Organ-Specific Autoimmunity: 
A 1986 Overview

Gian Franco Botazzo, Ian Todd, Rita Mirakian, Antonio Belfiore & Ricardo Pujol-Borrell

INTRODUCTION

Organ-specific autoimmunity is nowadays largely synonymous with endocrine autoimmunity. Clinically, these disorders usually affect a single organ or gland in the body, but serological evidence (i.e. autoantibodies) often indicates subclinical disturbances in other related tissues. The target antigens of the immunological response are unique to the affected organ, thus giving rise to the organ-specific and even cell-specific recognition. The precedent for autoimmune disease was set in 1956 with the demonstration that autoimmunity is the basis of Hashimoto's thyroiditis (Roitt et al. 1956). This concept was rapidly extended to atrophic fundal gastritis, pernicious anemia, Addison's disease and ovarian failure (reviewed by Botazzo & Doniach 1985), reaching full circle with the histological description of lymphocytic hypophysitis (Goudie & Pickerton 1962). It was more than a decade later that the latter findings were substantiated by the description of pituitary antibodies (Botazzo et al. 1975), which followed the first demonstration of islet cell antibodies (ICA) in insulin-dependent diabetic patients (Botazzo et al. 1974). Since then the list of organ-specific autoimmune diseases has grown steadily (Table I) and, except for the pineal gland, autoantibodies to other endocrine cells, e.g. to vasopressin cells in the hypothalamus in patients with idiopathic diabetes insipidus (Scherbaum & Botazzo 1983) or to gastrin cells in the antrum in Type B antral gastritis (Vandelli et al. 1979) have been identified. The presence of organ-specific autoantibodies usually correlates well with the corresponding clinical symptoms or local histology and impairment of hormone secretion. However, we have found this not always to be strictly so as in the case of autoantibodies to glucagon and somatostatin cells in the pancreatic islets (Botazzo & Lendrum 1976), or to gastrin inhibitory peptide cells and secretin

Department of Immunology, The Middlesex Hospital Medical School, London W1P 9PG, U.K. Correspondence to: Dr. G. F. Botazzo, Department of Immunology, Arthur Stanley House, The Middlesex Hospital Medical School, 40–50 Tottenham Street, London W1P 9PG, U.K.
cells in the gut (Mirakian et al. 1981, Jones et al. 1983). However, all these findings have helped to consolidate the concept of a “polyendocrine autoimmune syndrome” in which different autoimmune conditions co-exist at the clinical or sub-clinical levels in predisposed individuals or families (Valenta et al. 1982), more often than one would expect by chance: an idea which, interestingly, was suggested as long ago as the early 1920s.

Organ-specific autoimmunity can affect target organs through several mechanisms:

a) A slow destructive process, by which the normal parenchyma is attacked by lymphocytes (bearing markers of immune activation) and antibodies and is gradually replaced by connective tissue. Loss of physiological function may eventually occur.

b) A stimulating process, primarily involving antibodies which react with hormone receptors on the cell surface, mimicking some of the effects of the trophic hormones. An excessive production of the specific peptides/chemical mediators, or stimulation of growth are usually the end result.

c) A blocking process, in which non-stimulatory antibodies play a major role by competing with hormones or other mediators for binding to cell-surface receptors (or close by). An impairment of cell function and gradual atrophy of the attacked organ become clinically manifest.

DESTRUCTIVE AUTOIMMUNITY: THE LATEST DEVELOPMENTS

Despite repeated attempts, many investigators have failed to demonstrate specific autoantibodies to enterocytes (EC-Ab) in inflammatory bowel diseases considered to be of autoimmune origin, e.g. Crohn’s disease. Autoantibodies which react with colonic mucosal cells were originally described in patients with ulcerative colitis (Broberger & Perlmann 1961), but were shown to crossreact with E. Coli. Recently, however, specific EC-Ab have been demonstrated in about 50% of children with idiopathic protracted diarrhoea (Mirakian et al., in press). Their cytoplasmic reactivity, more pronounced towards the apical border of the villous epithelium, closely resembles the classical pattern of organ-specific autoimmune reactivity. High titres of IgG EC-Ab and their complement-fixing ability indicated a poor prognosis in young patients, despite efforts to ameliorate the disease with aggressive immunosuppressive therapy. Partial or severe atrophy of the jejunal villi with a substantial degree of lymphocytic infiltration was the predominant histological pattern in the biopsy material examined and, in preliminary detailed immunological studies, immunoglobulins and activated T lymphocytes were detected.

In contrast to adult organ-specific autoimmunity in which females predominate over males and which are most commonly associated with other organ-specific autoimmune disorders, in childhood autoimmune protracted diarrhoea the sexes
ORGAN-SPECIFIC AUTOIMMUNITY: A1986 OVERVIEW

TABLE I

Destructive organ-specific autoimmune diseases

| Disease                                      |
|----------------------------------------------|
| Hashimoto’s Thyroiditis                      |
| Primary Myxedema                             |
| Fundal Gastritis (Type A)                    |
| Antral Gastritis (Type B)                    |
| Addison’s Disease                            |
| Gonadal Failure                              |
| Idiopathic Hypoparathyroidism                |
| Partial Hypopituitarism                      |
| Idiopathic Diabetes Insipidus                |
| Protracted Diarrhea of Infancy               |
| Autoimmune Diabetes Mellitus                 |
| Vitiligo                                     |
| Alopecia Areata/Totalis                      |

Tend to be more equally affected and the association with non-organ-specific autoimmune diseases (i.e. connective tissue disorders, liver diseases, etc. [Scherbaum et al. 1986a]) is more pronounced. Although at first sight these findings are somewhat unexpected they are comparable to similar clinical and immunological characteristics described in the Candida-Endocrinopathy syndrome, centred around idiopathic hypoparathyroidisms and again primarily affecting children (Neufeld & Blizzard 1980).

However, the main question remains: how do enterocytes evoke an efficient humoral response against themselves? As mentioned, autoantibody production against enterocytes seems to occur rarely. It is possible that in predisposed young children and infants whose gut mucosal permeability is still generally at a critical stage, the local immune defence mechanisms are still not entirely efficient, thus allowing the entry of external antigens which, in turn, are responsible for the production of harmful cross-reacting antibodies. The existence of these specificities has recently been revealed in coeliac disease, another complex gut disorder, by the demonstration that anti-gliadin antibodies cross-react with the Erb protein of Adenovirus 12 (Kagnoff et al. 1984).

DESTRUCTIVE AUTOIMMUNITY: THE MAJOR IMPACT IN THE PATHOGENESIS OF TYPE I (INSULIN-DEPENDENT) DIABETES

Following the first description of islet cell antibodies (ICA) in polyendocrine autoimmune diabetic patients (Bottazzo et al. 1974) and their subsequent identification in uncomplicated juvenile cases (Lendrum et al. 1975), speculation arose as to whether these markers merely represented a secondary phenomenon following a specific attack from a common environmental agent(s), responsible for the initial injury to the pancreatic beta cells. However, although Type I diabetes has
an acute clinical onset, ICA were demonstrated in predisposed individuals years before the onset of the disease: this led to reconsideration of the 'common viral dogma' as the sole cause of diabetes. The new concept of a primary autoimmune attack emerged initially from studies of unaffected members of diabetic families and was subsequently confirmed in retrospective and prospective studies in identical twins discordant for the disease, in polyendocrine non-diabetic patients and even in single sporadic cases (reviewed by Bottazzo et al. 1986). A proportion of these individuals eventually became overtly diabetic. We believe that, because of this new evidence, previously advocated environmental factors should be considered to act more as precipitating rather than initiating factors of beta cell damage. This strongly suggests that 'something' more subtle and definitely more complicated is involved in the pathogenesis of this disease.

Full-blown immunological aggression has been uncovered around and inside islets in an acute diabetic patient who died of the disease close to the time at which overt symptoms began (Bottazzo et al. 1985). Most facets of autoimmune attack were represented in the frozen pancreatic blocks, with abundant evidence of immune complex and complement deposition. CD8+ (?cytotoxic) T cells were a predominant feature of the diseased tissue, with the lymphocytes expressing activation markers. No evidence of Coxsackie, Mumps or other common viruses was detected in the diabetic islets.

Regardless of the nature of the initial trigger, the major concern of most investigators and diabetologists is to try to efficiently halt the autoimmune attack against the beta cells once it has been mounted. The initial pilot study with cyclosporin A (Stiller et al. 1984) and the more recent double blind trial in newly diagnosed diabetic patients (Feutren et al. 1986) are, in this context, the best indication that general opinion is coming round to the idea that autoimmunity plays a major role in the attack on the beta cell. If more evidence is needed for the role of autoimmune aggression this has been provided by the unexpected outcome of segmental pancreatic transplantation to diabetic identical twins from their unaffected co-twins who were discordant for the disease for many years (Sutherland et al. 1985). It is generally accepted that discordance for at least 5 yr from the time that the first twin becomes diabetic strongly indicates that the non-diabetic co-twin will remain disease-free, despite the latter still showing certain immunological abnormalities (Alviggi et al. 1984). Hopes for a successful outcome of the transplantations were contradicted by the rapid decompensation of beta cell function in the transplanted diabetic twin in a matter of weeks to a few months. Serial biopsies showed the typical pattern of insulitis with CD8+ (?cytotoxic) lymphocytes being predominant in the infiltrate invading the islets (Sibley et al. 1985). Glucagon and somatostatin cells were spared, thereby resembling the histological pattern of the original disease process (Gepts & De May 1978). It thus appears that over a period of many years (in the case of one of the twins, this was more than 20) the anamnestic autoimmune repertoire against
beta cells has remained intact, especially in its most dangerous and efficient form, i.e. cytotoxic T cells. We believe that it will only be by further dissecting the intricacies of the autoimmune process that, hopefully in the not too distant future, diabetes will be efficiently controlled and prevented (Bottazzo 1984).

DESTRUCTIVE AUTOIMMUNITY: THE CHALLENGE OF IDENTIFYING AND CHARACTERIZING THE RELEVANT AUTOANTIGENS

As mentioned, organ-specific autoimmunity is characterised by a strictly cell-specific response where the patients' autoantibodies are directed against antigens which are unique to the target tissues but are present in all individuals. Classically, these autoantibodies are identified by immunofluorescence (Scherbaum et al. 1986b) and recognise cytoplasmic components which, following conventional separation procedures, are found in the 'microsomal' fraction (Roitt et al. 1964). The precise nature of the thyroid microsomal autoantigen is emerging with the demonstration that it is at least partially identical with thyroid peroxidase (Czarnocka et al. 1985, Portmann et al. 1985). Whether similar enzymes serve as autoantigens in other organs remains to be investigated: however, although the microsomal antigens in different target tissues may share certain biochemical properties, they clearly differ in some structural features. Thus, when sera containing both thyroid and gastric parietal cell antibodies were absorbed with thyroid extract the thyroid reactivity was lost but gastric antibodies were unaffected (Knight et al. 1984). In addition, thyroid antibodies precipitate a 105-107 Kd molecule (Banga et al. 1985, Hamada et al. 1985), ICA a molecule of 64 Kd (Baekkeskov et al. 1982) and melanocyte antibodies a 75 Kd protein (Naughton et al. 1983).

Much discussion has followed the unexpected finding that some hybridomas produced from lymphocytes of diabetic patients (Satoh et al. 1983) and also from normal individuals (Prabhakar et al. 1984) synthesize monoclonal antibodies which cross-react with several tissues, mainly involved in organ-specific autoimmunity. The distinct specificity of these reagents compared with patients' autoantibodies was confirmed by their ability to precipitate a 35 Kd protein from all the organs with which they react (Satoh et al. 1984). Clearly, these fusions have amplified a cryptic autoantibody response not normally detected by conventional assays. The significance of naturally occurring autoantibodies of this type and their relationship to autoimmunity has recently been the subject of lively debate (13th Forum in Immunology of the Annales Institut Pasteur, 1986) in which we participated (Todd et al. 1986d). It has proved very difficult to produce monoclonal antibodies with exactly the same specificities as patients' autoantibodies: the reasons for this are unclear. One possible explanation is the sequestration of the relevant B lymphocytes to the target organ and hence their poor representation in the patients' blood. Furthermore, the differentiation and activation state
of the B lymphocytes may be relevant, since many experimental monoclonal
antibodies are IgM, whereas patients' autoantibodies are predominantly of the
IgG class.

