Immunology 1980 **41** 1

Review

Recent studies on the regulation of IgE antibody synthesis in experimental animals and man

D. H. KATZ *Department of Cellular and Developmental Immunology, Scripps Clinic and Research Foundation, La Jolla, CA, U.S.A.*

Accepted for publication 20 May 1980

CONTENTS

Introduction

The IgE antibody response system is of obvious interest to both basic researchers and clinical immunologists and allergists because of its role in the pathogenesis of IgE-mediated allergic diseases. Beyond this clinical significance of understanding the system is the fact that it appears to be both exemplary and relatively unique in certain of the regulatory mechanisms controlling it, as will be pointed out in this review. Accordingly, it has been the impression of some of us working with the system that delineation of the control mechanisms

Correspondence: Dr D. H. Katz, Department of Cellular and Developmental Immunology, Scripps Clinic and Research Foundation, La Jolla, CA 92037, U.S.A.

0019-2805/80/0900-0001$02.00

regulating IgE synthesis may provide invaluable clues and insights into the nature of the general regulatory events governing the immune system at the genetic, cellular and molecular levels. At the same time, such new insights could ultimately provide us with new and more effective immunotherapeutic tools for the management of IgE-mediated allergic diseases of humans. This review will touch upon work performed in the author's laboratory and those of other investigators concerned with delineating the mechanisms controlling the IgE antibody system, with particular emphasis on the more recent studies of this type, in both experimental animals and man. Several comprehensive reviews have previously been published to which interested readers should refer for greater detail on the earlier studies in this field (Ishizaka, 1976; Katz, 1977 a, b, c; Möller, 1978; Tada, 1975).

Features of the IgE antibody system

At the outset, it is pertinent to point out certain aspects of IgE antibody synthesis that are somewhat unique. First, IgE antibodies are present in only minute quantities in the serum, as compared to other immunoglobulin (Ig) classes; this is true even in atopic individuals, although their circulating levels are higher than in non-atopic individuals. In view of the short half-life of circulating IgE, it seems clear therefore, that IgE antibodies are continuously being formed in atopic patients and that the production is considerably greater than that expected from the serum concentration (reviewed by Bloch, 1967, 1973; Ishizaka, 1975). Second, IgE is synthesized locally in respiratory and gastrointestinal mucosa, as well as in regional lymph nodes under normal circumstances; this suggests an important role for these antibodies in protecting the host against agents, most notably parasites, likely to invade at these sites (see below). The predominant function of IgE is to fix to tissue mast cells and basophils, which sensitizes such cells resulting in the release of vasoactive amines upon exposure to antigen.

Third, the nature of the antigens capable of *readily* stimulating IgE antibody production are in some ways distinctive, though not entirely, from other conventional antigens capable of stimulating responses of other Ig classes. For example, grass pollens, certain fungi, allergenic components of food substances, and other products are all highly complex and heterogeneous substances. Parasitic nematodes and trematodes usually induce high titres of IgE antibodies, whereas serum proteins, bacteria and viruses do not, despite the fact that they are highly immunogenic for IgM and IgG responses. Simple haptens, such as dinitrophenyl (DNP) or benzylpenicilloyl (BPO) are capable of inducing high IgE antibody titres when administered on an appropriate carrier. Interestingly, haptenic conjugates of T-independent antigens usually do *not* stimulate IgE antibody responses (Tada, 1975), an observation related perhaps to the failure of bacteria or viruses to do so. Finally, studies in experimental animals indicate that particular attention must be given to the dose of antigen and type of adjuvant employed in order to obtain IgE antibody production. Indeed, the general rule appears to be that high doses of antigen and certain strong adjuvants are particularly unfavourable to the generation of IgE responses; on the other hand, certain adjuvants capable of eliciting IgE synthesis (with an appropriate dose of antigen) are also inherently strong.

In general terms, IgE antibody synthesis displays different characteristics depending upon the animal species, the antigen, and the adjuvant employed. Hence, it has been known since the early studies of Mota (1964) and Binaghi & Benacerraf (1964) that rats immunized with protein antigens, together with *Bordetella pertussis* as an adjuvant develop primary IgE antibody responses that are transient in nature; moreover, such animals fail to develop secondary IgE antibody responses upon subsequent challenge, although secondary responses occur in the IgG antibody class to such antigens. The latter phenomenon of transient IgE antibody production is quite the reverse of what occurs in the rat following infestation with the nematode *Nippostrongylus brasiliensis* in which the IgE antibody titre persists at high levels for many months, even after total expulsion of the worms and in the absence of reinfection (Ogilvie, 1967). Moreover, reinfection with the same parasite results in a sharp secondary IgE antibody response (Ogilvie & Jones, 1971). In contrast to these effects of active infestation with live parasites, the deliberate immunization of most strains of rats with extracts derived from parasites, although inducing IgE antibody synthesis, fails to give other than a transitory response in most strains of rats and will not induce secondary responses (Ogilvie, 1967). Although most rat strains display the characteristic transitory IgE antibody synthesis pattern, thus making them appear to be analogous to non-atopic humans, several years

ago, Jarrett & Stewart (1972) discovered that the Hooded Lister rat strain develops unusually high levels of IgE antibody following immunization with small doses of conventional antigen; moreover, these rats are capable of producing marked secondary responses as well, thus making this strain of rat relatively analogous to the situation in atopic human individuals in terms of regulatory control mechanisms governing IgE synthesis.

