ness of those antisera in stimulation of DNA synthesis might be related to the methods of immunization and the 
sources of the antigens employed. A steep dose response 
curve for DNA stimulation by ALG with some reduction 
of response at the highest ALG concentration has also 
been reported using guinea-pig anti-rabbit-lymphocyte 
serum on lymph node cell cultures.

The narrow limits of stimulating activity expressed by 
ALG probably relate to an inherent complement-inde-
pendent cytotoxic activity. The low number of viable leu-
kocytes found in the presence of high concentrations of 
ALG indicates that these concentrations did not simply 
inhibit DNA per se, but instead destroyed the viability of 
the cells. This is probably why the non-specific stimulation 
of DNA synthesis by PHA is also prevented in high con-
centrations of ALG. After dilution of the ALG to a point 
that cell viability as measured by dye exclusion remained 
at 45% or above, PHA was again active in the presence of 
ALG. This confirms the findings of Lundgren et al.,
Simons et al., and Woodruff et al. that the stimulatory 
effect of PHA may be inhibited by ALG. However, the 
inhibition may reflect cell death or injury rather than a 
more specific biochemical effect.

In the case of ALS, the lack of 3H-thymidine uptake at 
the 2 highest concentrations was associated with a cell 
viability which, while reduced, was as good or better than 
that at the peak DNA response to ALG alone. This sug-
gests that either the dye exclusion test is an inadequate 
measure of cell injury or an additional mechanism is in-
volved in the failure of response to the highest concentra-
tions of ALS.

Peak DNA synthesis occurred with only 2.1 mg of ALG 
protein as compared to 3.75 mg of ALS protein, suggesting 
a higher specific activity of ALG. Whereas the ALS con-
tains all of the serum proteins, the ALG is the purified 
7S IgG fraction, which is known to contain the specific 
antilymphocyte activity. Since the stimulation of DNA 
synthesis occurs in such a narrow dilution range of ALS or 
ALG, this in vitro technique appears not to be an ideal 
assay for antilymphocyte activity.

Résumé. La faculté qu’ont le sérum (ALS) antithymo-
cyte du cheval et son dérivé IgG (ALG) de stimuler la 
synthèse du DNA avec les leucocytes périphériques hu-
 mains a été contrôlée in vitro. Sauf déviation même faible 
de dosage, l’ALS et l’ALG stimulent la synthèse du DNA. 
Une forte concentration de ALG inhibe l’effet stimulant 
de la phytohémagglutinine. Cela peut contribuer en partie 
à la mort de la cellule ou à sa dégradation à cause de la 
grande concentration de l’ALS ou de l’ALG.

N. Prasad and J. J. Trentin

Division of Experimental Biology, Baylor College of 
Medicine, Houston (Texas 77025, USA), 
20 September 1971.

Immunological Blockade of the Adenohypophysis and its Possible Application in Prophylaxis and Therapy of Neoplasia

Introduction. Immunological intervention provides one 
method to block organ function. Since antisera to organs 
can be prepared, it should be possible, therefore, to inhibit 
specifically or to modulate function by varying doses of 
antiserum or immunoglobulins. In particular, we wish to 
discuss the inhibition of the adenohypophysis. This gland, 
besides secreting stimulating factors for various target 
glands, such as adrenocorticotropic hormone (ACTH), 
thyrotropic hormone (TTH) and gonadotropic hormones 
(GH), is also secreting daily a large amount of somatotro-
pic or growth hormone (STH). We wish to propose in 
this paper that STH is probably involved in the growth 
of many types of tumours and that consequently blocking 
its production should lead to tumour growth inhibition.

The hormone dependence or the sensitivity to hormones 
of many malignant or benign tumours in humans is well 
known. In the attempt to control growth of many tumours, 
hormones are therefore used extensively. Hormones have 
been and are administered even in very high doses, the 
so-called ‘pharmacological dosage’ in many types of neo-
plasia such as the localized or systemic tumours of the 
lymphatic and haematopoietic systems, carcinoma of the 
breast, carcinoma of the prostate, myelomatosis and many 
others. However, no serious attempt has been made to try 
to interfere in a specific manner with the function of the 
hypophysis which receives the inhibiting or secretory 
stimuli both from the periphery and from the hypothala-
mus and which regulates the entire endocrine system.

Role of growth hormone. STH is a phylogenetically old, 
polypeptide molecule, which, like prolactin, is present even 
in primitive species. It has probably acquired new func-
tions in higher organisms but preserved its former func-
tions present in the lower species. One of these acquired 
functions in mammals is presumably that of controlling 
cell proliferation either alone or in chronological synergism 
with other hormones. These actions of STH become evident 
when the target cells, as for example in the epiphyseal 
cartilage of the long bones, appear during growth in post-
natal life. It is therefore important to establish in man 
which tumour cells have acquired or maintained the cha-
acteristics of STH dependence of certain tissues for their 
growth. This concept of hormone dependence may be 
useful for adopting the appropriate hormone therapy for 
certain tumours.

