

The Impact of Peptide Hormone Receptor Research on Clinical Medicine

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For a hormone to act upon its target cell, it must initially make contact with some cell constituent. The lipid soluble steroid and thyroid hormones freely permeate the cell membrane and interact with specific binding proteins in the cytoplasm and nucleus of the cell. In contrast, the water soluble polypeptide hormones (and the catecholamines and other neurotransmitters) bind to specific receptor sites on the surface of the cell membrane, and the formation of this hormone-receptor complex initiates a process of message transmission. Using radioactively labelled hormones, which not only retained much of their biological activity but also had a high specific activity, the presence of receptors for many peptide hormones have been demonstrated on the plasma membrane surface of a wide variety of target cells (Table 1). Some hormones such as ACTH have been difficult to label successfully because of the molecular damage incurred by the labelling procedure. However, in other situations it has been possible to use more stable analogues or antagonists as markers; for example, to identify adrenergic receptors. Where this has not proved practicable, membrane purification procedures have improved the preparation of biologically active hormones such as FSH and TSH by abstracting the intact hormone that remains after labelling.

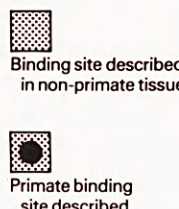
BIOLOGICAL RESULTS OF HORMONE-RECEPTOR INTERACTION

The most important criterion for a hormone receptor is the demonstration of a direct functional relationship between receptor occupancy and a biological response. The pioneering work of Sutherland and his colleagues (Robison *et al.*, 1971) demonstrated that hormones which circulated as 'first messengers' interacted with the membrane-bound enzyme adenylate cyclase on the plasma membrane surface of the target tissue, as shown in Fig. 1. The cyclic AMP produced subsequently binds to the regulatory site of a protein kinase which, in turn, activates its own catalytic sub-unit and transmits the 'message' to the appropriate target. A large number of hormones act via adenylate cyclase but the biological second messengers for many others, for example insulin, prolactin, and growth hormone, are still unknown.

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Table 1

| | ADRENAL | FAT | LIVER | PROSTATE SEMINAL VESICLES | KIDNEY | MAMMARY TISSUE | LYMPHOCYTES | MONOCYTES | TESTIS/OVARY | THYROID | UTERINE MYOMETRIUM |
|-------------|---------|-----|-------|------------------------------|--------|-------------------|-------------|-----------|--------------|---------|-----------------------|
| ACTH | ■ | | | | | | | | | | |
| ADH | | | | | ■ | | | | | | |
| ANGIOTENSIN | ■ | | | | | | | | | | ■ |
| FSH | | | | | | | | ■ | | | |
| GLUCAGON | | ■ | ■ | | | | | ● | | | |
| hGH | | | ● | | | | ● | | | | |
| INSULIN | | ● | ■ | | ■ | | | ● | | | |
| LH/hCG | | | | | | | | | ● | ● | |
| OXYTOCIN | | | | | | ■ | | | | | ● |
| PTH | | | | | ■ | | | | | | |
| PROLACTIN | ■ | | ■ | ■ | | ■ | | | ● | | |
| TSH | | ■ | | | | | | ● | ■ | ● | |



■ Binding site described in non-primate tissue

● Primate binding site described.

The biological effects of hormones have been most commonly correlated with cyclic AMP production in cell membrane preparations but evidence of biological activity has also been obtained using isolated intact target cells. In such systems it has been possible to measure protein kinase activation, ion transport and, where appropriate, end hormone production in addition to cyclic AMP. This technique has been widely applied, using cells prepared from the thyroid, parathyroid, adrenal, testis, ovary, and pituitary. Although the second messenger for insulin is not known, its biological activity can be measured by its direct effect on glucose oxidation, for example in adipocytes (Olefsky, 1976) and in the same way the actions of prolactin have been monitored by a number of different techniques such as measurement of ornithine decarboxylase activity (Richards, 1975), steroid binding proteins (Chamness *et al.*, 1975), cholesterol accumulation (Bartke, 1969), and mRNA synthesis.

It is at present uncertain how the binding of a hormone to its receptor leads to activation of the relevant second messenger system. There is evidence that hormone binding sites are separate and relatively independent from the adenylate cyclase, and these two sites may be freely mobile and able to float within the plane of the cell membrane (Singer and Nicholson, 1972; Jacobs and Cuatrecasas, 1976). Such separate units would associate only as a result of an