Cytoplasmic antibodies still remain an invaluable clinical tool for diagnostic
and prognostic purposes but the pathogenic role of any autoantibody must lie
in its ability to bind autoantigens expressed on the cell surface. This is a prerequi-
site for activating the complement cascade and killer lymphocytes. Surface reac-
tive antibodies have been demonstrated in several organ-specific systems but
there are substantial differences in the nature of their reactivity patterns in various
tissues. In the thyroid, for example, it was initially demonstrated that virtually
all sera containing thyroid microsomal antibodies also recognised surface antigens
of viable thyroid cells in culture and in suspensions (reviewed by Pinchera et al.
1984), and the addition of complement led to lysis of the thyrocytes (Khoury et
al. 1981b). This indicated that the cytoplasmic microsomal antigen was also
expressed on the cell surface, suggesting that the specific autoantibodies could
play a direct pathogenic role. However, this situation was complicated by the
subsequent demonstration that the surface expression of this autoantigen was
restricted to the microvillar apical border facing the colloid space on the interior
of the thyroid follicles (Khoury et al. 1984). These results unexpectedly demon-
strated the existence of another sequestered antigen, which, like the eye and the
sperm, is apparently inaccessible to the immune system. However, further work
indicated that some thyroid follicles isolated from the glands of patients with
autoimmune thyroid disease showed a spontaneous reversal of the cellular po-
larity with the microvillar border exposed at the vascular pole (Hanafusa et al.
1984). The precise stimuli which induce this phenomenon in vivo in predisposed
individuals is unknown, but it is interesting to note that a similar 'inside-out'
effect can be obtained in vitro by culturing follicles in media with high protein
content (Hanafusa et al. 1984), a phenomenon originally described with rat
thyroid follicular cells (Nitsch & Wollman 1980).

The second autoantigen relevant to destructive thyroid autoimmunity is thyro-
globulin (Tg). Surface binding of anti-Tg autoantibodies could be demonstrated
by some workers (Fenzi et al. 1982) but not by others (Khoury et al. 1981).
However, asialoagalacto-Tg (but not native Tg) binds to the surface of cultured
thyrocyte monolayers at sites distinct from thyroid microsomal antibody where
it can bind the appropriate autoantibodies (Roitt et al. 1984). The anti-Tg
autoantibodies may therefore also play a role in the autoimmune destruction.
However, it remains to be established whether this incomplete Tg molecule can
be expressed at the vascular pole of thyroid follicles since all the experiments so
far have been performed on monolayer cultures in which only the apical/microvil-
lar pole of the cells is exposed.

Surface expression of cytoplasmic antigens has also been demonstrated in
adrenal (Khoury et al. 1981a) and gastric parietal cells (Masala et al. 1980),
although in the latter system autoantigens unique to the plasma membrane have
been identified by testing some sera of patients with pernicious anemia but which
lack cytoplasmic reactivity (De Aizpurua et al. 1983a, b). Whether the problem
of cell-polarization also applies to these cells in vivo is presently unknown.

The situation in pancreatic autoimmunity is more complicated and remains
unsettled. It was initially claimed that sera of Type I diabetic patients contained
islet-cell surface antibodies (ICSA) which reacted with viable rodent islets
(Lernmark et al. 1978) and these findings were confirmed on human fetal islets
(Pujol-Borrell et al. 1982). The fact that there was no direct correlation with the
presence of cytoplasmic ICA in the serum led to the conclusion that islet cells
have surface autoantigens distinct from those of the cytoplasm (Freedman et al.
1979). However, the existence of ICSA was strongly questioned when it was
shown that this specificity could be mainly due to antibodies reacting with bovine
serum albumin (BSA), which is normally present in the medium used for culturing
islets (Colman et al. 1985). Diabetic sera were also unable to precipitate radioac-
tive material from islets surface-labelled with $^{125}$I, indicating that they lack autoan-
tibodies specific for surface components which can be labelled in this way.
However, the same sera were able to precipitates a 64 Kd protein when the islets
were, as previously, metabolically labelled with $^{35}$S-methionine (Baekkeskov et al.
1982). This suggests that the organ-specific antigen so far identified in the islets
may be a cytoplasmic component rather than being expressed on the surface
(Colman et al., submitted). It is only by repeating immunofluorescence studies
with patients’ and control sera preincubated with BSA that the existence of ICSA
can be finally clarified. Other work has suggested that gangliosides may, together
with proteins, form an integral part of the cytoplasmic islet autoantigens (Nayak
et al. 1985).

One clear-cut example, which has been documented, of a disease having surface
antibodies in the absence of cytoplasmic reactivity was in patients with uncom-
plicated vitiligo, when their sera were tested on viable melanocyte preparations
(Naughton et al. 1983). Interestingly, the 9 cases described which did possess
cytoplasmic melanocyte antibodies were all polyendocrine cases centred on idio-
pathic hypoparathyroidism (reviewed by Betterle et al. 1984). Although idiopathic
hypoparathyroidism is conventionally included in the list of organ-specific auto-
immune diseases, it has proved difficult to consistently demonstrate specific
autoantibodies in this disorder. The original description of cytoplasmic antibodies
in these patients (Blizzard et al. 1966) has not been confirmed in larger series
which, however, identified antibodies to oxyphil cells (Swana et al. 1977, Betterle
et al. 1985), although these actually reacted with mitochondrial antigens, and were
not disease-specific. The possibility that the humoral response against parathyroid
chief cells is confined to their surface (by analogy with vitiligo) has recently been
suggested (Posillico et al. 1986). However, a word of caution should be added here
since viable parathyroid cells from adenomas show atypical antigen expression, so
that false positive reactions can easily occur (Mirakian, unpublished observation). Furthermore, expression of Fc receptors, as on viable pituitary cells (particularly the ACTH-producing cells) can mask organ-specific surface reactions (Pouplard et al. 1976).

It is thus apparent that the precise identification and characterization of relevant autoantibodies and the autoantigens which they recognize is still a major challenge in organ-specific autoimmunity. The data produced so far clearly indicate the antigenic heterogeneity from one organ to another, and also between patients affected by apparently similar clinical conditions.

STIMULATING ANTIBODIES: A GROWING FAMILY

As for classical anti-thyroglobulin antibodies, 1986 is the 30th anniversary of the discovery of the Long Acting Thyroid Stimulators (LATS) in Graves’ disease (Adams 1956). It is now well-established that thyroid stimulating antibodies (TSAb) are directed against the TSH receptor (TSH-R), mimicking the action of TSH by stimulating thyroid hormone production. However, it is postulated that there is more than one binding site on the TSH-R itself and the multiplicity of methods devised over the years to detect TSAb in affected patients illustrates the diversity of their antibodies (reviewed by Todd & Bottazzo 1985a). The production of monoclonal antibodies by fusing lymphocytes from Graves’ patients with suitable immortal cell lines should further help to clarify this important issue (reviewed by Kohn et al. 1984). In comparing assays for TSH-R antibodies it is worth emphasizing that binding does not necessarily correlate with ability to stimulate. Mixtures of ‘stimulating’ and ‘blocking’ antibodies in the same serum complicate the matter still further, but if the problem is approached correctly, and assays of greater specificity devised, this combination of antibodies could provide a plausible explanation for the heterogeneous clinical picture of thyrotoxicosis, which includes rapid and prolonged remission in certain patients and sudden relapse in others (Bottazzo & Doniach 1986).

Until recently, non-toxic simple and nodular goitres were not considered to have an autoimmune etiology. However, they are known to occur more frequently than expected by chance in families with autoimmune thyroid diseases and 45% of these patients have low titres of autoantibodies to thyroid microsomal antigen and/or thyroglobulin in their sera. The discrepancy between toxicity and goitre size in Graves’ disease and the flat TRH responses in some cases of non-toxic goitre first led to the hypothesis that some forms of thyroid hyperplasia might be due to growth-promoting antibodies (Doniach 1976). The actual occurrence of growth-stimulating immunoglobulins (TGI) was first established by Drexhage et al. (1980) using a sensitive cytochemical bioassay (Drexhage et al. 1983). These autoantibodies are now known to be a cause of goitre formation in Graves’ disease, in two thirds of sporadic non-toxic nodular goitres (Van der Gaag et al.
1985b, Smyth et al., in press), and in a proportion of Hashimoto goitres (Drexhage et al. 1980). The original method used for the detection of TGI is still very labor-intensive and is not suitable for extensive population studies. Advances in this direction have been made by measuring $^{3}$H-thymidine incorporation into reconstituted rat thyroid follicles incubated with suitable patient's sera, but at the expense of a much lower sensitivity of detection (Chiovato et al. 1983). The right balance between 'ease' in performing the assay and 'sensitivity' should be achieved by measuring TGI on the FRTL-5 cells (an immortalized rat thyroid cell line): this assay is based on a rise of the mitotic index from 0 to 10% when these cells are incubated with the patient's autoantibodies (Ealey et al. 1985).

Stimulating antibodies are also entering into the field of gastric autoimmunity. In experiments performed in rats, Dobi & Lenkey (1982) initially showed that immunoglobulins from patients with hyper-secretory duodenal ulcer stimulated gastric secretion in the animal stomach and the size and the number of gastric parietal cells were increased. Furthermore, in some families in which duodenal ulcers occurred in association with hyper-gastrinemia and elevated levels of pepsinogen I, hypertrophy of gastric parietal cells was documented, and other members of these families had thyrotoxicosis and/or atrophic gastritis (Taylor et al. 1981). This raised the possibility that, as in thyroid autoimmunity, both destructive and stimulating antibodies might also occur in gastric autoimmunity. This prompted Franca de Lazzari to examine whether a subgroup of patients with duodenal ulcer do indeed possess stimulating autoantibodies. This was investigated by determining the ability of patients' immunoglobulins to stimulate cyclic-AMP production by parietal cell-enriched suspensions prepared from the stomachs of young male guinea pigs (De Lazzari et al., submitted). Thirteen out of 30 patients had immunoglobulins with stimulatory effects in this assay, which suggested that they could act either on histamine (H$_2$)-receptors on gastric parietal cells or on chief cells to stimulate pepsinogen production. In either case, their role in maintaining and perpetuating the gastric secretion would be of pathogenic importance. However, more than half of our cases with stimulating antibodies did not respond to anti-H$_2$-R drugs. This might indicate in vivo occupancy of the target receptor by antibody and suggests the potential prognostic value of the test in predicting the responsiveness to specific treatment in these patients.

A careful analysis of the characteristics of the patients studied indicated that stimulatory gastric autoimmunity is not directly analogous to autoimmune thyroid diseases. In thyroid autoimmunity, there is a remarkable overlap between destructive and stimulatory features and females are mainly affected. In pernicious anemia the sex ratio is more equal, but in the case of duodenal ulcer there is a total reversal of the ratio, especially in hyper-secretors, with men being most frequently affected. Moreover, immunofluorescent autoantibody tests in our recent report, and in previous population studies, suggest that destructive and stimulatory autoantibodies against the stomach are not correlated: for example,
duodenal ulcer patients show a low prevalence of parietal cell antibodies, even when compared with healthy controls. Gastric autoantibodies with growth stimulatory effects are presently under investigation. Table II summarizes the known receptor-stimulating antibodies in human disease, including the latest addition concerning adrenal Cushing's syndrome (Teding van Berkhout et al. 1986).

‘BLOCKING’ ANTIBODIES: A LENGTHENING LIST

Non-stimulatory blocking antibodies can bind to the same receptors as the stimulating antibodies discussed above and hence cause clinical symptoms. Myasthenia Gravis is still the prototype disease involving receptor-blocking autoantibodies in which an extensive loss of acetylcholine receptors occurs (reviewed by Compston & Vincent 1985, Dawkins & Garlepp 1985). Similarly, TSH-receptor-associated 'blocking' antibodies may stop the pathway of thyroid hormone synthesis, or the growth of thyroid cells. The latter thyroid growth blockers are found in primary myxedema at all ages, while in atrophic thyroiditis autoantibodies impair thyroid hormone synthesis (reviewed by Konishi et al. 1984) or prevent re-growth of thyroid follicles despite increased pituitary output of TSH (Drexhage et al. 1981). Both types of blocking antibodies are also involved in neonatal hypothyroidism, causing different clinical symptoms. Blockers of function transmitted through the placenta cause temporary hypothyroidism (Matsurura et al. 1980), but the growth blockers interfere with normal development of the thyroid in the fetus and are responsible for almost half the cases of athyreotic cretinism (Van der Gaag et al. 1985a).