In the mouse, the capacity to develop high titres of persistent IgE antibody and secondary IgE responses is genetically controlled and linked to the H-2 major histocompatibility complex (MHC). This was first suggested by studies of Revoltella & Ovary (1969) and then demonstrated clearly by Levine & Vaz (1970). Moreover, these latter investigators made the important observation that persistent high titres of IgE antibody production in the mouse could be stimulated by extremely low doses of antigen (1 μg or less) administered in a form precipitated on aluminium hydroxide gel or alum (Levine & Vaz, 1970; Vaz, Vaz & Levine, 1971). Responses obtained in this manner were additionally significant in that the mice so primed could be restimulated to develop secondary responses. Whereas low doses of antigen were capable of stimulating such responses, high doses of the same antigen elicited little or no IgE antibody production, although good levels of IgG antibody were induced (Levine & Vaz, 1970).

In addition to the MHC-linked genetic control of IgE low versus high responder phenotype, studies in our laboratory defined the existence of an H-2-linked immune response (Ir) gene controlling responses to extracts of ragweed (RE) antigen and the DNP derivative of RE (Dorf, Newburger, Hamaoka, Katz & Benacerraf, 1974). The Ir-RE gene was mapped to the I region of H-2 by studying responses of appropriate H-2 recombinant inbred mouse strains. It was demonstrated that the Ir-RE gene affects the IgG and IgE antibody responses in parallel implying that T-cell function at the level of this gene is the same for these two antibody classes. In view of the likely existence of distinct T cells governing responses of IgG and IgE B lymphocytes, respectively, as first proposed by Kishimoto & Ishizaka (1973b), this means that the Ir-RE gene exerts specificity control over responses developed by each of these T-cell subpopulations. In man, an analogous Ir gene controlling responses to ragweed pollen extracts and linked to the HLA complex has been postulated to exist by Levine, Stember & Fotino (1972) and by Marsh *et al.* (Marsh, Bias, Hsu & Goodfriend, 1973; March & Bias, 1977; Marsh, Goodfriend & Bias, 1977; Marsh, Chase, Friedhoff, Meyers & Bias, 1979).

Regulation of IgE antibody synthesis by T lymphocytes

The first direct demonstration that T lymphocytes were required for development of IgE antibody responses was obtained by Okumura & Tada (1971a) who demonstrated that neonatally thymectomized rats were unable to produce IgE antibody responses upon subsequent immunization with a DNP-carrier conjugate. This defect could be reconstituted by supplementation of such neonatally thymectomized rats with normal or with carrier-primed thymocytes (Taniguchi & Tada, 1974). The first direct demonstration of T and B cell co-operation in the development of IgE antibody production in mice came from the studies of Hamaoka, Katz, Block & Benacerraf (1973b). Utilizing an adoptive cell transfer system (Hamaoka, Katz & Benacerraf, 1973a), we were able to demonstrate co-operative interactions between carrier-specific and hapten-specific mouse spleen cell populations in the production of IgE, as well as IgG antibodies, and, moreover, that the carrier-specific helper cells functioning in the system are T lymphocytes bearing the Thy-1 marker on their cell membranes.

While the aforementioned studies, as well as those of other investigators (Ishizaka & Okudaira, 1973; Okudaira & Ishizaka, 1973), clearly documented the requirement for T lymphocyte participation in the *development* of IgE antibody responses, a more intriguing question from a clinical viewpoint pertained to the mechanism(s) that served to limit IgE responses in most rats to a transient pattern and to prevent or minimize the development of significant IgE antibody responses in inbred mice of the low IgE responder phenotype. The seminal work in this regard was performed by Tada and his colleagues who utilized the rat model to demonstrate that certain perturbations such as moderate doses of whole body irradiation (Tada, Taniguchi & Okumura, 1971), adult thymectomy and/or splenectomy (Okumura & Tada, 1971a) or administration of various immunosuppressive drugs (Taniguchi & Tada, 1971) converted rats from the characteristic transitory, low level IgE antibody production to patterns of sustained IgE antibody synthesis of substantial magni-

tude. The finding that such enhanced IgE responses in rats could be terminated by passive transfer of syngeneic thymocytes or spleen cells (Okumura & Tada, 1971b) provided direct evidence that the limited, transitory IgE response patterns in unperturbed rats reflected the dominance of a suppressor T cell regulatory control mechanism that normally served to minimize antibody production in this Ig class. The effectiveness of whole body irradiation, immunosuppressive drug therapy, etc. to convert the normal IgE response pattern to one of persistent high magnitude reflects the elimination (or diminution) of these suppressive T lymphocyte mechanisms governing IgE antibody synthesis.