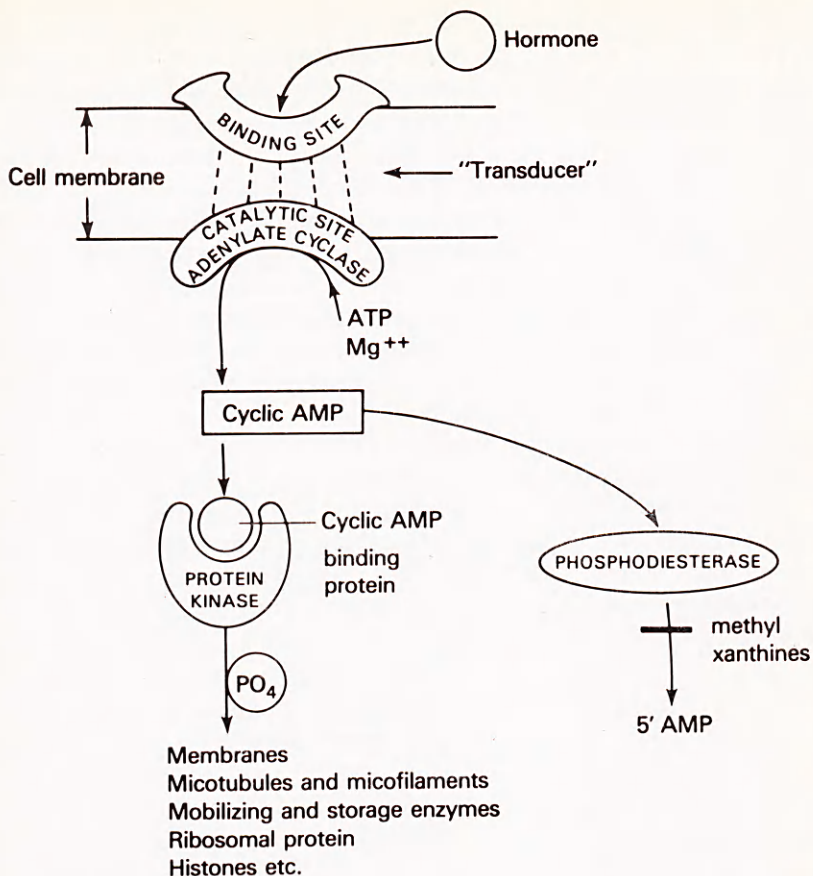


Fig. 1. Mechanism of hormone action.

increased affinity for each other secondary to the formation of a hormone-receptor complex (Swillens and Dumont, 1977). This system may involve an intermediate coupling mechanism often referred to as a transducer (Fig. 1) and would obviously be of critical importance in the biological response to the hormone. In keeping with this hypothesis has been evidence demonstrating that, in hepatic cell membranes, the formation of a hormone-receptor complex leads to enhanced binding of guanylyl nucleotides, which then activate adenylate cyclase (Rodbell *et al.*, 1974). Similar mechanisms may be involved in many hormone receptors.

In some situations, the stimulation of presumably cyclic AMP dependent responses were found to occur in the absence of a detectable rise in cyclic AMP formation. This finding has been reported in thyroid (Povey *et al.*, 1976), Leydig (Mendelsohn *et al.*, 1975), and adrenal cells (Sharma *et al.*, 1974). However, with

more sensitive methods of cyclic AMP detection the situation has recently been reconciled, at least for the Leydig cell, by the detection of small increases in the occupancy of protein kinase by cyclic AMP, coincident with the initiation of testosterone production (Dufau *et al.*, 1977).

THE LIFE CYCLE OF HORMONE RECEPTORS

Receptors are probably manufactured within the cell and transported to the membrane surface where, it has been suggested, they may be located in areas known as coated pits on electron microscopy (Anderson *et al.*, 1977). The formation of hormone-receptor complexes may be followed by simple dissociation of the hormone from its binding site, or the whole complex may be either shed from the surface or absorbed into the cell (Fig. 2). What is the evidence for such a hypothetical chain of events? Regulation of receptor concentration by the binding of the hormone itself has now been well established. LH, insulin, and hGH will cause a reduction in the number of binding sites in excess of those occupied (*see* 'Down-regulation' below). Preliminary studies have demonstrated that prolactin receptors may be manufactured in the Golgi apparatus and transported to the cell surface (Posner, 1977) and there is also evidence that LH and insulin hormone-receptor complexes may be internalised by the cell (Conn *et al.*, 1978; Goldfine *et al.*, 1977).

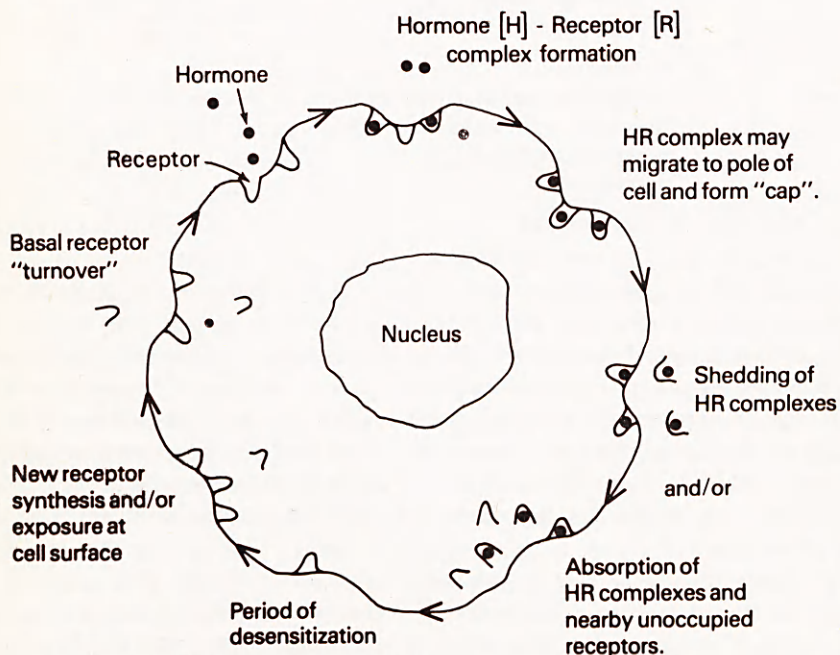


Fig. 2. The theoretical 'life cycle' of a peptide hormone receptor.