Anti-insulin receptor antibodies were first observed in patients with extreme insulin resistance and associated acanthosis nigricans by their ability to inhibit binding of $^{125}$I-insulin to peripheral blood mononuclear cells (reviewed by Kahn et al. 1982). More recently, antibodies to insulin receptors were described in a group of untreated, newly diagnosed diabetic patients using a rat adipocyte binding assay (Maron et al. 1983). The latter findings are still awaiting confirmation. However, comparison of the data relating to these two conditions indi-

| Disease                        | Antigen | Effect       | Reference                          |
|--------------------------------|---------|--------------|------------------------------------|
| Graves' thyrotoxicosis         | TSH-R   | $T_3-T_4$    | Adams (1958)                       |
| Graves'/Non-Toxic Goitre       | ?       | Growth       | Drexhage et al. (1980)             |
| Adrenal Cushing's disease      | ACTH-R  | Steroids     | Teding Van Berkhout et al. (1986)  |
| Duodenal Ulcer                | H$_2$-R | Acid         | De Lazzari et al. (submitted)      |
cates that, although they apparently involve similar antibodies directed against the same receptor, these antibodies produce different clinical effects and do not have the same immunological characteristics. In contrast to the insulin-resistant diabetic syndrome, in newly-diagnosed juvenile diabetic patients resistance to the injected hormone is uncommon and whereas the receptor antibodies were IgG in the former condition they were found to be predominantly IgM in the latter. Interestingly, both types of antibodies had a stimulating effect in the different assays used when this was assessed in the early phase of their incubation in vitro. This stimulation may cause subsequent down-regulation of insulin-receptor expression, and lead to the insulin resistance in the severe clinical syndrome.

As in destructive thyroiditis, other atrophic organ-specific autoimmune disorders seem to involve receptor blocking antibodies. This is emphasized by the demonstration of gastrin-receptor blockers in fundal gastritis (Loveridge et al. 1980) and the latest development in this area is the identification of immunoglobulins with similar properties in Addison’s disease (Wulffraat et al. 1986). Table III summarizes these and other less frequent cases of blocking antibodies against hormone receptors in relation to disease.

**ANTI-HORMONE ANTIBODIES: WHAT IS THEIR SIGNIFICANCE?**

It is well-established that autoimmune responses can often occur against large peptides: hormone precursors, such as Tg, and intrinsic factor (IF) are perhaps the best example. Antibodies to IF have an important influence on the outcome of fundal gastritis when they are secreted into the gastric juice and precipitate the onset of pernicious anemia by neutralizing the residual traces of IF made by the atrophic mucosa. However, these antibodies have no effect on the function of viable parietal cells and do not affect acid secretion (Doniach et al. 1981).

| Disease                        | Antigen                  | Reference                  |
|-------------------------------|--------------------------|----------------------------|
| Myasthenia Gravis             | Acetylcholine-R          | Lindstrom et al. (1976)    |
| Insulin-Resistant Diabetes    | Insulin-R                | Flier et al. (1976)        |
| with Acanthosis (Type B)      |                          |                            |
| Renal Insufficiency           | Parathormone-R           | Juppner et al. (1978)      |
| (some cases)                  |                          |                            |
| Fundal AI Gastritis           | Gastrin-R on parietal cells | Loveridge et al. (1980)    |
| Asthma (some cases)           | Beta-2-Adrenergic-R      | Fraser et al. (1981)       |
| Gonadal Deficiency            | Gonadotrophin-R          | Escobar et al. (1982)      |
| Atrophic AI Thyroiditis       | TSH-R (c-AMP)            | Endo et al. (1978)         |
| ADD (some cases)              | ?TSH-R (Growth)          | Drexhage et al. (1981)     |
| Addison's Disease             | ACTH-R                   | Wulffraat et al. (1986)    |
Much less frequent is the appearance of anti-T3, T4 and TSH antibodies (reviewed by Schatz & Doniach 1983). These autoantibodies are normally detected by their interference in the measurement of native hormone by radioimmunoassay (RIA) but, rarely, they also give rise to clinical symptoms.

In the context of pancreatic autoimmunity, the spontaneous development of insulin autoantibodies (IAA) is gaining prominence. The full 'insulin autoimmune syndrome' was initially described in Japan (reviewed by Hirata 1983) but has been documented in other countries to a lesser extent (Burden & Rosenthal 1983). The patients originally described in Japan were treated for thyrotoxicosis with methimazole (Okabe et al. 1983). They also had hypoglycemic attacks which spontaneously remitted after withdrawal of the anti-thyroid drug. Recently, insulin autoantibodies have been described in newly diagnosed patients with Type I diabetes (Palmer et al. 1983) and in some polyendocrine non-diabetic cases (Wilkin & Nicholson 1984). Using immunoglobulin class-specific conjugates in an ELISA, Dr. Betty Dean identified similar specificities in susceptible members of our diabetic families (Dean et al. 1986). IgG-IAA were found to be significantly associated with complement-fixing (CF)-ICA (Bottazzo et al. 1980) and 9 out of 12 CF-ICA+ individuals developed acute diabetes during an 8-yr follow-up study (reviewed by Bottazzo et al. 1986). One out of 18 first degree relatives who where CF-ICA-negative but positive for conventional ICA, also possessed IgG-IAA and progressed to overt disease. However, IgM-IAA, when detectable, did not confer an increased risk for Type I diabetes. Our results support recent observations suggesting that IAA measured by RIA are preferentially of the IgG class (Srikanta et al. 1986). However, the incidence of IAA in populations at risk appeared to be lower when measured by RIA than by ELISA. Furthermore, our own results differ from those of other investigators who also used an ELISA (Wilkin et al. 1985) in that they did not find an association of IAA with ICA. This latter discrepancy may be explained by the separate analysis of IgG-IAA and IgM-IAA in our study. Recently we have observed elevated levels of IgM-IAA in a high proportion of children with serological evidence of recent viral infections (Bodansky et al., in press). The significance of these findings is now under investigation but they may reflect a cross-reactivity between insulin and an environmental antigen leading to the production of IAA. These new data are of great theoretical interest in relation to pancreatic autoimmunity since it is obvious that we are not dissecting all the possible immunological components whose interplay masks the basic destructive process against beta cells.

The contribution, if any, of anti-hormone antibodies to the clinical picture of autoimmunity is not known. However, a destructive role for anti-insulin antibodies, for example, is certainly feasible given the observation that cultured animal (Kaplan et al. 1983) and human (Pujol-Borrell et al. 1986b) beta cells express insulin on their plasma membrane. Another possible, but not mutually exclusive role for anti-hormone antibodies is suggested by their theoretical anti-
idiotypic relationship to anti-hormone receptor antibodies (reviewed by Roitt 1984) which were discussed in the previous two sections. Thus, the idiotype of an anti-hormone antibody could be the substrate for the generation of ‘internal image’ anti-idiotypic antibodies whose binding sites would resemble the epitopes of the hormone itself. Some of the latter antibodies should therefore bind to the hormone receptor. For example, anti-idiotypic antibodies to anti-TSH might bind to the TSH receptor. This could explain the generation of some forms of thyroid stimulating/blocking antibodies, and possibly account for certain cases of intermittent or recurrent hyperthyroidism (Raines et al. 1985). The feasibility of this scheme centred around TSH has been experimentally demonstrated in both rabbits (Beall et al. 1986) and mice (Gafni et al. 1986). A similar murine model relating to anti-insulin/insulin-receptor antibodies has also been extensively investigated (Schechter et al. 1984).

Little direct evidence has so far emerged for the clinical relevance of these schemes, apart from isolated cases, including a Type I diabetic whose serum contained antibodies to both insulin and the insulin receptor (Shoelson et al. 1986). Testing predisposed first degree relatives of patients for anti-hormone and anti-hormone receptor antibodies may lead to further evidence. It may also be informative to carefully analyze circulating immune complexes which occur in patients at the acute onset of organ-specific autoimmune disorders (although only at low concentrations) including Graves’ disease (De Bruin et al. 1984) and Type I diabetes (reviewed by Pozzilli & Di Mario 1984). Finally, it should be borne in mind that, due to the mutuality of idiotypic interactions, the converse situation to that described above is perfectly feasible in which anti-hormone receptor antibodies precede, and give rise to, anti-hormone antibodies.

**EPITHELIAL EXPRESSION OF MHC CLASS II MOLECULES: AN IMPORTANT PATHOGENIC FACTOR IN ORGAN-SPECIFIC AUTOIMMUNITY**

Although much remains to be learned about effector mechanisms in organ-specific autoimmunity, still less is known about the precise etiology of autoimmune diseases. It is apparent, however, that the causes are complex, with contributions from both genetic and environmental factors. This is mirrored in the variety of animal models of autoimmune diseases which have been developed: at the one extreme are inbred strains in which the majority of individuals develop particular diseases at a similar age, regardless of their environment and at the other extreme are models in which disease is induced by deliberate immunization of animals which would otherwise remain healthy. It is thus clear that no single animal model can fully mimic the corresponding human diseases. This emphasizes the importance of investigating all aspects of human autoimmunity in order to determine those features which are central to the pathogenesis.
Epithelial expression of Class II in autoimmunity

An interesting property of thyroid epithelial cells (thyrocytes) is their ability to express major histocompatibility complex (MHC) Class II molecules when preparations of human thyroid cells are cultured with phytohemagglutinin or other plant lectins (Pujol-Borrell et al. 1983). The relevance of this finding to autoimmunity is suggested by the fact that, although thyrocytes are normally HLA Class II-negative, they do express these molecules in patients with Graves’ thyrotoxicosis and Hashimoto’s thyroiditis as well as having enhanced expression of HLA Class I products (Hanafusa et al. 1983).

The importance of this inappropriate HLA Class II expression is indicated by the well-known involvement of these molecules in the presentation of antigens leading to T cells stimulation. These considerations led to the hypothesis that the inappropriate expression of MHC Class II molecules by epithelial cells might enable these cells to present their own surface molecules to autoreactive T cells, by-passing a requirement for “conventional” antigen-presenting cells like macrophages and dendritic cells (Bottazzo et al. 1983). Such a process could make an important contribution to the potentiation, and also possibly the initiation of the autoimmune process.

The applicability of our findings in thyroid to a variety of autoimmune diseases is indicated by the growing list of autoimmune conditions in which abnormal expression of HLA Class II molecules by specific cells of the target organs has been demonstrated (Table IV). This list can be roughly divided into three categories, the first of which includes the autoimmune endocrinopathies involving the thyroid or pancreas. The second category of organ-specific conditions to be included are those involving the gut where the situation is somewhat different.

| TABLE IV |
|-----------------|-----------------|-----------------|
| **Disease**     | **Cells aberrantly expressing** | **Reference**   |
|                 | **Class II**     |                 |
| Autoimmune thyroid diseases | Thyroid epithelium | Hanafusa et al. (1983). |
| Type I (insulin-dependent) diabetes mellitus | Pancreatic beta cells | Jansson et al. (1985). |
| Inflammatory bowel disease | Gut epithelium | Aichinger et al. (1985). |
| Autoimmune protracted diarrhea of infancy | Immature jejunal enterocytes | Bottazzo et al. (1985). |
| Alopecia areata | Hair follicular cells | Foulis & Farquharson (1986). |
| Primary biliary cirrhosis | Bile duct epithelium | Mirakian et al., unpublished. |
| Sjögren’s syndrome | Salivary ducts | Messenger et al. (1984). |
|                 |                 | Ballardini et al. (1984). |
|                 |                 | Lindhal et al. (1985). |
because Class II is normally synthesized by mature villous enterocytes of the small intestine (Selby et al. 1981). This physiological expression could play an important role in the handling of environmental antigens from micro-organisms of the gut, and/or the education of gut-associated intra-epithelial lymphocytes. By contrast, abnormal Class II expression by cells of the gut could upset the normal immune regulatory mechanisms in these tissues and play a similar role in autoimmune activation to that postulated in the thyroid. A third category includes primary biliary cirrhosis (PBC) and Sjögren's syndrome. These conditions are not fully organ-specific in the sense that, although they affect particular tissues (i.e. the bile ducts and exocrine glands, respectively), they are characterized by organ non-specific autoantibodies: mitochondrial antibodies in PBC and antibodies to the ribonucleoprotein La/SS-B in Sjögren's syndrome. In these diseases, Class II expression by epithelia of the affected tissues could contribute to the tissue localization of the attack and also, possibly, to the autoantibodies produced if, for example, bile duct epithelial cells can express mitochondrial antigens on their surface.

Put into a wider context, the model we have proposed for the role of inappropriate epithelial Class II expression in autoimmunity accords with the suggestion of a more general relationship between aberrant or excessive MHC Class II expression and pathogenesis (Unanue et al. 1984). For example, in rheumatoid arthritis the large number of Class II+ macrophages/dendritic cells in affected joints may stimulate excessive T cells activation (Janossy et al. 1981, Klareskog et al. 1982). Similarly, classical antigen-presenting cells may play a critical role in autoimmune chronic active hepatitis (CAH), since, in contrast to the bile duct epithelium in PBC discussed above, the target hepatocytes in CAH show very little Class II expression, but Kupffer cells are increased in numbers and Class II positivity in the affected tissue (Ballardini et al., submitted).