The realization that the IgE response phenotype of a given experimental animal could be wilfully manipulated in instances such as those observed in the rat system described above, represented an important advance in both our understanding of regulation of IgE synthesis and in the subsequent development of certain concepts as will be discussed below. Subsequent to the observations in rats, studies in the author's laboratory (Chiorazzi, Fox & Katz, 1976; Chiorazzi, Fox & Katz, 1977a; Chiorazzi, Tung, Eshhar & Katz, 1977b; Chiorazzi, Tung & Katz, 1977c) and in that of Ovary and colleagues (Watanabe, Kojima & Ovary, 1976; Watanabe, Kojima, Shen & Ovary, 1977) demonstrated that various manipulations selectively increase the magnitude of IgE antibody production in mice. These manipulations include low dose whole-body irradiation, moderate doses of immunosuppressive drugs such as cyclophosphamide, adult thymectomy, and administration of appropriate doses of antilymphocyte serum. The collective implications of all of these studies has been that regulation of IgE antibody synthesis is dominated by a suppressive or 'damping' mechanism which normally serves to limit the magnitude of IgE antibody production following antigen sensitization. Under appropriate circumstances, however, certain perturbations can effectively disturb this damping mechanism resulting, in turn, in heightened production of IgE antibodies. We shall return to this issue later in this review.

Effects of parasite infestation on the IgE antibody system

It has been recognized for many years now that infestation by helminthic parasites results in production of high levels of IgE antibodies both in experimental animals and man (Hogarth-Scott, Johansson & Bennich, 1969; Jarrett & Bazin, 1974). Since helminth-specific IgE comprises only a portion of the increased quantities of IgE antibodies that develop in such circumstances, it soon became clear that helminthic infestation exerts a dramatic adjuvant effect facilitating IgE antibody production. This was first recorded in experiments by Orr & Blair (1969) and subsequently by other investigators as well (Orr, Riley & Doe, 1972; Jarrett & Stewart, 1972; Bloch, Ohman, Waltin & Cygan, 1973; Jarrett & Ferguson, 1974; Jarrett & Bazin, 1974, 1977; Carson, Metzer & Bloch, 1975; Kojima & Ovary, 1975a,b; Kojima, Kamijo & Ovary, 1980). Curiously, this potentiating effect of parasite infection is selective for antibody production of the IgE class (Jarrett, Henderson, Riley & White, 1972; Meacock & Marsden, 1976), and has been shown to be T-cell dependent (Jarrett & Ferguson, 1974; Jarrett, 1978).

Although definitive evidence is lacking, it seems clear that parasite-specific IgE antibodies play a significant role as a protective mechanism of the infected host against the parasite. Thus, some years ago it was shown that a positive correlation existed between the ability to produce IgE antibodies and the extent of effective immunity against *Schistosoma mansoni* (Sadun & Gore, 1970). This interpretation has gained additional support from more recent experimental studies in rat models of experimental schistosomiasis (Rousseaux-Prevost, Capron, Bazin & Capron, 1978) and infection with *Taenia taeniaeformis* (Musoke, Williams & Leid, 1978). The precise mechanism by which such parasite-specific IgE antibodies protect the host is still unknown, although at least part of the explanation may relate to the demonstration that specific IgE antibodies foster immune adherence of normal rat macrophages to *S. mansoni* schistosomules and that the adhered macrophages are cytotoxic for the organisms (Capron, Dessaint, Capron & Bazin, 1975; Capron, Dessaint, Joseph, Rousseaux, Capron & Bazin, 1977). These same investigators have recently shown that IgE antibody molecules bind to specific Fc receptors for IgE on the macrophage surface and upon being cross-linked (by specific anti-IgE antibodies and presumably by specific antigens) generate activating signals to macrophages resulting in release of lysosomal enzymes (Dessaint, Capron, Joseph & Bazin, 1979a; Dessaint, Torpier, Capron, Bazin & Capron, 1979b). In addition to this type of mech-

anism, it is also possible that IgE-mediated release of inflammatory mediators may participate directly and/or indirectly in host protection as suggested recently by Musoke *et al.* (1978).

If parasite-specific IgE antibody molecules are, indeed, significant participants in host protective immunity against parasitic infections, then the prevelant effect of parasites on the IgE antibody system is understandable, at least with regard to specific IgE antibody formation. However, the reason why such infections exert such a powerful polyclonal stimulation of IgE antibody synthesis remains a curious question. It should be emphasized that the hyperproduction of IgE associated with parasitic diseases appears to result from the effects of parasites (and their products) in *stimulating* the IgE antibody-producing apparatus; this contrasts with the hyperproduction of IgE in association with certain clinical immunodeficiency diseases in which the explanation for high levels of IgE synthesis seem to reflect the diminution or loss of a normal controlling suppressor T cell mechanism (see below).

The mechanism by which parasites exert potent stimulatory effects on the IgE antibody system has been under investigation in several laboratories. Kojima & Ovary (1975a,b) provided some of the early direct insight on this question in studies in mice infected with *N. brasiliensis*. In their studies, it could be shown that infection with the living organisms resulted in the induction of helper T cells specific for antigenic extracts of *N. brasiliensis* (Nb) which were capable of engaging in co-operative responses with DNP-specific B lymphocytes in typical adoptive transfer responses to DNP–Nb. More importantly, they were able to show that stimulation of such carrier–specific T cells by the specific Nb antigen activated such cells to participate non-specifically in the potentiation of IgE responses to an unrelated antigen. Recently reported studies of Kojima *et al.* (1980) extend these observations by demonstrating the capacity of spleen and lymph node cells from *N. brasiliensis*-infected mice to respond to *in vitro* antigen stimulation by Nb by releasing into culture supernatants a soluble mediator effective in selectively enhancing IgE production when administered to intact mice. Moreover, Kojima *et al.* (1980) obtained evidence that this IgE-selective enhancing factor exerted its effects on precursor helper T cells which in turn provide co-operative inductive signals for IgE B cells.