NEW CONCEPTS OF DISEASE AETIOLOGY

Research into hormone-receptor interactions has influenced clinical medicine in three ways. First, it has clarified the normal physiology of hormone mechanisms. Secondly, it has allowed the development of important new concepts of aetiology. Lastly, there has been a direct impact on clinical practice, particularly in the fields of diagnostic and prognostic investigations. It is not possible to review all this work in depth, hence a few examples have been chosen to emphasise these developments. Of particular interest has been the investigation of unexpected target organs for a number of peptides, the changes in receptor concentration associated with disease, and the discovery of antibodies to cell surface receptors, especially to the TSH receptor.

Unexpected Hormone Targets

On the whole, the targets of peptide hormones have proved to be the plasma membranes of the appropriate cell, but a number of surprising findings have occurred when so called 'non-target' tissues have been investigated (Table 1). A few such examples will be discussed.

Prolactin. Of the many actions associated with prolactin, those on the mammary gland have been the most investigated. Prolactin probably stimulates mammary growth as well as initiating and maintaining milk secretion. The specific binding of prolactin to mammary tissue has been demonstrated by many workers, but prolactin receptors have also been found in liver and adrenals as well as testis, ovary, prostate and seminiferous glands (Frantz *et al.*, 1974; Posner *et al.*, 1974a; Friesen and Shiu, 1977; Aragona and Friesen, 1975; Saito and Saxena, 1975). Many metabolic functions have been attributed to prolactin, including effects on protein, lipid, and carbohydrate metabolism, and its specific hepatic effects may be confined to the regulation of free fatty acid synthesis (Winkler *et al.*, 1971). In the adrenal, prolactin has been suggested as a stimulant of androgen production (Carter *et al.*, 1977) but appears to have no direct influence on aldosterone production (Holland *et al.*, 1977). As far as gonadal function is concerned, most evidence suggests that prolactin has a permissive role on sex steroid production in physiological concentrations (Bartke, 1976), and it probably has an inhibitory role when present in excessive amounts (McNatty *et al.*, 1974; Fang *et al.*, 1974; Magrini *et al.*, 1976). These effects may be exerted by means of a direct intracellular mechanism or by influencing LH receptor concentration or responsiveness (Bohnet and Friesen, 1976). The recognition of hyperprolactinaemia in association with impotence and hypogonadism in men (Thorner *et al.*, 1974) and with amenorrhoea and infertility in women (Tolis *et al.*, 1974) also supports an important role for prolactin in human gonadal dysfunction. While there is evidence suggesting a direct action by prolactin on the pituitary, principally by inhibition of gonadotrophin release (Besser *et al.*, 1972; Beck and Wuttke, 1977),

it is possible that the direct effect on the ovary and testis is of much greater importance.

Thyrotrophin (TSH). TSH binds to the surface of thyroid cells and stimulates thyroid hormone release through adenylate cyclase activation (Dumont, 1971). In Graves's disease, the presence of thyroid-stimulating antibodies (TSAb) causes excessive thyroid hormone output by stimulation of the TSH receptors (Smith, 1976). In hyperthyroid Graves's sera a number of biochemical abnormalities are present in addition to the thyroid hormone excess. There are increased circulating levels of LH and FSH, with a resulting excess of both free and total sex steroids. The sex-hormone binding globulin is correspondingly increased but does not make the free testosterone and oestradiol levels normal (Chopra, 1975). These abnormalities may be secondary to the influence of excessive thyroid hormones on the pituitary, causing an enhanced production and release of gonadotrophins in response to gonadotrophin-releasing hormone (Gn-RH) (Chopra, 1976). However, the finding of TSH binding sites in the guinea-pig testis, and their interaction with thyroid-stimulating antibodies from patients with Graves's disease, has suggested another possible explanation for some of these abnormalities (Davies *et al.*, 1978a). Such abnormal thyroid stimulators may contribute to the gonadal dysfunction found in hyperthyroid patients.

There has been some controversy over the presence of TSH receptors in human fat and retro-orbital tissue as an explanation for Graves's exophthalmos. While it seems that TSAb are not directly related to the development of the eye signs of Graves's disease, much of the evidence suggests that such abnormalities are the result of some autoimmune phenomenon (Doniach, 1975). It has been reported that a fragment of TSH may bind to human retro-orbital TSH receptors and initiate the development of exophthalmos (Winand and Kohn, 1972; Mullin *et al.*, 1976). TSH receptors are present in non-primate adipocyte membranes (Teng *et al.*, 1975) but their presence in human fat and retro-orbital tissue has not yet been confirmed (Davies *et al.*, 1978b). There is, in addition, indirect evidence that TSH has no physiological role in human fat metabolism. Only large amounts of TSH have lipolytic effects on human fat when compared to the rat (Storring *et al.*, 1972) and TSH does not stimulate cyclic AMP production in human fat cells (Kather and Gelger, 1976). It seems unlikely therefore that TSH receptors or their antibodies are directly related to the aetiology of Graves's exophthalmos. The work of Kriss and his colleagues, implicating thyroglobulin-antithyroglobulin complexes as an important determinant of Graves's exophthalmos, remains the most attractive hypothesis at present (Konishi *et al.*, 1974).

