmic receptor proteins and fail to transport steroid-hormones across the nuclear membrane. In respect to this group of neoplasms, a matter of practical importance that requires clarification is whether there is any potential for controlling cell proliferation with methods that would promote the entry of steroid-hormones into the nucleus of the autonomous cell to activate homeostatic processes such as those which suppress DNA synthesis or stimulate cellular autolysis. Clinical experience derived from the treatment of human mammary and prostatic cancers suggests that in selected cases the application of high doses of steroid may be sufficient for this purpose, but compounds which increase the permeability of the nuclear membrane to the passage of steroid-hormones should be sought.

In summary, growth of a normal hormone responsive organ appears to be ordered by the function of three constraint mechanisms which are sensitive to the intranuclear concentration of steroid-hormone. For the complete expression of these constraint mechanisms several properties underlying hormonal responsiveness must be manifested by the cell, including the presence of cytoplasmic receptor, the ability to transfer steroid-hormone into the nucleus, the competence to form nuclear receptor, and the fidelity of the interaction between steroid-hormone and chromatin.

Cytoplasmic receptor is not an exclusive indication of hormonal dependence or hormonal responsiveness *in vivo*, but its presence is associated with enhanced ability of the cell to incorporate steroid-hormone into the nucleus. Steroid-hormone is required for the initiation of DNA synthesis and cell proliferation, and nuclear receptor may not be required for these responses. On the other hand, it is possible that the function of the latter molecule is concerned with negative feedback or cellular autolysis.

**18. Hormone-responsive mammary tumours in GR-mice**
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Continuous treatment of castrated female GR-mice with estrone and progesterone leads to the appearance of mammary tumours within 3–4 months. Such tumours usually are hormone dependent, i.e. they are only transplantable in castrated mice if these animals are given estrone and progesterone. During serial transplantations in hormone-treated animals the tumours progressively lose their responsiveness towards estone and progesterone, and finally they become autonomous. We have obtained evidence from estrogen receptor assays that the hormone-responsive mammary tumours are mixed populations of hormone-dependent cells (which contain estrogen receptor) and autonomous cells (which are practically devoid of estrogen receptor). The hormone-dependent tumour cells do not multiply in the absence of estrone and progesterone, but the autonomous cells multiply in the absence of these hormones. The finding that the mammary tumours lose their hormone responsiveness after repeated serial transplantations appears to be due to the faster multiplication of the autonomous cells in the tumour as compared to the hormone-dependent cells. We have extended these studies to characterize these two types of mammary tumour cells in more detail. The investigations include comparative morphological studies of hormone-responsive and autonomous tumours, assays of various steroid receptors, assays of virions and antigens of the mammary tumour virus, and assays of peroxidase in the tumour cells. A pilot study has been started to determine whether the GR-mouse system can be used as a model to investigate optimal conditions for combined hormonal and chemotherapy.

**19. Growth pattern and estrogen receptor levels of dimethylbenzanthracene-induced tumor during pregnancy and lactation,**
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Hormonal influences on tumor growth and estrogen receptor (ER) in breast cancer of rats induced by dimethylbenzanthracene were studied during pregnancy and lactation to elucidate the mechanism of prolactin-estrogen action and interaction. During pregnancy, palpable tumors were stimulated to grow rapidly and new active sites were initiated. Just prior to or immediately after delivery, rapid regression of tumor was observed. Some regressed tumors were reactivated, some continued to regress, and some remained static during the latter part of lactation. When cytoplasmic ER of tumors from pregnant rats was examined by the Dextran-charcoal assay, only one of the 23 identified adenocarcinomas did not contain measurable levels of ER. Significant reduction of ER occurred just prior to delivery and during early lactation. Among the 30 regressed tumors from early lactating rats, 19 had very low ER levels ($<1{\cdot}5$ fmol/mg protein) while the rest had significant but lower ER levels