A more extensive analysis of the biology of lymphocytes from *N. brasiliensis*-infected rodents has been conducted by Ishizaka and colleagues during the last few years (reviewed in Ishizaka & Ishizaka, 1978). The nature of their results will be described in detail below.

The high levels of IgE antibody synthesis associated with helminthic infestation does not result in an unusually high frequency of allergic disorders in humans afflicted with such parasitic diseases. Although initial observations suggested that such a correlation might exist (Tullis, 1970; Chacko, 1970), subsequent studies have failed to support such a conclusion (Van Dellen & Thompson, 1971; Cheah & Khan, 1972; Alcasid, Chiaramonk, Kim, Zohn, Bongiorno & Mullin, 1973; Turner, Rosman & O'Mahoney, 1974; Turner, Baldo & Anderson, 1975). Indeed, if anything, there appears to be a paradoxically low incidence of the more common allergic syndromes, such as asthma and hay fever, in tropical populations which are endemically infected with parasites (Anderson, 1974; Godfrey, 1975). This inverse relationship between parasitism and clinical allergy prompted speculations that perhaps parasitic infestation exerted anti-allergic effects either by creating a polyclonal form of antigenic competition, thus inhibiting the induction phase of IgE antibody synthesis, or perhaps by the fact that since high levels of IgE antibodies existed in such individuals there was a state of 'saturation' of mast cell Fc receptors for IgE thus blunting allergic manifestations by competition at the effector phase of such responses. However, recent studies in man by Turner, Quinn & Anderson (1978) and in experimental animals by Jarrett, Mackenzie & Bennich (1980) clearly show that neither antigenic competition nor mast cell Fc receptor saturation operates to inhibit either the induction or effector phases of the IgE antibody system in individuals infected with parasites. This means that if it is true that an inverse relationship exists between the existence of parasitism and manifestations of clinical allergic diseases, then some other mechanism(s) must be responsible for such a relationship.

The experimental rat model of *N. brasiliensis* infection has been useful in another area concerning the biological role of IgE antibodies. In view of the similarity in localization of both IgA and IgE antibodies and particularly their presence in certain mucosal secretions, studies by Mayrhofer, Bazin & Gowans (1976) were designed to determine whether IgE might also be a secretory immunoglobulin with a

physiology analogous to that of IgA. A careful examination of the tissue and cellular localization of IgE in rats infected with *N. brasiliensis* demonstrated that the major site of IgE synthesis in such animals was the mesenteric lymph node in which large numbers of IgE-secreting plasma cells could be found. In contrast, gut-associated lymphoid tissues, intrapulmonary bronchial lymphoid tissue and spleen do not contain significant numbers of IgE-secreting plasma cells. On the other hand, the lamina propria of the small intestine and the colonic and pulmonary mucosal surfaces in infected rats contained substantial numbers of mast cells bearing IgE molecules on their surface membranes. Surprisingly, the mast cells in these mucosal tissues also contained intracellular IgE, differing in this respect from connective tissue mast cells. These investigators suggested that the presence of IgE antibodies in exocrine secretions may very well be explained by the existence of intracellular IgE in mast cells which, upon degranulation, would release such IgE molecules into the surrounding fluids.

Specific Fc receptors for IgE (FcR_ε) on lymphocytes

Receptors for determinants present on the Fc portions of Ig molecules have been known for some time to exist on the cell membranes of macrophages and lymphocytes as well as neutrophils (reviewed in Katz, 1977b). During recent years, Fc receptor (FcR) heterogeneity on T lymphocytes both in experimental animals and man has received increasing attention. Thus it was first shown with human T lymphocytes that segregation of subpopulations with FeR specific for IgM (FcR_μ) or IgG (FcR_γ) corresponded to those subpopulations predominantly serving as helper and suppressor T lymphocytes, respectively (Grossi, Webb, Zicca, Lydyard, Moretta, Mingari & Cooper, 1978; Hayward, Layward, Lydyard, Moretta, Dagg & Lawton, 1978; Moretta, Mingari & Moretta, 1979a; Moretta, Mingari, Moretta & Cooper, 1979b). Recently, human T lymphocytes bearing FcR specific for IgA have also been identified (Lum, Muchmore, Keren, Decker, Koski, Strober & Blaese, 1979).