Human Chorionic Gonadotrophin (hCG). Mild hyperthyroidism is a recognised accompaniment of hCG secreting tumours such as choriocarcinoma (Higgins *et al.*, 1975). Although the mechanism for the thyroid overactivity has been in dispute for many years, most of the hyperthyroid patients had high levels of serum hCG

and there was evidence that the excessive thyroid stimulation in such patients was due to the abnormal amount of hCG present (Kenimer *et al.*, 1975). This was confirmed when Nisula and Ketelslegers (1974) demonstrated that hCG was active in the TSH mouse bioassay with a unique time course of activity distinct from TSH. With the advent of the TSH radioreceptor assays hCG was found to interact with both animal and human thyroid tissue in concentrations comparable with serum hCG levels in such patients (Davies *et al.*, 1978a). Furthermore, urinary concentrates from thyrotoxic patients with choriocarcinoma caused marked inhibition of labelled TSH binding to thyroid membranes (Davies *et al.*, in preparation). Human chorionic gonadotrophin is, therefore, a weak thyroid stimulator that increases thyroid hormone output when present in sufficient quantity and when there has been no prior thyroid damage.

Changes in Receptor Concentration Associated with Disease

Changes in receptor concentration, affinity and structure may all lead to abnormal endocrine function. In addition, abnormalities may occur in the coupling process and the second messenger systems. Present evidence suggests that changes in receptor concentration may be a normal control mechanism for endocrine function and that in some situations such changes may be excessive and result in disease.

Down Regulation of the LH Receptor. In male patients with hCG secreting tumours it was difficult to understand why their testosterone levels remained in the normal range despite the excessive level of hCG, which was known to interact with the LH receptor (Kirschner *et al.*, 1970). It has now been shown that even small increases in circulating LH or hCG reduce the number of LH receptors in laboratory animals, and the subsequent responses of the testicular Leydig cells and ovarian luteal cells are also reduced (Hsueh *et al.*, 1977; Conti *et al.*, 1976). This phenomenon has been termed down-regulation, and is best considered as one of a number of possible causes of the phenomenon of tachyphylaxis or desensitisation. Such down-regulation is a temporary phenomenon, receptor concentration being restored with the return of physiologically normal hormone levels. This may be an important mechanism for the control of ovarian function during the menstrual cycle in response to the LH surge.

Down-regulation of Insulin and Growth Hormone Receptors. Obesity, hyperinsulinism and insulin resistance have been found to be associated with a decrease in the number of insulin receptors on circulating human monocytes (Bar *et al.*, 1976). When the metabolic abnormalities returned to normal, for example by dieting, the number of insulin receptors also returned to normal. This inverse relationship between insulin levels and insulin receptor concentration is now well established although this may not be universal to all races. This regulation of insulin receptor sites is a secondary response to the altered insulin output since it can be demonstrated in both the intact animal and isolated cells in culture as a

direct result of changes in insulin concentration. These findings indicate a sensitive mechanism for the modulation of insulin action.

Another example of hormonal control of receptor concentration is the influence of human growth hormone (hGH) on the human growth hormone receptor. Occupancy of only a small number of hGH receptors has been shown to produce significant receptor loss (of up to 90 per cent) although, as for LH and insulin, total loss of receptors does not occur (Lesniak and Roth, 1976). It is possible to predict a number of physiological interrelationships between growth hormone levels and receptor concentration. Certainly it would explain why exogenous growth hormone has no effect in small children with normal hGH levels; it would simply induce receptor loss and hormone resistance. However, in children deficient in hGH, the exogenous hGH would find receptors able to respond appropriately (Lesniak and Roth, 1976).

Other Mechanisms of Receptor Regulation. Tachyphylaxis, by which is meant a reduced response to repeated target organ stimulation, may also occur without a change in hormone binding capacity. Such a situation applies, for example, to TSH stimulating the thyroid (Manley *et al.*, 1974a), and glucagon stimulating the liver (Liljenquist *et al.*, 1974; Felig *et al.*, 1976). In these tissues the inhibition of hormone action occurs at a site distant from the hormone binding site, but adenylate cyclase and phosphodiesterase are not the rate-limiting steps (Smith *et al.*, 1977). A possible explanation for this type of desensitisation would be the uncoupling of the binding site from the catalytic unit. While such a phenomenon may be important in the self regulation of the target cell, its role in endocrine disease has not yet been defined.

There are a number of other examples of hormonally induced receptor loss, for example by catecholamines, but only a few situations where hormones actually induce receptors. FSH and PMSG are known to 'prime' ovaries and to induce LH/hCG receptors, and both LH and FSH appear to be trophic to the gonads during development (Catt *et al.*, 1975a). Prolactin has been reported to 'up-regulate' its hepatic receptor in laboratory animals (Posner *et al.*, 1975; Costlow *et al.*, 1975). In addition, prolactin receptors in the liver and prostate can be induced by sex steroid supplements (Posner *et al.*, 1974b; Charreau *et al.*, 1977) and prolactin itself may influence the LH receptor (Aragona *et al.*, 1977). In fact, LH receptors appear to be especially sensitive to regulatory influences and this is emphasised by the association between body weight and gonadal function.