Evidence of a role for Class II in autoimmune pathogenesis

In order to determine whether HLA Class II+ thyrocytes can really function as antigen-presenting cells, their ability to stimulate a cloned human T cell line was investigated in collaboration with Drs. M. Londei and M. Feldmann. The line employed, HA1.7, is specific for a defined peptide fragment (p20) of the influenza A hemagglutinin molecule, which it recognizes in association with DQw1 (Lamb & Feldmann 1983). Class II+ thyrocytes from a Graves' disease patient of the appropriate HLA type were indeed found to stimulate proliferation of HA1.7 in the presence of p20, but not an irrelevant peptide of hemagglutinin, and this presentation was blocked by monoclonal anti-Class II antibodies (Londei et al. 1984). However, unlike autologous monocytes, the thyrocytes were unable to present the whole virus (fixed or live), suggesting that they cannot process
complex antigens for presentation at the cell surface. This did not necessarily mean that thyroid cells would be unable to present their own surface molecules as autoantigens since, by their very nature, these are inserted in the plasma membrane where they could be recognised by T cells together with Class II molecules. Indeed, other experiments showed that autoreactive cloned T cell lines, derived from the activated lymphocytes infiltrating Graves' disease thyroids, proliferated upon exposure to autologous thyrocytes, but were not stimulated by either autologous peripheral blood mononuclear cells or allogeneic thyrocytes (Londei et al. 1985). Furthermore, the interaction with autologous thyrocytes could be blocked with monoclonal anti-Class II antibodies. This experiment thus demonstrated directly that thyrocytes are capable of presenting directly their own autoantigens in an MHC Class II-restricted, tissue-specific fashion to autoreactive T cells infiltrating the diseased thyroid.

Consistent with the above experiments are findings in a murine system, in which the I-A restricted primary sensitization of murine lymphocytes by syngeneic thyrocytes generates activated T cells capable of inducing thyroiditis (Charreire & Michel-Bechet 1982) and also thyroid-specific cytotoxic T cells (Salamero & Charreire 1985).

The enhanced expression of HLA Class I molecules by thyrocytes in ATD should also not be overlooked, since this could facilitate killing by Class I-restricted CD8+ autoreactive T cells. Indeed, CD8+ T cells with natural killer activity are the principal clones derived from Hashimoto's disease thyroid glands (Del Prete et al. 1986, Londei et al. 1986).

If HLA Class II expression by thyrocytes really does play an important role in the pathogenesis, then as well as permitting demonstrations of direct interactions between thyrocytes and T cells, the occurrence of this aberrant expression would be expected to correlate with other features of the autoimmune pathology. In this regard, we have analyzed a large series of patients and found a significant relationship between HLA Class II expression by thyrocytes and the occurrence of circulating autoantibodies to thyroglobulin and thyroid microsomal antigen (Todd et al. 1986b, Lucas Martin et al., submitted). This relationship was not restricted to cases of overt thyroid autoimmune disease, thus suggesting a role for thyrocyte Class II expression in autoimmune pathogenesis at the subclinical as well as clinical levels.

A more detailed analysis of a similar type was performed in Graves' disease patients in whom we examined expression of the HLA-D subregions DR, DQ and DP. The incidence and intensity of Class II subregion expression by thyrocytes was found to vary between patients, with DR being most expressed, followed by DP, and DQ least expressed. In this analysis, the most significant relationships were observed between high serum titres of thyroglobulin autoantibodies and thyrocyte expression of HLA-DQ, and between autoantibodies to microsomal antigen and HLA-DR. These findings are consistent with different HLA-D
subregion products expressed by thyrocytes being dominant in stimulating responses to different thyroid autoantigens (Todd et al. 1986b).

**Regulation of epithelial Class II expression**

In view of its potential role in autoimmune pathogenesis, it was important to investigate the regulation of HLA Class II expression in the epithelial cells expressing these molecules in autoimmune diseases. What has clearly emerged from our collaborative studies with Dr. M. Feldmann is that such regulation is complex, with a variety of factors modulating Class II expression, and differences in susceptibility depending on the cell type. These principles are best exemplified by our studies on thyrocytes in relation to thyroid autoimmunity, and on pancreatic islet cells in relation to Type I diabetes mellitus. Interferon (IFN)-gamma has been found to induce or enhance Class II expression by a variety of cell types and, indeed, we found that recombinant human IFN-gamma induced strong surface and cytoplasmic expression of Class II molecules in cultured normal human thyrocytes (Todd et al. 1985b). The surface expression was detectable within 24 h and as little as 1 U/ml was effective, thus being within the physiological range. By contrast, IFN-alpha and IFN-beta did not induce Class II expression although, like IFN-gamma, they did enhance HLA Class I expression by the thyrocytes. IL-2 had no effect on thyrocyte expression of either Class I or Class II.

These findings suggest that IFN-gamma may well be an inducer of the Class II expressed by thyrocytes in ATD: the production of this lymphokine by activated autoreactive T cells infiltrating the gland could enable the spread of Class II expression by the epithelial cells, and hence the propagation of the autoimmune process. IFN-gamma can also determine the quality of Class II subregion expression by thyrocytes. Thus, low doses of IFN-gamma (5–10 U/ml) induce expression of DR, but very little DP or DQ, whereas DR, DP and DQ are all induced in a high proportion of thyrocytes cultured with 500 U IFN-gamma/ml (Todd et al. 1986a and in preparation). This may help to explain the heterogeneity of thyrocyte HLA-D subregion expression by Graves' disease patients, noted above.

All cells are responsive to a variety of regulatory stimuli, and it would be naive to assume that IFN-gamma is the only stimulus relevant to epithelial Class II expression: indeed, investigations in Type I diabetes highlight the involvement of other factors. In this disease, the insulin-producing beta cells, which are the target of the pathogenic process, aberrantly express Class II molecules, although the other islet endocrine cells and the exocrine cells of the pancreas remain Class II− (Bottazzo et al. 1985, Foulis & Farquharson, in press). By contrast, only a small proportion of cultured human beta cells are induced to express Class II by rIFN-gamma, although the exocrine and ductal cells in these cultures become strongly Class II+ (Pujol-Borrell et al. 1986c). However, induction of Class II in cultured
islet cells can be achieved with a combination of IFN-gamma and tumor necrosis factor (TNF) or lymphotoxin (LT), although TNF or LT alone have no effect (Pujol-Borrell et al. 1986a, and submitted for publication). Unlike the in vivo pathological situation, Class II was induced in the glucagon cells and exocrine/ductal cells, as well as in the beta cells of the pancreatic cultures. This raises the possibility that synergism between IFN-gamma and TNF or LT is not the mechanism initiating beta cells Class II expression in diabetes, although it could have a potentiating effect. Alternatively, effective beta cell specificity could be explained by localized release of these mediators in vivo with their short half-life limiting their sphere of action, possibly together with yet another signal acting specifically on beta cells. In any case, it is clear that our in vitro systems do not fully reproduce the in vivo situation as yet.

A requirement for combinations of factors to optimally induce epithelial Class II expression should limit the circumstances in which such activation occurs, and hence the opportunities for autoimmune stimulation. This is clearly applicable to the pancreatic islet, where either signal alone is ineffective, but could also apply to the thyroid, particularly in circumstances where the exposure to IFN-gamma is limited. As in the islets, TNF synergizes with IFN-gamma to induce Class II expression by thyrocytes (Todd et al., in preparation). However, a more potent enhancer of thyrocyte Class II expression in vitro is thyroid stimulating hormone (TSH). This is most effective in combination with a suboptimal dose of IFN-gamma, and although TSH added alone to thyroid cultures has some effect, this is probably secondary to activation of Class II genes by some other means (Todd et al. 1986c and in preparation). The enhancing effect of TSH is apparent on the expression of all three HLA-D subregions, and is mimicked by dibutyryl-cyclic AMP, suggesting that cyclic AMP is the second messenger for this activity, as it is for many effects of TSH on thyrocytes. The optimal in vitro concentration of TSH for Class II stimulation is 0.1 mU/ml, which is within the range of serum concentrations in hypothyroid patients with Hashimoto’s disease. The raised TSH levels in these patients might therefore exacerbate the pathogenic process by enhancing the aberrant Class II expression within the thyroid. Thyroid stimulating antibodies, which mimic the actions of TSH, could have similar effects in Graves’ disease.

Since IFN-gamma is a lymphocyte product, induction of epithelial Class II by IFN-gamma alone, or in combination with synergizing factors, must involve immune mechanisms. These could be related or unrelated to the autoimmune activation: in the latter case involving a response to a local viral infection, for example. However, the possibility that other mechanisms could also stimulate epithelial class II expression should be considered, particularly since, as already noted in relation to diabetes, Class II induced in vitro by mechanisms involving IFN-gamma can be found in a wider range of cell types than it is in the diseased tissues. One possibility is that certain viruses might directly induce Class II. This
is supported by recent experiments in our laboratory in which epithelial cell lines were derived from thyroid monolayers by transfection with a plasmid containing the early region of SV-40 viral DNA: a proportion of the cells in these lines showed constitutive Class II expression (Belfiore et al. 1986 and in preparation). A different example is provided by the finding that rat astrocytes express Class II following non-infective interaction with a murine neurotropic coronavirus (Massa et al. 1986).

Another possibility is that factors other than IFN-gamma, derived from non-lymphocytic cells (e.g. macrophages or endothelial cells), might activate Class II genes. Precedents for this include the production of a novel form of interferon by macrophages infected with lentiviruses (Kennedy et al. 1985) and the production of an Ia-inducing factor by a murine macrophage tumor cell line treated with IFN-gamma (Walker et al. 1984).

Turning to the other side of the coin, we have also investigated mechanisms whereby epithelial Class II expression could be down-regulated, since these could be just as important as stimulating mechanisms in determining the level of Class II expression and the course of autoimmunity. Epidermal growth factor (EGF) has been reported both to stimulate thyroid growth in culture and suppress TSH-stimulated processes, such as efflux and organification of iodide (Westermark et al. 1983). In the present context, we found that EGF suppressed, by at least 50%, Class II expression by cultured thyrocytes induced by IFN-gamma alone, or IFN-gamma + TSH (Todd et al. 1986c and in preparation).

The implications of these various investigations are summarized in Fig. 1. First of all, it appears likely that a variety of courses may lead to epithelial Class II expression. This may depend not only on those substances which directly activate Class II genes, but also on synergizing co-factors. The importance of the latter's contribution will be determined by the nature and amount of the primary inducer (e.g. IFN-gamma), and the particular cell type involved. Furthermore, the nature and levels of the various stimulators will influence not only the quantity of Class II expressed, but also its quality in terms of HLA-D subregion expression. Secondly, the extent and duration of Class II expression will be affected by the balance between Class II enhancing and suppressive influences, which may thereby contribute to the severity and duration of autoimmune attack. The autoimmune processes will themselves contribute to the position of this balance: some of these effects will be direct, e.g. by autoreactive lymphocytes infiltrating the diseased tissue producing lymphokines, including IFN-gamma and lymphotoxin; others will be indirect, e.g. changes in hormone production by the thyroid as a result of autoimmune processes will effect the levels of TSH and EGF (for further details, see Todd et al. 1986c). Finally, the effect of a particular factor may vary with the cell type: for example, whereas EGF suppresses Class II expression by thyrocytes (Todd et al. 1986c, and in preparation), it has been found to enhance Class II expression by human monocytes (Acres et al. 1985).
**Figure 1.** Modulation of epithelial HLA Class II expression in relation to autoimmunity.

**SPECULATIONS AND PROSPECTS FOR THE FUTURE**

In recent years, the unexpected results of novel investigations in organ-specific autoimmunity have required us to modify our conception of the mechanisms involved. For example, the target cells no longer appear to be 'passive', as previously thought, but their role is now seen to be much more prominent with the demonstration that they can express HLA Class II molecules. The current debate is thus focused on whether the process should be visualized as 'homicidal', i.e. attack by common environmental factors and autoreactive immunocytes, either separately or in combination, on 'unsuspecting' target cells, or as 'suicidal', with the target making itself vulnerable by expression of Class II and enhanced expression of Class I molecules (Bottazzo 1986). The latter possibility certainly has a conceptual advantage in that both the afferent and efferent limbs of the autoimmune response then take place within the same location, i.e. at the surface of the target cells themselves. This may be contrasted with the conventional, but more complex models which require release of surface autoantigens from damaged target cells, their presentation by classical antigen-presenting cells in distant specialized lymphoid organs, and the subsequent re-circulation of activated autoreactive lymphocytes to the target tissues. These steps clearly pose a number of logistical problems.