Pertinent to the topic of this review are the demonstrations in recent years of FcR specific for IgE antibody molecules (FcR_ε). These have been discovered on the membranes of macrophages (Capron *et al.*, 1975; Dessaint *et al.*, 1979a,b) and on subpopulations of lymphocytes. The first clear demonstration of FcR_ε on lymphocytes was reported by Gonzalez-Molina & Spiegelberg (1976) who observed and characterized Fc-specific binding of IgE myeloma proteins to eight human lymphoblastoid cell lines. Subsequently, these same investigators were successful in demonstrating FcR_ε on a subpopulation of normal human peripheral B lymphocytes (Gonzalez-Molina & Spiegelberg, 1977). Fritsche & Spiegelberg (1978) made a thorough analysis of FcR_ε-bearing lymphocytes in various lymphoid organs of normal rats. Their studies revealed a relatively high percentage of normal rat B lymphocytes possessing such FcR_ε, particularly the spleen (18·7%), peripheral blood (13·3% and bone marrow (12·3%); lower numbers of such cells were found in Peyer's patches (5·5%) and lymph nodes (4·1%). The binding of IgE to these FcR_ε on both human and rat lymphocytes was highly species-specific (Gonzalez-Molina & Spiegelberg, 1976, 1977; Fritsche & Spiegelberg, 1978).

In a more thorough analysis of human peripheral lymphocytes and lymphoid organs, Hellström & Spiegelberg (1979) found that most of the FcR_ε^+ lymphrocytes isolated from blood and lymphoid organs were B cells inasmuch as they were positive for surface Ig of the IgM and/or IgD classes and, moreover, none of the FcR_ε^+ cells bore typical surface markers of T lymphocytes. However, when peripheral lymphocytes of patients with allergic disorders were similarly analysed, Spiegelberg, O'Connor, Simon & Mathison (1979) found that the patients manifesting severe hyper-IgE production had significantly greater quantities of FcR_ε^+ lymphocytes than normal individuals; moreover, although again the majority of such FcR_ε^+ cells were B lymphocytes, a few of these patients had small numbers of T cells with FcR_ε on their surface. Attempts by these investigators to induce further expression of FcR_ε by incubating lymphocytes from either normal or atopic individuals with human myeloma IgE were unsuccessful.

The suspicion that FcR_ε^+ T lymphocytes were detectable in atopic patients, particularly those with high serum IgE levels, was confirmed in studies reported by Yodoi & Ishizaka (1979a) who examined T-lymphocyte enriched fractions of peripheral blood lymphocyte samples obtained from ragweed-sensitive individuals. In addition, these investigators examined T lymphocytes in the mesenteric lymph nodes of rats infected with *N. brasiliensis* and found that about 3% of such cells were FcR_ε^+. Similarly, rat T cells activated by adoptive priming in irradiated

histo-incompatible recipients contained 5–10% FcR_{ε}^{+} T cells. Yodoi, Ishizaka & Ishizaka (1979) confirmed that rats infected with *N. brasiliensis* manifested significantly increased levels of FcR_{ε}^{+} cells in mesenteric lymph nodes, such increases becoming evident between 10 and 14 days after infection and persisting for 5 weeks. Suspecting that there may be a correlation between the high levels of IgE antibody synthesis in parasite-infected animals and the increased levels of FcR_{ε}^{+} cells, Yodoi *et al.* (1979) cultured normal rat mesenteric lymph node cell preparations in the presence of varying quantities of rat IgE. After 18 h of exposure in culture to 1 μg/ml or more of rat IgE, they were able to detect a significant increase in the frequency of FcR_{ε}^{+} cells in such cultures. Somewhat lower, though significant, increases in FcR_{ε}^{+}, cells were observed in cultures of normal rat peripheral blood lymphocytes and bone marrow cells exposed to rat IgE, but not in cultures of rat thymocyte suspensions. This induction of FcR_{ε}^{+} lymphocytes was both IgE class- and species-specific, required at least 8 h of exposure to rat IgE and involved both RNA and protein synthesis, but no DNA synthesis (Yodoi *et al.*, 1979).

Similar findings have been made by Yodoi & Ishizaka (1980a) with cultured human peripheral blood lymphocytes. Thus, when peripheral lymphocytes from ragweed-sensitive individuals were exposed in culture to both antigen E and purified human IgE, the quantities of FcR_{ε}^{+} cells in such cultures significantly increased within 3 days; neither antigen E nor IgE alone was capable of inducing FcR_{ε}^{+} cells, nor was it possible for the mixture of these components to induce increased quantities of such cells in cultures of lymphocytes obtained from non-ragweed sensitive individuals. Nevertheless, it was possible to induce FcR_{ε}^{+} cells in cultures of normal human lymphocytes stimulated by purified human IgE during the course of mixed lymphocyte reactions. It was reported that a portion of the FcR_{ε}^{+} cells obtained in these various culture conditions were T cells, although only limited data was presented on this point (Yodoi & Ishizaka, 1980a).

An important point from these studies was the demonstrated requirement of the presence of FcR_{γ}^{+} cells for the successful induction of increased numbers of FcR_{ε}^{+} cells in cultures of lymphocytes from ragweed-sensitive patients exposed to antigen E and IgE, since depletion of FcR_{γ}^{+} cells prior to culture abolished the induction phenomenon. It is not possible to conclude from such data, however, whether the FcR_{γ}^{+} cells are direct precursors of the FcR_{ε}^{+} population or that their presence is required in some way for other precursor cells to express the FcR_{ε} marker. Nonetheless, other studies by these same investigators (Yodoi & Ishizaka, 1979b) using mesenteric lymph node cells from either normal rats or rats infected with *N. brasiliensis* suggested that FcR_{ε}^{+} lymphocytes may indeed originate from FcR_{γ}^{+} cells. This conclusion was supported by the fact that during induction by rat IgE in culture, a significant proportion of cells bearing both FcR_{γ} and FcR_{ε} arose and appeared to convert to FcR_{ε} single-bearing cells with further incubation time. This evidence taken together with the fact that FcR_{ε} cells cannot be induced in cultures of lymphocytes depleted of FcR_{γ}^{+} cells and the fact that induction of FcR_{ε}^{+} cells by IgE could be inhibited by rabbit IgG or soluble antigen–IgG antibody complexes, indicates that FcR_{γ}^{+} cells may indeed by the precursors of FcR_{ε}^{+} cells (Yodoi & Ishizaka, 1979b).