Weight loss and the LH Receptor

In the male, chronic malnutrition causes loss of Leydig cell function followed by a reduction in spermatogenesis (Leathem, 1975). The association between amenorrhoea and weight loss in young girls is well known and the result of subsequent weight gain is often the return of regular menstrual cycles. Deprivation of dietary carbohydrate or protein is also known to reduce fertility and litter size

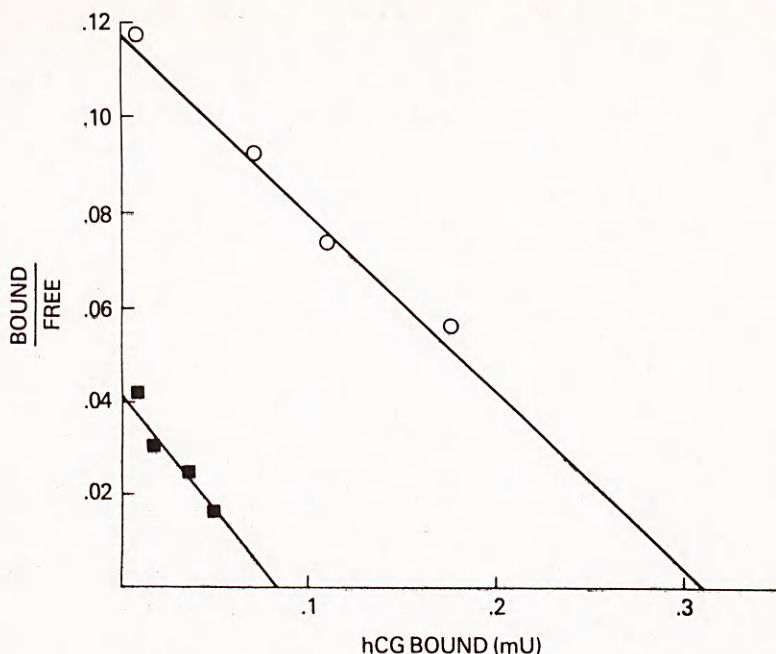


Fig. 3. Loss of LH receptors induced by food deprivation. Scatchard analysis of labelled hCG binding to testicular homogenate from control guinea-pigs (○) and food deprived guinea-pigs (■) who had lost a third of their original body weight. A marked loss of binding sites is shown with no change in the binding affinity.

in laboratory animals (Widdowson and Cowen, 1972) and it was noted by Srebnik and Nelson, in 1962, that pituitary LH concentrations were reduced after malnutrition. These data were in agreement with the concept of functional hypopituitarism induced by starvation (Perloff *et al.*, 1954) and with the later findings of reduced circulating LH levels and a reduced response to Gn-RH in patients with anorexia nervosa (Beumont *et al.*, 1976). In addition, amenorrhoea and weight loss of a milder degree were associated with delayed LH output in response to Gn-RH (Vigersky *et al.*, 1977). The finding that a reduction in circulating LH levels induced by hypophysectomy in rats resulted in loss of testicular LH receptors (Catt *et al.*, 1974) prompted us to examine the LH receptors in male rats and guinea-pigs after dietary deprivation. These animals lost over half of their LH receptors (Davies and Lewis, 1978) (Fig. 3) and their capacity to respond to hCG stimulation was similarly reduced. This suggested that weight reduction probably caused loss of ovarian and testicular LH receptors as a consequence of reduced pituitary LH output and may be the explanation for the amenorrhoea and infertility in some low weight patients. This functional hypopituitarism following food restriction is of uncertain cause but it is possible

that changes in oestrogen metabolism associated with loss of body fat are responsible for the altered gonadotrophin dynamics (Howland and Ibrahim, 1973) and results in excessive LH suppression. Such a hypothesis may also help to explain the close association between menarche and body weight (Frisch and McArthur, 1974) and the postulated association between food intake and infertility (Frisch, 1978).

Receptor Antibodies

There is evidence that in certain diseases the concentration of hormone receptors may be altered, but little data to implicate abnormal receptors in the aetiology of disease. However, all hormone receptors must be exposed to the immune system and, therefore, the development of abnormal receptors would be expected to initiate antibody production as a result of abnormal antigenic stimulation. A failure of immune tolerance, which may occur in autoimmune diseases, would also predispose to the production of receptor antibodies. Such antibodies have been identified in three conditions: Graves's disease, myasthenia gravis, and the syndrome of insulin resistance and acanthosis nigricans. There is no direct evidence to indicate that these antibodies are the result of abnormal immune mechanisms rather than abnormal receptors, although their close association with other autoantibodies suggests an immune defect. Recent theories explaining the aetiology of autoimmune disease suggest that the release of antibody production from its normal suppression by specialised suppressor T-cells may be the continuing abnormality in autoimmune disorders (Allison, 1976). These theories, however, and their supporting evidence (Penhale *et al.*, 1975; Abdou *et al.*, 1976), do not easily explain the initiation of such a disease process, which is likely to be secondary to the interaction of an environmental agent and a genetically predisposed individual.