STH has a structural similarity with another hormone, 
prolactin, which is seemingly secreted by the same or very 
similar so-called acidophilic cells of the adenohypophysis. 
Both of them have a ‘trophic’ action as shown in many 
experimental systems. Another main point to be considered 
is that the acidophilic cells secreting somatotropic hor-
mone, constitute to a large extent the cell population of 
the adenohypophysis. The reason for this is unknown. It is
also not clear why such a large amount of STH is secreted by the anterior hypophysis since there is no indication for a specific fundamental function being performed by it in the adult age. In fact, the effect of hypophysectomy in adult mammals indicates that severe metabolic disfunctions or death of the operated animals can be prevented by replacement with thyroxine and corticosteroids, STH being not needed for maintenance of normal health. Hypophysectomy can even be performed in pregnant primates\(^1\) and humans\(^8\) without consequences, provided thyroxine and corticosteroids are supplied. Also in this case STH is not needed for growth of the embryo and for normal delivery. Endogenous STH is also not required for growth of hypophysectomized fetal lambs\(^8\). The fact remains that STH-producing cells populate the hypophysis in very large number until old age\(^1\). It is possible that STH is needed in large amounts because there is no specific target gland to mediate its action, and many tissues, thyroid and adrenal glands included, need its constant trophic action\(^8\). The endocrinological concept that hormones and in particular STH act as 'amplifiers' of functions, strongly suggests that inhibition of growth of STH-dependent tumours might be achieved by blocking the hormone from which tumour cells depend for their rapid and invasive proliferation. STH has also been shown to be very active on many tissues but mainly on the thymus and thymus-derived cells during their formation, and to be required for the maintenance of a functioning immunolymphatic system. These aspects have been discussed extensively in previous papers\(^5,10\).

**Endocrine control of tumours.** In our view, up to now, endocrine control of tumours has been partially unsuccessfully, due to the technical impossibility of precise manipulation of the endocrine system. Without this exact control, damaging side effects or serious consequences may happen to functions which depend on efficient and well balanced hormonal regulation. One is in fact incapable of predicting the effects of a long-lasting inhibition of certain hormones such as STH.

The possibilities available for a therapeutic regulation of hormone-dependent tumours will now be shortly considered.

1. **Ablation of the hypophysis and/or of other endocrine glands by operational techniques or by radioisotopes.** This procedure is being used as 'extrema ratio' in advanced cancer of the breast, when formation of metastasis has occurred. The consequences of such a drastic traumatizing procedure are evident. It can only be considered as a palliative method, especially to reduce the pains from bone metastasis. Removal of other endocrine glands has also been performed for retarding growth of several other tumours.

2. **Inhibition of hormones by anti-hormone sera or by specific chemical inhibitors or competitors of hormones.** This approach is still largely theoretical. Aside from the technical difficulties, the main problem remains that when a hormone is neutralized by various means, more hormones of the same type might be produced and released by the corresponding endocrine gland, unless one could provide an inhibitor which selectively damages the respective hormone-producing cells. This might be a specific endocrine gland inhibitor such as alloxan, which destroys the insulin-producing β-cells in the pancreas.

3. **Administration of hormones in high doses.** This method is being widely used, especially with regard to corticosteroids. There are, however, several reasons against its application: the direct toxic action of such high dosages of hormones, this action being controversial on the respective hypophyseal cells secreting the stimulating hormone, the side effects and the fact that more antagonistic hormones will be produced to balance the levels of the hormone administered. Examples of antagonistic hormones are growth hormone and insulin, growth hormone and corticosteroids.

4. **Inhibition of the 'releasing factors' in the hypothalamus by chemical means or by specific antibodies.** This possibility has the same contraindications as mentioned under 2. In addition, its application is actually highly hypothetical as too little is known about the chemistry and properties of these factors. However, development of a specific inhibitor of growth hormone releasing factor is urgent. It might lead to a specific block of growth hormone synthesis and consequent block of growth hormone-dependent tumours.

We believe that if any possibility exists to prevent or control tumour onset or growth by interfering with hormones, it is STH which is the key-hormone. This view is supported by abundant literature about a) the determining role of STH in onset of some tumours\(^11-22\), b) its role in growth of primary tumours or of metastasis\(^11-22\), c) its direct application: the direct toxic action of such high dosages of hormones, this action being controversial on the respective hypophyseal cells secreting the stimulating hormone, the side effects and the fact that more antagonistic hormones will be produced to balance the levels of the hormone administered. Examples of antagonistic hormones are growth hormone and insulin, growth hormone and corticosteroids.

---