These demonstrations of the existence of FcR_{ε} on subpopulations of both human and rodent lymphocytes, particularly the fact that such cells increase in frequency in circumstances associated with increased synthesis of IgE antibodies, represent a fascinating area of new and important information toward our understanding of immunoregulation of the IgE antibody system. Studies currently underway in several laboratories should help to unravel the biological significance of these FcR_{ε}-bearing lymphocytes and the receptor molecules themselves. Some indication of a regulatory role of molecules produced by FcR_{ε}^{+} T lymphocytes in rats will be discussed below.

Regulatory effects of soluble factors on IgE antibody responses *in vivo* and *in vitro*

The first studies demonstrating the effects of soluble T-cell factors on IgE antibody synthesis were those of Kishimoto and Ishizaka. These investigators developed a system with rabbit lymphocytes in which it was possible to obtain *in vitro* anti-DNP IgE antibody responses with cultured mesenteric lymph node cells (Ishizaka & Kishimoto, 1972; Kishimoto & Ishizaka, 1972, 1973a, b). These studies defined conditions in which soluble T-cell factors could be generated, which in turn were capable of regulating IgE or IgG anti-DNP antibody responses in such cultures (Kishimoto & Ishizaka, 1973c, 1974). Out of such studies came the interesting observation that the

soluble T-cell factors responsible for regulating the two antibody responses, respectively, appeared to be clearly different, both in terms of the cell populations from which they were derived (i.e. mode of immunization) and in their physicochemical properties (i.e. molecular size) (Kishimoto & Ishizaka, 1975).

More recently, studies from the author's laboratory and those of other investigators have defined several different soluble mediators whose activities can regulate IgE antibody synthesis. Since the terminology and characteristics of these factors have grown progressively more complex, it seems worthwhile to describe in some detail this area of the field.

Soluble factors obtained from normal murine spleen cells

Studies of Watanabe *et al.* (1976, 1977) made use of IgE antibody responses in low responder SJL mice which they were able to enhance by a combination of infection with *N. brasiliensis* and exposure to whole body irradiation. Under such circumstances, low responder SJL mice developed high and persistent titres of hapten-specific IgE antibody. Such responses could be suppressed and terminated by passive transfer of normal SJL spleen cells. In subsequent studies, Watanabe & Ovary (1977) reported that extracts of normal SJL spleen cells, prepared by repeated freezing and thawing of spleen cell suspensions, contained a soluble mediator that could suppress the enchanced IgE antibody responses of SJL mice. This soluble suppressive factor exerted its effects in a relatively IgE-selective fashion, was labile to heating (56 °, 2 h) and to proteolytic enzyme digestion. Further characterization of the factor indicated that it was of large size (mol. wt greater than 300,000), was not reactive with antimouse Ig antibodies and manifested no antigen specificity.

Soluble factors obtained from antigen-sensitized murine spleen cells

Another class of soluble factors manifesting inhibitory effects selective for IgE antibody responses are those studied by Kishimoto and colleagues. These investigators developed a system in which administration of DNP-derivatized *Mycobacterium* (DNP-Tbc) induced DNP-reactive suppressor T cells capable of exerting selective suppressive effects on antibody responses of the IgE class (Kishimoto, Hirai, Suemura & Yamamura, 1976). Extension of these studies revealed the ability of such DNP-reactive suppressor T cells to inhibit in a selective manner IgE antibody responses of murine lymphocytes *in vitro* either when intact cells were incorporated into such cultures or with soluble mediators present in culture supernatants of DNP-Tbc-stimulated DNP-reactive suppressor T cells (Suemura, Kishimoto, Hirai & Yamamura, 1977). Kishimoto, Hirai, Suemura, Nakanishi & Yamamura (1978) analysed the characteristics of the soluble factors produced in this way and found that (1) DNP-specific stimulation of DNP-reactive T cells was absolutely required for the induction of the suppressive factor; (2) although antigen-specific stimulation was required for induction of the factor, its activity was totally antigen-non-specific; (3) the suppressive activity was selective for the IgE class, apparently by acting on precursor B lymphocytes of the IgE type; (4) MHC identity between the factor and its target cells was required for suppressive activity; and (5) immunoadsorption studies revealed that the factor bore determinants encoded by genes of the I region of the H-2 complex. Convincing evidence that the factor responsible for these effects is derived from T lymphocytes has been obtained as a result of the successful construction of a T-cell hybridoma capable of continuously producing the relevant suppressive factor (Watanabe, Kimoto, Maruyama, Kishimoto & Yamamura, 1978).