Thyroid-stimulating Antibodies (TSAb)

TSH stimulates the release of iodine from the thyroid gland, and in 1956 Adams and Purves found that sera from Graves's patients, when injected into guinea-pigs pre-treated with radioactively labelled iodine, caused release of the label over the following 12 to 24 hours rather than the 3 hours usually seen with TSH. This factor was termed Long Acting Thyroid Stimulator (LATS) and was found to be associated with the 7S IgG fraction of Graves's sera and was neutralised by antihuman IgG antibody but not by antihuman TSH antibody. Although some LATS sera were shown to stimulate adenylate cyclase activity in human thyroid tissue (Kendall-Taylor, 1973) most reports concluded that LATS levels in Graves's patients failed to correlate with the severity of the thyrotoxic state as assessed by radioiodine uptake studies (Adams *et al.*, 1976). LATS could not be demonstrated

in many grossly hyperthyroid Graves's patients and, therefore, the role of LATS as a causative factor in Graves's hyperthyroidism was open to question.

LATS activity was neutralised by human thyroid homogenates (Kriss *et al.*, 1964) but the degree of neutralisation was often unrelated to the amount of LATS present. Adams and Kennedy (1967) explained this phenomenon by demonstrating the presence of another immunoglobulin G that inhibited the binding of LATS to the human thyroid tissue. The presence of this LATS-Protector did not inhibit the LATS effect in the mouse bioassay and this indicates that LATS-P binds preferentially to human thyroid tissue but not to mouse thyroid. LATS-P has been detected in 60-90 per cent of Graves's patients, depending upon the criteria used for their selection, and has not been found in the normal population. LATS-P activity correlated with early iodine uptake studies, and infusion of LATS-P sera into human volunteers caused significant thyroid stimulation (Adams *et al.*, 1974, 1976).

LATS and LATS-P are TSH Receptor Antibodies. Detailed fractionation studies of Graves's sera by ion-exchange chromatography, gel filtration and isoelectric focusing showed that the thyroid-stimulating activity was associated with a heterogeneous population of IgGs. The binding site was formed by a combination of heavy and light chains in the Fab part of the molecule, confirming the presence of an antibody (Smith, 1976). Some Graves's immunoglobulins stimulated cyclic AMP formation in isolated thyroid cells, tissue slices, and thyroid membranes. Graves's thyroid was less responsive than normal thyroid tissue, because of desensitisation induced by TSAb *in vivo* (Kendall-Taylor, 1973). The same immunoglobulin fractions were found to inhibit the binding of labelled TSH to thyroid cells and membrane preparations, suggesting that TSAb and TSH interacted with similar membrane-binding sites (Fayet *et al.*, 1973; Manley *et al.*, 1974b; Smith and Hall, 1974; Mehdi and Nussey, 1975) and the studies with semi-purified soluble GSH receptors from human thyroid indicates that TSAb and TSH binds to the same or closely related receptors and that Graves's IgG contained antibodies to the TSH receptor (Petersen *et al.*, 1977). Furthermore, it has now become possible to induce TSAb production in cultured lymphocytes obtained from patients with hyperthyroid Graves's disease and to confirm its biological activity (McLachlan *et al.*, 1977). The inhibitory effect of TSAb on the binding of labelled TSH to human thyroid membranes has been utilised as an effective, and clinically useful, radio-receptor assay for thyroid-stimulating antibodies by Smith and Hall (1974). The titres of TSAb in this assay demonstrated a highly significant correlation with early iodine uptake studies suggesting that the receptor assay usually measured biologically active TSAb (Mukhtar *et al.*, 1975). The presence of TSAb corresponded with the absence of TSH control of thyroid function on the basis of T3 suppression tests and the TSH response to TSH-releasing hormone (Clague *et al.*, 1976). The incidence of TSAb in Graves's patients when measured by receptor assay has been reported to be

between 40 and 100 per cent. This variation is probably due to the differing assay conditions, together with the criteria for patient selection as mentioned for LATS-P.

Graves's sera therefore contain thyroid-stimulating antibodies which interact with TSH receptors and cause hyperthyroidism. These antibodies are a heterogeneous population which exhibit species and probably individual specificity. They may be detected by bioassay as LATS if, by chance, they interact with mouse thyroid, and by the LATS-P and receptor assays by their interaction with human thyroid tissue. The situation is, however, complicated by the occasional presence or development of biologically inactive, but receptor binding, TSAB which can only be confirmed by sensitive bioassay.

Other Receptor Antibodies

Immunisation of rabbits with acetylcholine (ACh) receptors prepared from electric eels readily induced experimental myasthenia gravis that resembled the human disease in all the criteria examined (Patrick and Lindstrom, 1973). ACh receptor antibodies were detected by their inhibition of the binding of radioactively labelled alpha bungarotoxin that bound specifically to acetylcholine receptors *in vitro* (Almon *et al.*, 1974). Antibodies to the ACh receptor have been identified in experimental myasthenia and in as many as 80 per cent of myasthenic patients. Myasthenia gravis appears, therefore, to be similar to Graves's disease, with an underlying autoimmune process leading to the development of receptor antibodies. It is not, therefore, very surprising that the two diseases are sometimes found together.

As mentioned earlier, alterations in insulin receptor concentration have been shown to be important in some states of altered insulin sensitivity. A rare example of such alterations has been described in the syndrome of insulin resistance and acanthosis nigricans associated with reduced insulin binding to the patient's monocytes *in vitro* (Kahn *et al.*, 1976). One variety of this syndrome has a number of features similar to the autoimmune disorders and there are circulating antibodies which bind to the cell membrane and interfere with insulin receptor function. These antibodies have now been shown to interact with the insulin receptor (Flier *et al.*, 1977). Furthermore, some of these receptor antibodies appeared to act as stimulating antibodies causing an increase in basal glucose oxidation (Kahn *et al.*, 1977).