With regard to the forces promoting infiltration of the target tissues, an
important part could be played by capillary endothelial cells, which physiologically constitute a discrete and selective barrier between the blood and the tissues. In organs affected by autoimmunity, these structures are hypertrophic and strongly Class II-positive, as indicated by the observations in diabetic pancreases where this phenomenon occurs selectively around islets which are otherwise normal (Bottazzo et al. 1985, Foulis & Farquharson, in press). This suggests an important role for the capillaries in facilitating the 'homing' of potentially autoreactive lymphocytes (Gallatin et al. 1983, Naparstek et al. 1984). The enhanced Class II expression by endothelial cells could be important in this process, and might possibly enable these cells to present antigens which are cross-reactive with those expressed by the target endocrine cells. We have already mentioned the possibility that the endothelium might also secrete factors affecting MHC expression by the adjacent epithelial cells.

An intriguing question is what might be the role of epithelial Class II expression in non-autoimmune situations? It is apparent that such expression can contribute to autoimmune pathology, but the fact that these cells have the capacity to express Class II at all and that, in thyrocytes for example, Class II is relatively easily induced, suggests that this may be advantageous to the organism in certain circumstances. Indeed, some epithelia, particularly where exposed to external environments, are normally Class II+: we have already mentioned possible roles for such physiological Class II expression by epithelium of the gut. Pathological situations in which an immune response to certain cells would be desirable is when these cells are virally infected or malignantly transformed. Expression of Class II by such cells would facilitate an immune response to the viral or tumor antigens, and the subsequent destruction of the same cells would abrogate the spread of infection or growth of the tumor. The possibility that certain viruses might directly induce Class II expression has been discussed, and Class II expression by thyroid papillary carcinomas has been noted (Lloyd et al. 1985, Lucas-Martin et al., submitted). Only when the balance of mechanisms regulating Class II expression and/or immune activation is upset would the phenomenon progress to overt autoimmunity.

Other important factors in autoimmune pathogenesis could include, firstly, suppressor T cells, which may normally tip the balance in favor of self non-responsiveness. The possible existence of organ-specific suppressor T cells (Topliss et al. 1983, Vento et al. 1985) remains attractive, although it is presently difficult to devise strategies for their isolation and unambiguous characterization. Turning to the possible involvement of anti-idiotypic responses, it is hard to envisage these making a major contribution to destructive autoimmunity, as has been suggested (Plotz 1983), particularly since the lack of MHC restriction of such responses is difficult to reconcile with the observations of aberrant MHC expression by the target cells (reviewed by Bottazzo et al. 1984). On the other hand, we have discussed how the idiotype theory could explain the generation of
antibodies to hormone receptors and it is possible that growth stimulating antibodies of this type could account for the regeneration of target tissues which is postulated to occur during the long latency period preceding the onset of clinical symptoms in many autoimmune diseases (Bottazzo 1984).

Advances in immunological techniques are facilitating a more detailed understanding of human organ-specific autoimmunity. For example, the recent application of T cell cloning (Hohlfeld et al. 1984, Londei et al. 1985) has greatly facilitated dissection of the processes involved in the autoimmune attack (reviewed by Feldmann et al. 1985). With regard to Graves' disease, intrathyroidal lymphocytes from autoimmune glands proved to be the best source of starting material for the establishment of thyroid-specific, autoreactive cloned T cell lines. (This followed several unsuccessful attempts over the years using peripheral blood lymphocytes from patients affected by the same disorders). Once again, epithelial HLA Class II expression proved to be a key factor, since autologous Class II+ thyocytes were successfully employed to stimulate expansion of the autoreactive T cells (Londei et al. 1985). On the other hand, major problems still exist in applying T cell cloning technology to diabetes. Lack of sufficient numbers of insulin cells for in vitro studies is one of the main limitations, but most important is the fact that the pancreas cannot be biopsied, so that the T cells most relevant to the diabetic process (i.e. those involved in the insulitis process) are not available. The T cell clones which would most probably be derived from the diabetic pancreas are cytotoxic ones, since these appear to be the cells which dominate the infiltrate and finally destroy the beta cells. With regard to thyroid autoimmunity, only CD4+ (?helper) T cell clones have so far been derived from the infiltrate of Graves' disease thyroids, whereas CD8+ clones with cytotoxic activity similar to natural killer cells are more easily raised from Hashimoto's glands (Londei et al. 1986, Del Prete et al. 1986). By analogy, the latter situation should also apply in 'destructive pancreatic insulitis'.

Given the apparent importance of cytotoxic cells in destructive autoimmunity, therapeutic drugs directed against these cells could obviously be very beneficial. Autoreactive cytotoxic clones would be a valuable substrate for testing such agents. Recently developed drugs do not appear to act in this way: thus newly diagnosed diabetics given cyclosporin A or ciamezone (a new compound used in the attempt to halt progressive beta cell damage [Bicker et al. 1986]) quickly relapsed after withdrawal of the treatment (Stiller and Usadel, personal communications) and cyclosporin A did not prevent an anamnestic anti-islet response in diabetics given pancreatic transplants from HLA-matched siblings (Sutherland et al. 1986).

A more refined analysis of tissue-derived autoreactive lymphocytes should also permit investigations into the T cell receptors directed against specific autoantigens. Due to the organ-specific localization of the response, one would expect the frequency of the relevant T cells in the peripheral blood to be very low. Thus, T cell clones obtained from the lymphocytes invading the tissue would be the best
material for these studies. One could then accurately characterize the receptors at the genetic level, and also probe whether viral infection and integration might play a role in promoting the expansion of these self-reactive specificites.

Appreciation of the prominent role that the target cells play in autoimmune pathogenesis has highlighted the need for appropriate epithelial cell lines to facilitate further in vitro investigation. The usefulness of primary cultures of human epithelial cells is limited by their cellular heterogeneity and short life span. Furthermore, in diabetes research, for example, the lack of sufficient beta cells curtails experimentation. Endocrine cell lines only of animal origin are presently available and therefore the development of human cell lines is a high priority. Physiological mechanisms occasionally differ markedly between rodents and humans but these interspecies variations are most critical when studying immunological phenomena since antigenic differences can interfere with recognition by antibodies, and more especially by T cells. One approach to the development of human epithelial cell lines is exemplified by our experiments in transformation of thyroid cells with portions of the SV-40 genome. This has given insights into possible mechanisms of Class II induction, as discussed in the previous section, but it has also resulted in the establishment of stable cell lines which have been cloned several times. However, these lines no longer display all the features of the original cells. In fact, they have lost TSH receptors, they synthesize thyroglobulin but do not secrete it into the medium and the microsomal/microvillar antigenic system is poorly represented on the cell surface. This implies that future efforts must be concentrated on devising new strategies which will allow cells to grow while maintaining their original features. These include the use of suitable mutant viruses, the implementation of various culture conditions, more effective combinations of nucleic and cytoplasmic oncogene products and the use of the somatic cell fusion technique, so successful in monoclonal antibody technology. Some success with the latter technique in developing thyroid cell lines has been reported by Karsenty et al. (1985).

The feasibility of these and other techniques, together with our present state of knowledge, bode well for exciting advances in the field of organ-specific autoimmunity.

The jigsaw puzzle is taking shape.

SUMMARY

The normally functioning immune system is subject to intricate networks of regulatory mechanisms: it is therefore not surprising to find that autoimmune diseases present a complex pathogenic picture in which the relative contributions of various factors probably determine the precise nature and course of disease.

This is particularly evident in the effector mechanisms of organ-specific autoimmunity which are described in this chapter. These ultimately give rise to the
disease symptoms, and can be directly cytotoxic, or may either stimulate or block functional activity or growth of the target cells. Their various contributions to human diseases are becoming more firmly established, as in Type I diabetes, or are only now being described, as in the case of EC-Ab in protracted diarrhea of infancy and as evidenced by the growing lists of receptor-stimulating or -blocking antibodies. The nature and precise location of relevant autoantigens is also coming under closer scrutiny.

The answers to the question of why these diseases arise in the first place remain more elusive. However, it is again likely that a variety of factors can contribute. The attractive possibility of a role for idiotypic interactions is gaining ground, particularly within the context of antibodies to hormones and their receptors. Another potential mechanism which we believe may be of central importance, particularly in the development of organ-specific destructive autoimmunity, and which we have discussed here in detail, is the aberrant expression of HLA Class II molecules by target cells. Whether this is actually an initiating factor is presently not known, but its potential for promoting pathogenesis both early and late in the process is clear. Furthermore, the complex nature of the regulation of epithelial Class II expression may help to explain the heterogeneity of features and course of disease in different patients with the same underlying pathology. All these advances in our basic understanding of the disease processes should ultimately lead to more effective and specific means of therapeutic intervention.

ACKNOWLEDGMENTS

We would like to thank all our colleagues who contributed so much to the advance of the subject while working or collaborating with us in the last decade. We are particularly grateful to Prof. Deborah Doniach, who initiated us into the field of endocrine autoimmunity and to Prof. Ivan Roitt for his constant support and encouragement throughout the years. The generous financial support of the Medical Research Council, the British Diabetic Association, the Wellcome Trust Foundation, the Juvenile Diabetic Foundation (USA) and Novo Research Institute (Copenhagen) continues to support the new developments in our research. Miss Marian Pine helped us with accuracy and patience in editing the manuscript.

REFERENCES

Acres, R. B., Lamb, J. R. & Feldmann, M. (1985) Effects of platelet-derived growth factor and epidermal growth factor on antigen induced proliferation of human T-cell lines. *Immunology* 54, 9–16.

Adams, D. D., (1956) The clinical status of patients whose sera have given the abnormal response when assayed for thyrotropin. *Proc. Univ. Otago. Med. Sch.* 34, 29–35.

Adams, D. D. (1958) The presence of an abnormal thyroid-stimulating hormone in the serum of some thyrotoxic patients. *J. Clin. Endocrinol. Metab.* 18, 699–712.
Aichinger, G., Fill, H. & Wick, G. (1985) In situ immune complexes, lymphocytes subpopulations and HLA-DR positive epithelial cells in Hashimoto thyroiditis. Lab. Invest. 52, 132–140.

Alviggi, L., Johnston, C., Hoskins, P. J., Tee, D. E. H., Pyke, D. A., Leslie, R. G. D. & Vergani, D. (1984) Pathogenesis of insulin dependent diabetes: A role for activated T-lymphocytes. Lancet ii, 4–6.

Baekkeskov, S., Nielsen, J. H. Marner, B., Bilde, T., Ludvigsson, J. & Lernmark, A. (1982) Autoantibodies in newly diagnosed diabetic children immunoprecipitate human pancreatic islet cell proteins. Nature 298, 167–169.

Ballardini, G., Bianchi, F. B., Mirakian, R., Pisi, E. & Bottazzo, G. F. HLA-A, B, C and HLA-D/DR on liver biopsies from patients with chronic liver disease. (submitted for publication).

Ballardini, G., Mirakian, R., Bianchi, F. B., Pisi, E., Doniach, D. & Bottazzo, G. F. (1984) Aberrant expression of HLA-DR antigens on bile duct epithelium in primary biliary cirrhosis: relevance to pathogenesis. Lancet ii, 1009–1013.

Banga, J. P., Pryce, G., Hammond, L. & Roitt, I. M. (1985) Structural features of the autoantigens involved in thyroid autoimmune disease: the thyroid microsomal/microvillar antigen. Mol. Immunol. 22, 629–642.

Beall, G. N., Rapoport, B., Chopra, I. J. & Kruger, S. R. (1986) Further studies of the production by rabbits of thyroid-stimulating anti-idiotypic antibodies to TSH. In: Proceedings of the 9th International Thyroid Congress, Sao Paulo, September 1985. Plenum Press, New York (in press).

Belfiore, A., Pujol-Borrell, R., Mauerhoff, T., Mirakian, R. & Bottazzo, G. F. (1986) Effect of SV-40 transformation on HLA expression by thyroid follicular cells: a rise of a population of DR positive thyrocytes. Annales d'endocrinol 47, 17 (abstract).

Betterle, C., Caretto, A., Zeviani, M., Pedini, B. & Salviati, C. (1984) Demonstration and characterization of anti-human mitochondria autoantibodies in idiopathic hypoparathyroidism and in other conditions. Clin. Exp. Immunol. 62, 353–360.