Soluble factors obtained from lymphocytes of N. brasiliensis*-infected rats*

The potentiating factor obtained from cultured spleen and lymph node cells of *N. brasiliensis*-infected mice described by Kojima *et al.* (1980) has been discussed above and need not be reiterated here.

In the course of extensive studies on the cellular events involved with IgE antibody synthesis in rats infected with *N. brasiliensis*, Ishizaka, Urban & Ishizaka (1976) demonstrated that associated with such infections was the development of a substantial increase in IgE-bearing lymphocytes in both mesenteric lymph nodes and spleen. [It should be noted that the finding of large numbers of IgE-bearing *lymphocytes* in spleens of such rats in these studies contrasts with the results of Mayrhofer *et al.* (1976) who failed to find increased IgE-bearing cells in spleens of similarly infected rats.] Since further evidence indicated that neonatally thymectomized rats displayed similar increases in IgE-bearing lymphocytes following *N. brasiliensis* infection [although such rats failed to synthesize the typically increased

quantities of circulating IgE (Urban, Ishizaka & Ishizaka, 1977a)], these investigators explored the possibility that a soluble mediator may be involved in the development of IgE-bearing cells in these circumstances. Indeed, Urban, Ishizaka & Ishizaka (1977b) found that culture supernatants of mesenteric lymph node cells obtained from infected rats contained a biologically active factor, mol. wt approximately 10,000–20,000, capable of stimulating the development of IgE-bearing lymphocytes in cultures of normal mesenteric lymph node cells and bone marrow cells. They termed this activity 'IgE B-cell generating factor' in view of its selective ability to induce the appearance of IgE-bearing lymphocytes. It was shown that the activity was unrelated to IgE molecules also secreted in the culture supernatants of lymph node suspensions from infected rats, and the factor was sensitive to the activities of both trypsin and ribonuclease A (but not chymotrypsin) indicating that the active factor may contain both RNA and polypeptides.

Subsequent studies designed to determine the source and mechanism of action of this factor have indicated that the IgE B-cell generating factor is actually secreted by IgE-bearing B-cells (Urban, Ishizaka & Ishizaka, 1978). This conclusion followed from the fact that (1) cultures of lymphocyte suspensions fractioned into T-cell enriched and B-cell enriched fractions released significantly greater quantities of the factor in cultures of the latter rather than the former cell type; (2) depletion of IgE-bearing cells from mesenteric lymph node suspensions prior to culture abolished the production of the IgE B-cell generating factor; and (3) treatment of mesenteric lymph node cells with specific anti-IgE antibodies enhanced the formation of IgE B-cell generating factor. Further analysis (Urban & Ishizaka, 1978) revealed that the activity of the IgE B-cell generating factor appears to be exerted on immature B lymphocytes bearing surface IgM which, following exposure to the factor, differentiate into IgM plus IgE double-bearing B cells; these results are consistent with studies reported by Ishizaka, Ishizaka, Okudaira & Bazin (1978) on the ontogeny of IgE-bearing lymphocytes in rats which indicated that all such cells in bone marrow suspensions were actually IgM-IgE double-bearing cells.

Very recent studies of Urban, Ishizaka & Bazin (1980) have revealed that, in fact, greater than 90% of IgE-bearing cells from mesenteric lymph node suspensions of *N. brasiliensis*-infected rats express three Ig isotypes on their surface membranes, namely, IgM, IgD and IgE. Similarly, such triple-bearing lymphocytes appear to be the major source of IgE B-cell generating factor. Interestingly, bridging of either IgE or IgD cell surface molecules by anti-IgE or anti-IgD antibodies, respectively, resulted in enhanced factor production by such cells; cross-linking by anti-IgM antibodies failed to enhance factor production by such cells. On the other hand, pre-treatment of cells with anti-IgM antibodies inhibited the abilities of either anti-IgE or anti-IgD antibodies to induce increased factor production by these cells. Collectively, the aforementioned studies provide some of the best evidence to date for the important regulatory activities that B lymphocytes can apparently exert on target cells (in this case cells of the same lineage) by soluble molecules distinct from conventional Ig anti-bodies, thus fulfilling a prediction made by this author several years ago (Katz, 1977c).

Another factor studied by the Ishizaka laboratory, distinct from IgE B-cell generating factor, has been termed IgE-potentiating factor. The latter factor is identified by its ability to stimulate enhanced development of IgE-containing cells (plasma cells) in cultures of mesenteric lymph node cells from rats previously primed with DNP-ovalbumin (OA) in response to stimulation by the homologous antigen (DNP-OA). This potentiation was selective for IgE, having no comparable effect on development of IgG-containing cells in such cultures (Suemura & Ishizaka, 1979). The IgE-potentiating factor was shown not to be a typical T-cell replacing factor in two important respects. First, the IgE-potentiating factor could be recovered in the supernatants of cultures of unstimulated mesenteric lymph node cells from infected rats, whereas T-cell replacing factor secreted into culture supernatants of the same mesenteric lymph node cell populations required specific stimulation with the *N. brasiliensis* antigen. Second, while the IgE-potentiating factor enhanced the development of IgE-containing cells in cultures of DNP-OA-primed lymph node populations in their responses to the homologous antigen, DNP-OA, this factor had no capacity to stimulate development of IgE-containing cells in cultures exposed to an unrelated antigen such as DNP-human serum albumin (HSA). On the contrary, T-cell replacing factor present in culture supernatants from antigen-stimulated lymph node cells, enhanced development of Ig-containing cells both of IgE and IgG classes (i.e. not IgE-selective), and could do so not only in cultures

stimulated by the homologous DNP-OA, but also in cultures stimulated with the heterologous DNP-HSA antigen (Suemura & Ishizaka, 1979). Furthermore, preliminary size determination indicated that T-cell replacing factor and IgE-potentiating factor were of different ranges, the former being larger than the latter.