Although only the three receptor antibodies discussed have so far been identified, a new group of endocrine diseases is emerging and a number of other endocrine abnormalities may eventually be explained by a similar mechanism. Whether or not certain cases of Addison's disease or hypogonadism are caused by blocking receptor antibodies remains to be determined.

HORMONE RECEPTORS IN CLINICAL PRACTICE

The direct impact of peptide hormone receptor research has been felt principally in the fields of diagnostic and prognostic assessment. The clinical aspects of cyclic nucleotides have been extensively reviewed in the literature (Volicer, 1977) and therefore only a few brief examples of particular interest will be discussed.

Adenylate Cyclase Stimulation In vivo

Renal Function Studies. The renal response to intravenous cyclic AMP parallels the *in vitro* effects on renal tissue imitating the action of parathyroid hormone (PTH) and of anti-diuretic hormone (ADH). The plasma and urinary cyclic AMP responses to intravenous PTH and ADH have therefore been a useful measure of end organ sensitivity. Patients with nephrogenic diabetes insipidus are unable to respond normally to intravenous ADH (Fichman and Brooker, 1972) and similarly, patients with pseudohypoparathyroidism fail to respond adequately to intravenous PTH (Chase *et al.*, 1969). However, the precise localisation of these receptor abnormalities is not yet known. Another example of cyclic AMP being useful as an indicator of renal involvement in disease has been its measurement in renal veins. Like renal vein renin, renal vein cyclic AMP correlates with the degree of renal stenosis and may relate to the causative nature of renal pathology in systemic hypertension (Kuchel *et al.*, 1977).

Liver Function Studies. The intravenous glucagon test, which measures the plasma cyclic AMP and glucose response, has been shown to be normal in cirrhotic patients but considerably increased in extra-hepatic obstructive jaundice. It may, therefore, be useful in distinguishing extra-hepatic from intra-hepatic obstruction (Davies *et al.*, 1976; Francavilla *et al.*, 1977).

Thyroid Function. Plasma and urinary cyclic AMP are increased in association with the raised metabolic rate of hyperthyroidism and correspondingly decreased in thyroid failure. Similarly, the cyclic AMP response to intravenous glucagon is increased or decreased (Elkeles *et al.*, 1975; Guttler *et al.*, 1977). This test is the only useful measure of peripheral thyroid hormone action and deserves to be more widely known.

Radio-ligand Receptor Assays

The binding of a labelled hormone to intact target cells or cell membranes can be inhibited by unlabelled hormone. This simple principle is used to measure unknown amounts of either unlabelled hormone or actual receptor and forms the basis of radio-ligand receptor assay systems. An important advantage of receptor assays is their ability to assess the binding activity of hormones and their analogues, which is not possible by radioimmunoassay since the antibodies employed do not usually recognise the biologically active part of the peptide molecule. Other advantages include the fact that equilibrium is reached much more rapidly, and separation of bound and free hormone can be achieved by

simple centrifugation because of the particulate nature of the membrane preparation. In addition, radio-ligand receptor assays obviate the need to raise antibodies. However, the precision of radio-receptor assays is variable and at present few are of equal sensitivity to immunoassays, although far more precise than bioassays. Radio-ligand receptor assays provide a convenient way of estimating non-suppressible insulin-like activity (NSILA) for which a radio-immunoassay is not available (Roth *et al.*, 1975). They have not, however, found wide application in the routine laboratory because of their lower precision. A possible exception is the radio-receptor assay for hCG. Radioimmunoassay can detect hCG in human plasma approximately ten days after conception. Early reports of radio-ligand receptor assays being able to detect hCG at 4 to 6 days (Saxena *et al.*, 1974) were almost certainly due to the now well-known interference by plasma proteins (Catt *et al.*, 1975b). However, using urine rather than plasma, the radio-receptor assay can detect the initial production of hCG at the same time as conventional immunoassay (Saxena *et al.*, 1977) and it may produce a quicker result at less cost.

Biopsy Material

All biopsy material from endocrine glands contains binding sites for the appropriate labelled hormone. The potential diagnostic usefulness of this technique has not yet been fully exploited. Carr and Friesen (1976) have investigated hGH binding to human liver biopsy material and found the human liver growth hormone receptor to have the same characteristics as that described on cultured human lymphocytes (Lesniak *et al.*, 1977). Data on TSH binding to thyroid biopsies is sparse, although surgically removed thyroid cancers may retain their TSH receptors (Ichikawa *et al.*, 1976) and this may be helpful in prognosis.

Thyroid-stimulating Antibodies

Using the TSH receptor assay, it has been possible to measure TSAb as a clinical tool for the diagnosis of Graves's disease. TSAb has been detected in hyperthyroid and in 10 to 15 per cent of hypothyroid patients, emphasising the fact that the clinical presentation of autoimmune thyroid disease is the result of a balance between stimulating and destructive antibodies. Of considerable interest has been the detection of TSAb in 15 to 20 per cent of patients with thyroid cancer and their possible dependence on TSAb stimulation (Mukhtar *et al.*, 1975). Early evidence suggests that patients with high levels of TSAb are at risk from metastatic disease and require careful follow up. Detectable TSAb may also help in the diagnosis of unilateral exophthalmos, although CAT scans usually make such an investigation unnecessary. However, recent work has indicated the potential usefulness of TSAb in the prediction of thyrotoxic relapse and neonatal hyperthyroidism.