Betterle, C., Mirakian, R., Doniach, D., Bottazzo, G. F., Riley, W. & MacLaren, N. K. (1984) Antibodies to melanoocytes in vitiligo. Lancet i, 159 (letter).

Bicker, U., Pahlke, W., Romer, K. G., Teuber, J. & Usadel, K. H. (1986) In: Proceedings of Symposium on Immunology of Diabetes, Edmonton, Canada, June 1986. Elsevier Science Publishers (in press).

Blizzard, R. M., Chee, D. & Davis, W. (1966) The incidence of parathyroid and other antibodies in the sera of patients with idiopathic hypoparathyroidism. Clin. Exp. Immunol. 1, 119–128.

Bodansky, H. J., Grant, P. J., Grant, J. T. D., Dean, B. M., McNally, J. M., Bottazzo, G. F., Hambling, P. H. & Wales, J. K. Islet cell and insulin autoantibodies in association with common viral infections. Diabetic Med. (in press).

Bottazzo, G. F. (1984) Beta cell damage in diabetic insulitis: are we approaching the solution? Diabetologia 26, 241–249.

Bottazzo, G. F. (1986) Death of a Beta Cell: Homicide or Suicide? Diabetic Medicine 3 119–130.

Bottazzo, G. F., Dean, B. M., Gorsuch, A. N., Cudworth, A. G. & Doniach, D. (1980) Complement-fixing islet cell antibodies in Type I diabetes: Possible monitors of active beta-cell damage. Lancet i, 668–672.

Bottazzo, G. F., Dean, B. M., McNally, J. M., MacKay, E. H., Swift, P. G. F. & Gamble, D. R. (1985) In situ characterization of autoimmune phenomena and expression of HLA molecules in the pancreas in diabetic insulitis. N. Engl. J. Med. 313, 353–360.

Bottazzo, G. F. & Doniach, D. (1985) Polyendocrine Autoimmunity: An extended concept. In: Autoimmunity and Endocrine disease, ed. Volpe, R., pp. 375–403. Marcel/Dekker Inc., New York.
Bottazzo, G. F. & Doniach, D. (1986) Autoimmune thyroid disease. *Ann. Rev. Med.* 37, 353–359.

Bottazzo, G. F., Florin-Christensen, A. & Doniach, D. (1974) Islet cell antibodies in diabetes mellitus with autoimmune polyendocrine deficiencies. *Lancet* ii, 1279–1283.

Bottazzo, G. F. & Lendrum, R. (1976) Separate autoantibodies to human pancreatic glucagon and somatostatin cells. *Lancet* ii, 873–876.

Bottazzo, G. F., Pouplard, A., Florin-Christensen, A. & Doniach, D. (1975) Autoantibodies to prolactin-secreting cells of human pituitary. *Lancet* ii, 97–101.

Bottazzo, G. F., Pujol-Borrell, R. & Gale, E. (1986) Autoimmunity and diabetes: progress, consolidation and controversy. *The Diabetes Annual* 2, 13–29.

Bottazzo, G. F., Pujol-Borrell, R., Hanafusa, T. & Feldmann, M. (1983) Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. *Lancet* ii, 1115–1119.

Bottazzo, G. F., Todd, I. & Pujol-Borrell, R. (1984) Hypothesis for the genetic contribution to the aetiology of diabetes mellitus. *Immunol. Today* 5, 230–231.

Broberger, O. & Perlmann, P. (1961) Demonstration of an epithelial antigen in colon by means of fluorescent antibodies from children with ulcerative colitis. *J. Exp. Med.* 115, 13–25.

Burden, A. C., & Rosenthal, F. D. (1983) Methimazole and insulin autoimmune syndrome. *Lancet* ii, 1311.

Charreire, J. & Michel-Bechet, M. (1982) Syngeneic sensitization of mouse lymphocytes on monolayers of thyroid epithelial cells III. Induction of thyroiditis by thyroid-sensitized T lymphoblasts. *Eur. J. Immunol.* 12 421–425.

Chiovato, L., Hammond, L. J., Hanafusa, T., Pujol-Borrell, R., Doniach, D. & Bottazzo, G. F. (1983) Detection of thyroid growth immunoglobulins (TGI) by [3H] thymidine incorporation in cultured rat thyroid follicles. *Clin. Endocrinol.* 19, 581–590.

Colman, P. G., Campbell, I. L. & Harrison, L. C. (1985) Characterization of the 64,000 MW autoantigen in insulin-dependent diabetes. *Diabetes* 34 69A.

Colman, P. G., Campbell, I. L. & Harrison, L. C. Antibodies in insulin-dependent diabetics to pancreatic islet cells: reactivity with a 64,000 molecular weight surface protein with the properties of bovine albumin. (submitted for publication).

Compston, A. & Vincent, A. (1985) Multiple Sclerosis and Myasthenia Gravis. *Clin. Immunol. Allergy* 5, 569–584.

Czarnocka, B., Ruf, J., Ferrand, M., Carayon, P. & Lissitzky, S. (1985) Purification of the human thyroid peroxidase and its identification as the microsomal antigen involved in autoimmune thyroid diseases. *FEBS Lett.* 190, 147–152.

Dawkins, R. L. & Garlepp, M. J. (1985) Autoimmune diseases of muscle: myasthenia gravis and myositis. In: *The Autoimmune Disease*, eds. Rose, N. R. & MacKay, I. R., pp. 591–615. Academic Press, New York.

De Aizpurua, H. J., Toh, B. H. & Ungar, B. (1983a) Parietal cell surface reactive autoantibody in pernicious anaemia demonstrated by indirect membrane immunofluorescence. *Clin. Exp. Immunol.* 52, 341–349.

De Aizpurua, H. J., Ungar, B. & Toh, B. H. (1983b) Flow microfluorometric analysis of autoantibody reactions with parietal cell surface membranes in pernicious anaemia. *Clin. Exp. Immunol.* 54, 405–410.

Dean, B. M., Becker, F., McNally, J. M., Tarn, A. C., Schwartz, G., Gale, E. A. M. & Bottazzo, G. F. (1986) Insulin autoantibodies in the pre-diabetic period: Correlation with islet cell antibodies and development of diabetes. *Diabetologia* 29, 339–342.

De Bruin, T. W. A., Van De Heide, D., Querido, A. & Krol, M. C. (1984) Direct and quantitative measurement by immunoprecipitation assay of anti-thyrotropin receptor antibodies in sera of patients with Graves’ disease. *Clin. Endocrinol.* 20, 143–151.
De Lazzari, F., Mirakian, R., Hammond, L., Venturi, C., Naccarato, R. & Bottazzo, G. F. (1985) Are some duodenal ulcer cases due to autoimmunity? Studies on gastric parietal cell c-AMP stimulating autoantibodies. (Submitted for publication).

Del Prete, G. F., Maggi, E., Mariotti, S., Tiri, A., Vercelli, D., Parronchi, P., Macchia, D., Pinchera, A., Ricci, M. & Romagnani, S. (1986) Cytolytic T lymphocytes with natural killer activity in thyroid infiltrate of patients with Hashimoto’s thyroiditis: analysis at clonal level. *J. Clin. Endocrinol. Metab.* 62, 1-6.

Dobi, S. & Lenkey, B. (1982) Role of secretagogue immunoglobulin in gastric acid secretion. *Acta Physiol. Acad. Sci. Hung.* 69, 9–25.

Doniach, D. (1976) Clinical observations and hypotheses related to TSH receptors. In: *Biochemical basis of thyroid stimulation and thyroid hormone action*, eds. Muhlen, A. V. & Schleusener, H., pp. 24–36. Georg Thieme, Stuttgart.

Doniach, D., Bottazzo, G. F. & Drexhage, H. A. (1981) The autoimmune endocrinopathies. In: *Clinical Aspects of Immunology*, 4th Ed., eds. Peters, K. & Lachman, P. J., pp. 903–937. Blackwell, Oxford.

Drexhage, H. A., Bottazzo, G. F., Bitensky, L., Chayen, J. & Doniach, D. (1981) Thyroid growth-blocking antibodies in primary myxedema. *Nature* 289, 594–596.

Drexhage, H. A., Bottazzo, G. F. & Doniach, D. (1983) Thyroid growth stimulating and blocking antibodies. In: *Cytotoxic Bioassay Techniques and Applications*, eds. Chayen, J. & Bitensky, L., pp. 153–172. Marcel Dekker, New York.

Drexhage, H. A., Bottazzo, G. F., Doniach, D., Bitensky, L. & Chayen, J. (1980) Evidence for thyroid growth stimulating immunoglobulins in some goitrous thyroid diseases. *Lancet* ii, 287–292.

Ealey, P. A., Emmerson, J. M., Bidey, S. P. & Marshall, N. J. (1985) Thyrotrophin stimulation of the rat thyroid cell strain FRTL-5: a metaphase index assay for the detection of thyroid growth stimulators. *J. Endocrinol.* 106, 203–210.

Eno, K., Kasagi, K., Konishi, J., Ikekubo, K., Okuno, T., Takeda, Y., Mori, T. & Torizuka, K. (1978) Detection and properties of TSH-binding inhibitor immunoglobulins in patients with Graves’ disease and Hashimoto’s thyroiditis. *J. Clin. Endocrinol. Metab.* 46, 734–739.

Escobar, M. E., Cigorraga, S. B., Chiauzzi, V. A., Charrau, Eh. & Rivarola, M. A. (1982) Development of the gonadotropic resistant ovary syndrome in myasthenia gravis: suggestion of similar autoimmune mechanism. *Acta Endocrinol.* (Copenhagen) 99, 431–436.

Feldmann, M., Doniach, D. & Bottazzo, G. F. (1986) The heterogeneity of autoimmune response. In: *Immunology of Rheumatic Disease*, eds. Gupta, S. & Talal, N., pp. 271–300. Plenum Pub. Corp. New York.

Fenzi, G. F., Bartalena, L., Chiovato, L., Marcocci, C., Rotella, C. M., Zonefrati, R., Toccafondi, R. & Pinchera, A. (1982) Studies on thyroid cell surface antigens using cultured human thyroid cells. *Clin. Exp. Immunol.* 47, 336–344.

Feutren, G., Assau, R., Karrenty, G., DuRostu, H., Sizumai, J., Papoz, L., Vialettes, B., Vexian, P., Rodier, M., Lallemant, A. & Bach, J. F. (1986) Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset — results of a multicentre double-blind trail. *Lancet* i, 119–124.

Flier, J. S., Kahn, C. R., Jarrett, D. B. & Roth, J. (1976) Characterization of antibodies to the insulin receptor: a cause of insulin-resistant diabetes in man. *J. Clin. Invest.* 58, 1442–1449.

Foulis, A. K. & Farquharson, M. A. (1986) Aberrant expression of HLA-DR antigens by insulin containing beta cells in recent onset Type I (insulin-dependent) diabetes mellitus. *Diabetes* (in press).

Fraser, C. M., Veuter, J. C. & Kaliner, M. (1981) Autonomic abnormalities and autoantibodies to Beta-adrenergic receptor. *N. Engl. J. Med.* 305, 1165–1170.
Freedman, Z. R., Feed, C. M., Irvine, W. J., Rubenstein, A. H., Steiner, D. F. & Huen, A. (1979) Islet cell cytoplasmic and cell surface antibodies in diabetes mellitus. *Trans. Assoc. Am. Physicians* 96, 64–76.

Gafni, M., Ben David, H., Gordon, A. & Gross, J. (1986) The induction of immunoglobulins that stimulate thyroid growth, iodide concentration and cause TSH binding in the mouse. In: *Proceedings of the 9th International Thyroid Congress*, Sao Paulo, September 1985. Plenum Press, New York (in press).

Gallatin, W. M., Weissman, I. L. & Butcher, E. C. (1983) A cell-surface molecule involved in organ-specific homing of lymphocytes. *Nature* 304, 30–34.

Gepts, W. & DeMey, J. (1978) Islet cell survival determined by morphology: an immunohistochemical study of the islets of Langerhans in juvenile diabetes mellitus. *Diabetes* 27, 251–261 (Suppl. 1).

Goudi, R. B. & Pinkerton, P. H. (1962) Anterior hypophysitis and Hashimoto’s disease in young women. *J. Pathol. Bacteriol.* 83, 584–585.

Hamada, N., Grimm, C., Mori, H. & DeGroot, L. (1985) Identification of a thyroid microsomal antigen by Western blot and immunoprecipitation. *J. Clin. Endocrinol. Metab.* 61, 120–128.

Hanauska, T., Pujol-Borrell, R., Chiovato, L., Doniach, D. & Bottazzo, G. F. (1984) In vitro and in vivo reversal of thyroid epithelial polarity: its relevance for autoimmune thyroid disease. *Clin. Exp. Immunol.* 57, 639–646.

Hanauska, T., Pujol-Borrell, R., Chiovato, L., Russell, R. C. G., Doniach, D. & Bottazzo, G. F. (1983) Aberrant expression of HLA-DR antigen on thyrocytes in Graves’ disease: relevance for autoimmunity. *Lancet* ii, 1111–1115.

Hirata, Y. (1983) Methimazole and insulin autoimmune syndrome with hypoglycaemia. *Lancet* ii, 1037–1038.

Hohlfeld, R., Toyka, K. V., Heininger, K., Gross-Wilde, H. & Kalies, I. (1984) Autoimmune human T lymphocytes specific for acetylcholine receptor. *Nature* 310, 244–246.

Janossy, G., Panayi, G., Duke, O., Bofil, M., Poulter, L. W. & Goldstein, G. (1981) Rheumatoid arthritis: a disease of T-lymphocyte/macrophage immunoregulation. *Lancet* ii, 839–842.

Jansson, R., Karlsson, A. & Forsum, U. (1985) Intrathyroid HLA-DR expression and T lymphocyte phenotypes in Graves’ thyrotoxicosis, Hashimoto’s thyroiditis and nodular colloid goitre. *Clin. Exp. Immunol.* 58, 264–272.

Jones, H. W., Lendrum, R., Marks, J. M., Mirakian, R., Bottazzo, G. F., Sarson, D. L. & Bloom, S. R. (1983) Autoantibodies to gut secretin cells as markers of peptide deficiency. *Gut* 24, 427–432.

Juppner, H., Bialasiewicz, A. A. & Hesch, D. (1978) Autoantibodies to parathyroid hormone receptor. *Lancet* ii, 1222–1224.

Kagnoff, M. F., Austin, R. K., Hubert, J. J., Bernardin, J. E. & Kasarda, D. D. (1984) Possible role of a human adenovirus in the pathogenesis of celiac disease. *J. Exp. Med.* 160, 1544–1557.

Kahn, C. R., Kasuga, M., King, G. L. & Grunfeld, C. (1982) Autoantibodies to insulin receptors in man: Immunological determinants and mechanism of action. In: *Receptors, Antibodies and Disease* ed. Evered, D., pp. 91–105. CIBA Symposium 90. Pitman, London.

Kaplan, D., Colca, J. & McDaniel, M. (1983) Insulin as a surface marker on isolated cells from rat pancreatic islets. *J. Cell. Biol.* 97, 433–437.

Karsenty, G., Michel-Bechet, M. & Charriere, J. (1985) Monoclonal human thyroid cell line GEJ expressing human thyrotropin receptors. *Proc. Natl. Acad. Sci. USA* 82, 2120–2124.

Kennedy, P. G. E., Narayan, O., Ghotbi, Z., Hopkins, J., Gendelman, H. E. & Clements,
J. E. (1985) Persistent expression of Ia antigen and viral genome in Visna-Maedi virus-induced inflammatory cells. Possible role of lentivirus-induced interferon. *J. Exp. Med.* 162, 1970–1980.

Khoury, E. L., Bottazzo, G. F. & Roitt, I. M. (1984) The thyroid 'microsomal' antibody revisited: Its paradoxical binding in vivo to the apical surface of the follicular epithelium. *J. Exp. Med.* 159, 577–591.

Khoury, E. L., Hammond, L., Bottazzo, G. F. & Doniach, D. (1981a) Surface reactive antibodies to adrenal cells in Addison's disease. *Clin. Exp. Immunol.* 45, 48–58.

Khoury, E. L., Hammond, L., Bottazzo, G. F. & Doniach, D. (1981b) Presence of organ-specific 'microsomal' autoantigen on the surface of human thyroid cells in culture: its involvement in complement-mediated cytotoxicity. *Clin. Exp. Immunol.* 45, 577–591.

Klareskog, L., Forsum, U., Scheynius, A., Kabelitz, D. & Wigzell, H. (1982) Evidence in support of a self-perpetuating HLA-DR-dependent delayed-type cell reaction in rheumatoid arthritis. *Proc. Natl. Acad. Sci. USA* 79, 3632–3636.

Knight, A., Knight, J., Laing, P. & Adams, P. (1984) Coexisting thyroid and gastric autoimmune disease are not due to cross-reactive autoantibodies. *J. Clin. Lab. Immunol.* 14, 141–145.

Kohn, L. D., Valente, W. A., Alvarez, F. V., Rotella, C. M., Marconi, C., Toccafondi, R. S. & Grollman, E. F. (1985) New procedures for detecting Graves' immunoglobulins. In: *Autoimmunity and the Thyroid*, eds. Walfish, G., Wall, J. R. & Volpe, R., pp. 217–247. Academic Press, New York.

Konishi, J., Iida, Y., Kasagi, K., Endo, K., Misaki, T. & Torizuka, K. (1984) Thyrotropin-receptor blocking antibodies. In: *Endocrinology*, eds. Labrie, R. & Proulx, L., pp. 559–562. Excerpta Medica, Amsterdam.

Lamb, J. R. & Feldmann, M. (1983) Essential requirement for major histocompatibility complex recognition in T cell tolerance induction. *Nature* 308, 72–74.

Lendrum, R., Walker, S. G. & Gamble, D. R. (1975) Islet cell antibodies in juvenile diabetes mellitus of recent onset. *Lancet* 1, 880–882.

Lernmark, A., Freedman, Z. R., Hofman, C., Rubenstein, A., Steiner, D. F., Jackson, R. L., Winter, R. J. & Traisman, H. S. (1978) Islet cell antibodies in juvenile diabetes mellitus. *N. Engl. J. Med.* 299, 375–380.

Lindhal, G., Hedfors, E., Klareskog, L. & Forsum, U. (1985) Epithelial HLA-DR expression and T lymphocyte subsets in salivary glands in Sjögren syndrome. *Clin. Exp. Immunol.* 61, 475–482.

Lindstrom, J., Seybold, M. E., Lennon, V. A., Whittingham, S. & Duane, D. D. (1976) Antibody to acetylcholine receptor in Myasthenia Gravis. Prevalence, clinical correlates and diagnostic value. *Neurology (Minneap.)* 26, 1054–1059.

Lloyd, R. V., Johnson, T. L., Blaivas, M., Sisson, J. C. & Wilson, B. S. (1985) Detection of HLA-DR antigen in paraffin-embedded thyroid epithelial cells with a monoclonal antibody. *Am. J. Pathol.* 120, 106–111.

Londei, M., Bottazzo, G. F. & Feldmann, M. (1985) Human T cell clones from autoimmune thyroid glands: specific recognition of autologous thyroid cells. *Science* 228, 85–89.

Londei, M., Bottazzo, G. F. & Feldmann, M. (1986) Analysis of intrathyroid T cells from a Hashimoto’s thyroiditis gland. In: *Proceedings of the 9th International Thyroid Congress*, Sao Paulo, Sept. 1985. Plenum Press, New York (in press).

Londei, M., Lamb, J. R., Bottazzo, G. F. & Feldmann, M. (1984) Epithelial cells expressing aberrant MHC Class II determinants can present antigen to cloned human T cells. *Nature* 312, 639–641.

Loveridge, N., Bitesinsky, L., Chayen, J., Hausamer, T. U., Fischer, J. M., Taylor, K. B., Gardner, J. D., Bottazzo, G. F. & Doniach, D. (1980) Inhibition of parietal cell function by human gamma-globulin containing gastric parietal cell antibodies. *Clin. Exp. Immunol.* 41, 264–270.
Lucas-Martin, A., Foz, M., Todd, I., Bottazzo, G. F. & Pujol-Borrell, R. Inappropriate HLA Class II expression in a wide variety of thyroid diseases. (submitted for publication).

Maron, R., Elias, D., de Jongh, B. M., Bruining, G. J., Van Rood, J. J., Schechter, Y. & Cohen, I. R. (1983) Autoantibodies to the insulin receptor in juvenile onset insulin dependent diabetes. Nature 303, 817–818.

Masala, C., Smurra, G., Di Prima, M. A., Amendolea, M. A., Celestino, D. & Salsano, F. (1980) Gastric parietal cell antibodies: Demonstration by immunofluorescence of their reactivity with the surface of the gastric parietal cells. Clin. Exp. Immunol. 41, 271–280.

Massa, P. T., Dorries, R. & ter Meulen, V. (1986) Viral particles induce Ia antigen expression on astrocytes Nature 320, 543–546.

Matsuura, N., Yamada, Y., Nohara, Y., Konishi, J., Kasagi, K., Endo, K., Kojima, H. & Wataya, K. (1980) Familial neonatal transient hypothyroidism due to maternal TSH-binding inhibitor immunoglobulins. N. Engl. J. Med. 303, 738–741.

Messenger, A. G., Bleehen, S. S., Slater, D. N. & Rooney, N. (1984) Expression of HLA-DR in hair follicles in alopecia areata. Lancet ii, 287.

Mirakian, R., Richardson, A., Bottazzo, G. F. & Doniach, D. (1981) Humoral autoimmunity to gut-related endocrine cells. Clin. Immunol. Newslett. 2, 161–167.

Mirakian, R., Richardson, A., Mill, J., Unsworth, J., Walker-Smith, J., Savage, M. & Bottazzo, G. F. (1986) Idiopathic protracted diarrhoea of infancy: an autoimmune variant. Br. Med. J. (in press).

Naparstek, Y., Cohen, I. R., Fuks, Z. & Vlodavsky, I. (1984) Activated T lymphocytes produce a matrix-degrading heparan sulphate endoglycosidase. Nature 310, 241–244.

Naughton, G. K., Fisenger, M. & Bustry, N. J. C. (1983) Antibodies to normal human melanocytes in vitiligo. J. Exp. Med. 158, 246–251.

Nayak, R. C., Omar, M. A. K., Rabizadeh, A., Srikanta, S. & Eisenbarth, G. S. (1985) ‘Cytoplasmic’ islet cell antibodies: evidence that the target antigen is a sialoglycoprotein. Diabetes 34, 617–619.

Neufeld, M. & Blizzard, R. M. (1980) Polyglandular autoimmune disease. In: Autoimmune aspects of endocrine disorders, eds. Pinchera, A., Doniach, D., Fenzi, G. F. & Baschieri, L., pp. 357–365. Academic Press, New York.

Nitsch, L. & Wollman, S. H. (1980) Ultrastructure of intermediate stages in polarity reversal of thyroid epithelium in follicles in suspension culture. J. Cell. Biol. 86, 875–882.

Okabe, N., Inoue, K. & Mori, R. (1983) Effects of antithyroid drugs on lymphocyte proliferative responses to lectins: relationship between insulin autoimmune syndrome and methimazole. J. Clin. Lab. Immunol. 11, 167–171.

Palmer, J. P., Asplin, C. M., Clemons, P., Lyen, K., Tatpati, O., Raghu, P. K. & Paquette, T. L. (1983) Insulin antibodies in insulin-dependent diabetics before insulin treatment. Science 222, 1337–1339.

Pinchera, A., Fenzi, G. F., Mariotti, S., Vitti, P., Macchia, E., Chiovato, L., Marcocci, C. & Bartalena, L. (1984) Membrane antigens in thyroid autoimmune diseases. In: Endocrinology, eds. Labrie, F. & Proulx, L., pp. 469–472. Excerpta Medica, Amsterdam.

Plotz, P. H. (1983) Autoantibodies are anti-idiotypic antibodies to antiviral antibodies. Lancet ii, 824–826.

Portmann, L., Hamada, N., Heinrich, G. & Degroot, L. J. (1985) Antithyroid peroxidase antibody in patients with autoimmune thyroid disease: possible identity with antimicrosomal antibody. J. Clin. Endocrinol. Metab. 61, 1001–1003.

Posillico, J. T., Wortsman, J., Srikanta, S., Eisenbarth, G. S. & Brown, E. M. (1986) Parathyroid cell surface autoantibodies inhibit parathyroid hormone secretion from human parathyroid cells. Proceedings of the Americal Society for Clinical Investigation (1986) (Abstract).
Pouplard, A., Bottazzo, G. F., Doniach, D. & Roitt, I. M. (1976) Binding of human immunoglobulins to pituitary ACTH cells. *Nature* **261**, 142-144.

Pozzilli, P. & Di Mario, U. (1984) Lymphocyte subpopulations and circulating immune complexes: their relationship in the pathogenesis of Type I (insulin-dependent) diabetes. In: *Immunology in Diabetes*, eds. Andreani, D., Di Mario, U., Federlin, K. F. & Heding, L. G., pp. 133–142. Kimpton Medical Publications, London.