TSAb as a Predictor of Thyrotoxic relapse

More than half the patients treated for hyperthyroidism with anti-thyroid drugs relapse when treatment is withdrawn, and there is no simple or certain way of distinguishing such patients from those likely to continue in remission (Hershmann *et al.*, 1966). Since thyroid function in patients with Graves's disease is under the control of TSAb rather than TSH, persistent high levels of TSAb were associated with subsequent relapse after withdrawal of anti-thyroid drug therapy (Davies *et al.*, 1977). Figure 4 shows that 22 of 45 patients relapsed within 6 months of drug withdrawal and that all the patients with high levels of TSAb relapsed within 6 months compared with only 3 of the 21 TSAb negative patients. These data indicated, therefore, that an accurate and useful prediction of the early clinical course of Graves's disease could be made in patients with high levels of TSAb and are similar to the results obtained with T3 suppression tests (Alexander *et al.*, 1970).

TSAb as a Predictor of Neonatal Hyperthyroidism

IgG crosses the placenta, and high levels of maternal LATS and LATS-P are known to be associated with a self-limiting, although sometimes severe, disease

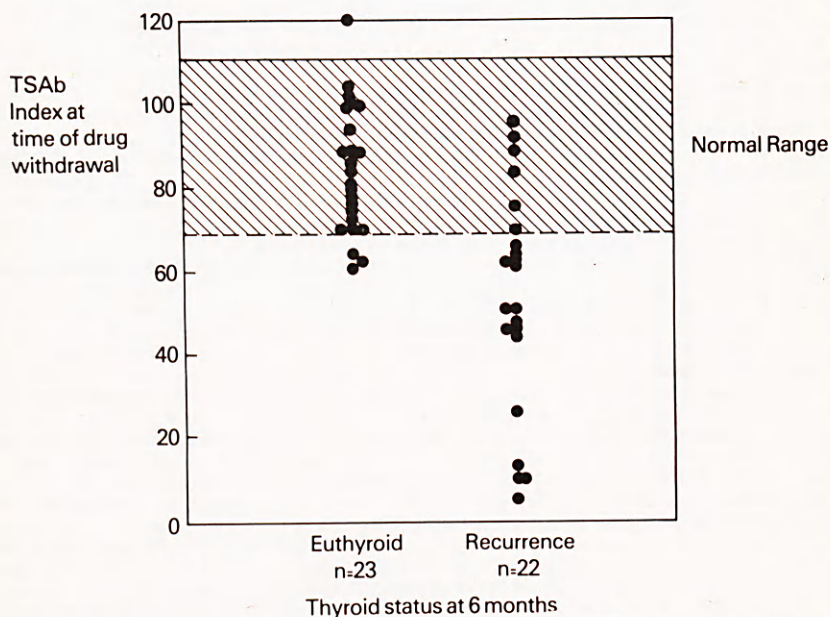


Fig. 4. TSAb titres in relation to thyroid status. The TSAb titres in relation to thyroid status are demonstrated six months after withdrawal of anti-thyroid therapy for Graves's disease. The normal TSAb index is greater than 72 and for details of its derivation see Mukhtar *et al.* (1975). Indices below 72 indicate the presence of TSAb.

of the newborn. The critical levels of TSAb activity in maternal serum for the subsequent development of neonatal disease have been defined by Munro and his co-workers in Sheffield (Dirmikis *et al.*, 1977). Maternal serum levels of more than 20 units/ml of LATS-P were associated with 11 cases of definite neonatal hyperthyroidism out of 12 such pregnancies. This test is now almost mandatory in pregnant women with a history of Graves's disease.

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Book Reviews

Essential Intensive Care by E. Sherwood Jones. MTP Press, 1978. Price £9.95.

It is all too easy for an intensive care unit to be run by a committee of specialists, often presided over by an anaesthetist who regards the unit as an extension of the postoperative recovery ward. This book is welcome as a personal and often dogmatic account of the practice of this hybrid specialty.

Dr Sherwood Jones has enlisted the help of several colleagues, but he remains the sole or part-author of 18 of the 22 chapters. Few physicians would have his temerity and write about the management of patients on ventilators, and some anaesthetists will doubtless be critical of his attempt to do so. Many physicians, however, will be grateful for his clear exposition on a subject in which they have little or no formal training.

One of the difficulties with intensive care is that junior staff are often involved in the care of patients with conditions or treatment of which they have little experience and this book will be helpful under those circumstances. However, any textbook of intensive care must be a compromise, as the readers' training will have been so varied. Assessment of the contents, therefore, will reflect the background of the reader (or reviewer).

Coronary care is covered in a rather cursory fashion without any illustrative cardiograms. I would have liked to see mention of the psychiatric effects of intensive care on both patients and staff. Disseminated intravascular coagulation, an important component of many of the conditions seen in the intensive care unit, receives only a passing mention in the chapter on renal failure. It is disappointing to find no mention of Metronidazole in an otherwise useful section on microbial infection. Neurological conditions are not discussed at all and the author's dogmatic approach is well illustrated by his dismissal in five lines of the use of steroids in endotoxic shock.