Prabhakar, B. S., Saegusa, S., Onedera, T. & Notkins, A. L. (1984) Lymphocytes capable of making monoclonal antibodies that react with multiple organs are a common feature of normal B cell repertoire. *J. Immunol.* **133**, 2815–2821.

Pujol-Borrell, R., Hanafusa, T., Chiovato, L. & Bottazzo, G. F. (1983) Lectin-induced expression of DR antigen on human cultured follicular thyroid cells. *Nature* **303**, 71–73.

Pujol-Borrell, R., Khoury, E. L. & Bottazzo, G. F. (1982) Islet cell surface antibodies in Type I (insulin-dependent) diabetes mellitus: use of human fetal pancreas cultures as substrate. *Diabetologia* **22**, 89–95.

Pujol-Borrell, R., Todd, I., Adolf, G. R., Feldmann, M. & Bottazzo, G. F. (1986a) In vivo and in vitro demonstration of HLA Class II products on human islet beta cells. In: *Proceedings of Symposium on Immunology of Diabetes*, Edmonton, Canada, June 1986, eds. Molnan, G. D. & Jaworski, M. A. Elsevier Science Publishers, Amsterdam (in press).

Pujol-Borrell, R., Todd, I., Becker, F., Foulis, A. & Bottazzo, G. F. (1986b) Surface antigens of the human beta cells: detection of insulin and study of MHC modulation. In: *Diabetes 1985*, eds. Serrano-Rios, M. & Lefebvre, P. J., pp. 505–508. Excerpta Medica, Amsterdam.

Pujol-Borrell, R., Todd, I., Doshi, M., Gray, D., Feldmann, M. & Bottazzo, G. F. (1986c) Differential expression and regulation of MHC products in the endocrine and exocrine cells of the human pancreas. *Clin. Exp. Immunol.* **65**, 128–139.

Raines, K. R., Baker, Jr., J. R., Lukes, Y. G., Wartofsky, L. & Burman, K. D. (1985) Antithyrotropin Antibodies in the Sera of Graves' Disease Patients. *J. Clin. Endocrinol. Metab.* **61**, 217–222.

Roitt, I. M. (1984) Prevailing theories in autoimmune disorders. *Triangle* **23**, 67–76.

Roitt, I. M., Doniach, D., Campbell, P. N. & Hudson, R. V. (1956) Autoantibodies in Hashimoto’s disease (lymphoadenoid goitre). *Lancet* ii, 820–822.

Roitt, I. M., Ling, N. R., Doniach, D. & Couchman, K. G. (1964) The cytoplasmic autoantigen of the human thyroid. I. Immunological and biochemical characteristics. *Immunology* **7**, 375–393.

Roitt, I. M., Pujol-Borrell, R., Hanafusa, T., Delves, P. J., Bottazzo, G. F. & Kohn, L. D. (1984) Asialoagalactothyroglobulin binds to the surface of human thyroid cells at a site distinct from the ‘microsomal’ autoantigen. *Clin. Exp. Immunol.* **56**, 129–134.

Salamero, J. & Charrere, J. (1985) Syngeneic sensitization of mouse lymphocytes on monolayers of thyroid epithelial cells (TEC) VII. Generation of thyroid specific cytotoxic effector cells. *Cell. Immunol.* **91**, 111–118.

Satoh, J., Essani, K., McClintock, P. R. & Notkins, A. L. (1984) Human multiple organ-reactive monoclonal autoantibody recognises growth hormone and a 35,000-molecular weight protein. *J. Clin. Invest.* **74**, 1526–1531.

Satoh, J., Prabhakar, B. S., Haspel, M. V., Ginsberg-Fellner, F. & Notkins, A. (1983) Human monoclonal autoantibodies that react with multiple endocrine organs. *N. Engl. J. Med.* **300**, 217–220.

Schatz, H. & Doniach, D. (eds) (1983) *Autoimmunity in Thyroid Disorders*. Georg Thieme, Stuttgart.

Scherbaum, W. A., Blaschek, M., Berg, P., Doniach, D. & Bottazzo, G. F. (1986a) Spectrum
and profiles of non-organ-specific autoantibodies in autoimmune diseases. In: Immunocytochemistry. Modern methods and applications. 2nd Ed., eds. Polak, S. M. & Van Norden, S. pp. 477–491. J. Wright, Bristol.

Scherbaum, W. A. & Bottazzo, G. F. (1983) Autoantibodies to vasopressin cells in idiopathic diabetes insipidus: evidence for an autoimmune variant. Lancet i, 889–901.

Scherbaum, W. A., Mirakian, R., Pujol-Borrell, R., Dean, B. M. & Bottazzo, G. F. (1986b) Immunocytochemistry in the study and diagnosis of organ-specific autoimmune diseases. In: Immunocytochemistry. Modern methods and applications 2nd Ed., eds. Polak, J. M. & Van Noorden, S. pp. 456–476. J. Wright, Bristol.

Selby, W. S., Janossy, G., Mason, D. Y. & Jewell, D. P. (1983) Expression of HLA-DR antigens by colonic epithelium in inflammatory bowel disease. Clin. Exp. Immunol. 53, 614–618.

Shechter, Y., Elias, D., Maron, R. & Cohen, I. R. (1984) Mouse antibodies to the insulin receptor developing spontaneously as anti-idiotypes. I. Characterization of the antibodies. J. Biol. Chem. 259, 6411–6415.

Shechter, Y., Maron, R., Elias, D. & Cohen, I. R. (1982) Autoantibodies to insulin receptor spontaneously develop as anti-idiotypes in mice immunized with insulin. Science 216, 542–544.

Shoelson, S. E., Marshall, S., Horikoshi, H., Kolterman, O. G., Rubenstein, A. H. & Olefsky, J. M. (1986) Antiinsulin receptor antibodies in an insulin-dependent diabetic may arise as autoantibodies. J. Clin. Endocrinol. Metab. 63, 56–61.

Sibley, D. K., Sutherland, D. F. R., Goetz, F. C. & Michael, A. F. (1985) Recurrent diabetes mellitus in the pancreas iso and allograft: a light and electron microscopic and immunohistochemical analysis. Lab. Invest. 53, 132–145.

Smyth, P. P. A., McMullan, N. M., Grubeck-Loebenstein, B. & O'Donovan, D. (1986) Thyroid growth-stimulating immunoglobulins in goitreous disease. Acta Endocrinol. (in press).

Srikanta, S., Ricker, A. T., McCulloch, D. K., Soeldner, J. S., Eisenbarth, G. S., & Palmer, J. P. (1986) Autoimmunity to insulin, beta cell dysfunction and development of insulin-dependent diabetes mellitus. Diabetes 35, 139–147.

Stiller, C. R., Dupre, J., Gent, M., Venner, M. R., Keown, P. A., Laupaesis, A., Martell, R., Rodger, N. W., Groffenied, B. V. & Wolfe, B. J. J. (1984) Effect of cyclosporine immunosuppression in insulin-dependent diabetes mellitus of recent onset. Science 223, 1363–1367.

Sutherland, D. E. R. (1986) Clinical and experimental islet and pancreas transplantation: overview of selected topic. In: Proceedings of Symposium on Immunology of Diabetes, Edmonton, Canada, June 1986, eds. Molnan G. D. & Jaworski, M. A. Elsevier Science Publisher, Amsterdam (in press).

Sutherland, D. E. R., Sibley, R. & Chinn, P. (1984) Twin to twin pancreas transplantations: Reversal and re-enactment of the pathogenesis of type I diabetes. Clin Res 32, 561A.

Swana, G. T., Swana, M. R., Bottazzo, G. F. & Doniach, D. (1977) A human mitochondrial antibody (AHMA). Its importance in the identification of organ-specific reactions. Clin. Exp. Immunol. 28, 517–525.

Taylor, I. L., Calam, J., Rotter, J. I., Vaillant, C., Samloff, I. M., Cook, A., Simkin, E. & Dockray, G. J. (1981) Family studies of hypergastrinemic, hyper-pepsinogenemic I duodenal ulcer. Ann. Intern. Med. 95, 421–425.

Teding Van Berkhout, F., Croughs, R. J. M., Kater, L. Schuurman, H. J., Gmelig Meyling, F. J. H., Kooyman, C. D., Van Der Gaag, R. D., Jolink, D. & Drexhage, H. (1986) Familial Cushing's syndrome due to nodular adrenocortical displasia, a putative receptor-antibody disease? Clin. Endocrinol. 24, 299–310.

Todd, I., Abdul-Karim, B. A. S., Pujol-Borrell, R., Feldmann, M. & Bottazzo, G. F. (1986a)
Dissection and characterization of the spontaneous and induced expression of HLA-D/DR by thyroid epithelium. In: Proceedings of 9th International Thyroid Congress, Sao Paulo, Sept. 1985. Plenum Press, New York (in press).

Todd, I. & Bottazzo, G. F. (1985a) Laboratory investigation of autoimmune endocrine diseases. Clin. Immunol. Allergy 5, 613–638.

Todd, I., Lucas Martin, A., Abdul-Karim, B. A. S., Hammond, L. J. & Bottazzo, G. F. (1986b) HLA-D subregion expression by thyrocytes is associated with the occurrence of circulating thyroid autoantibodies. Ann. d'Endocrinol. 47, 20 (Abstract).

Todd, I., McNally, J. M., Hammond, L. J. & Pujol-Borrell, R. (1986c) TSH enhances expression by thyrocytes of interferon-gamma induced HLA-D/DR. In: Proceedings of the 9th International Thyroid Congress, Sao Paulo, Sept. 1985. Plenum Press, New York (in press).

Todd, I., Pujol-Borrell, R., Bottazzo, G. F., Londci, M. & Feldmann, M. (1986d) Autoantigen presentation by target cells: its possible role in determining autoantibody specificity. Ann. Inst. Pasteur/Immunol. 137 D, 168–173.

Topliss, D., How, T., Lewis, M., Row, V. & Volpe, R. (1983) Evidence for cell-mediated immunity and specific suppressor T-lymphocyte dysfunction in Graves' disease and diabetes mellitus. J. Clin. Endocrinol. Metab. 57, 700–705.

Valenta, L. J., Bull, R. W., Hackel, E. & Bottazzo, G. F. (1982) Correlation of the HLA-A1 B8 haplotypes with circulating autoantibodies in a family with increased incidence of autoimmune disease. Acta Endocrinol. (Copenhagen) 100, 143–149.

Vandelli, C., Bottazzo, G. F., Doniach, D. & Franceschi, G. (1979) Autoantibodies to gastrin-producing cells in antral (Type B) chronic gastritis. N. Engl. J. Med. 300, 1406–1410.

Van der Gaag, R. D., Drexhage, H. A. & Dussault, J. H. (1985a) Role of maternal immunoglobulin blocking TSH-induced thyroid growth in sporadic forms of congenital hypothyroidism. Lancet i, 246–250.

Van der Gaag, H. A., Drexhage, H. A., Wiersinga, W. M., Brown, R. S., Docter, R., Bottazzo, G. F. & Doniach, D. (1985b) Further studies on thyroid growth-stimulating immunoglobulins in euthyroid nonendemic goiter. J. Clin. Endocrinol. Metab. 60, 972–979.

Vento, S., Hegarty, J. E., Bottazzo, G. F., Macchia, E., Williams, R. & Eddleston, A. L. W. F. (1984) Antigen specific suppressor cell function in autoimmune chronic active hepatitis. Lancet i, 1200–1204.

Walker, E. B., Maino, V., Sanchez-Lanier, M., Warner, N. & Stewart, C. (1984) Murine gamma interferon activates the release of a macrophage-derived Ia inducing factor that transfers Ia inductive capacity. J. Exp. Med. 159, 1532–1547.

Westmark, K., Karlsson, F. A. & Westmark, B. (1983) Epidermal growth factor modulates thyroid growth and function in culture. Endocrinol. 112, 1680–1686.

Wilkin, T., Armitage, M., Casey, C., Pyke, D. A., Hoskins, P. J., Rodier, M., Diaz, J. L. & Leslie, R. D. G. (1985) Value of insulin autoantibodies as serum markers for insulin-dependent diabetes mellitus. Lancet i, 480–482.

Wilkin, T. J. & Nicholson, S. (1984) Antibodies against human insulin. Br. Med. J. 288, 349–352.

Wulfraat, N. M. & Drexhage, H. A. (1986) Immunoglobulins stimulating and blocking adrenal growth. In: Proceedings of First International Conference on Hormones and Immunity, Toronto, July 1986 (Abstract).
This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.