Very recent studies by these investigators have revealed that the IgE-potentiating factor is produced by FcR_ε^+ T cells present in the mesenteric lymph node populations of infected rats and that it has affinity for rat IgE molecules. Moreover, its mechanism of action appears to be directed toward target cells of the B-cell lineage which bear IgE molecules on their surface membrane (Suemura, Yodoi, Hirashima & Ishizaka, 1980). In view of its affinity for IgE, it appears that IgE-potentiating factor is the same as the IgE-binding factor described recently by Yodoi & Ishizaka (1980b). The IgE-binding factor is released into the culture supernatants of mesenteric lymph node cells from rats infected with *N. brasiliensis*. The factor is identified by its ability to bind specifically to rat IgE and to inhibit rosette formation of FcR_ε^+ cells with IgE-coated erythrocytes. Yodoi & Ishizaka (1980b) have presented evidence suggesting that the IgE-binding factor is released from FcR_ε^+ T cells, and speculated that the binding factor may be the FcR_ε^+ molecule (from T cells, but not B cells) itself. In this sense, the IgE-binding factor may be analogous to the immunoglobulin-binding factor (IBF) derived from activated T cells expressing FcR_γ on their surface that has been studied extensively by Fridman and colleagues (Fridman & Golstein, 1974; Gisler & Fridman, 1976; Fridman, Guimezanes & Gisler, 1977; Neauport-Sautes & Fridman, 1977; Joskowicz, Rabourdin-Combe, Neauport-Sautes & Fridman, 1978; Rabourdin-Combe, Dorf, Guimezanes & Fridman, 1979). Recently, another type of IgE-binding factor obtained by exposing mesenteric lymph node cells from 8 day *N. brasiliensis*-infected rats (which fail to shed IgE-binding factor in unstimulated cultures) to rat IgE exerts precisely opposite regulatory effects (i.e. suppressive) on development of IgE plasma cells from DNP-OA-primed cells cultured with DNP-OA (K. Ishizaka, personal communication).

Soluble factors obtained from serum and ascites fluids of intact mice

Studies in the author's laboratory during the past several years have concentrated on delineating the differences underlying the IgE antibody response phenotypes of low and high responder mice. As pointed out above, we were able to demonstrate that various manipulations such as low dose whole-body irradiation, moderate doses of immunosuppressive drugs, adult thymectomy, or administration of appropriate doses of anti-lymphocyte serum selectively increased the magnitude of IgE antibody production in mice (Chiorazzi *et al.*, 1976, 1977a, b, c). The mechanism by which these manipulations result in enhanced IgE production is related to the removal or diminution of a suppressive mechanism that normally dampens the magnitude of IgE antibody production. Several points are worth emphasizing about this experimental model. First, the manipulations that effectively disturb normal damping of IgE production do so in mice of both the low and high IgE responder phenotypes. The relative effect is more dramatic in low IgE responder mice since, in many instances, such mice show full conversion to a high IgE response pattern following manipulations such as low dose irradiation (Chiorazzi *et al.*, 1977a, c). Second, these substantial changes in antibody response patterns are limited to responses of the IgE class; similar changes are not routinely observed in responses of other Ig classes. Finally, the ability to convert low responder mice to the high IgE response phenotype provides an excellent model system for (1) analysing the mechanism(s) by which such conversion takes place, and (2) developing contrasting manoeuvres that might be effective in reversing the process to the normal low response phenotype.

In the course of investigations aimed at approaching the aforementioned points, circulating regulatory factors were demonstrated in the serum (or induced ascites fluids) of mice with biological activities capable of exerting potent regulatory effects on the IgE antibody system. Two IgE-selective regulatory factors have been identified thus far, one of which is suppressive (termed 'suppressive factor of allergy' or SFA) and the other of which is enhancing (termed 'enhancing factor of allergy' or EFA). The respective activities of SFA and EFA have been demonstrated by their abilities to suppress or enhance IgE antibody synthesis in intact mice. The fine details of the experimental system and the data obtained with these factors have been reviewed elsewhere (Katz, 1978a, b, 1979a 1980) and will, therefore, only be summarized here.

The existence of SFA was first discovered in the serum of low IgE responder SJL mice that had been

inoculated one week prior to bleeding with *Mycobacterium*-containing Freund's complete adjuvant (Tung, Chiorazzi & Katz, 1978; Katz & Tung, 1978). When such serum was passively transferred to recipient SJL mice that had been exposed to low dose irradiation in order to convert their IgE response phenotype from low-to-high, the passively transferred serum completely reversed such enhanced IgE responses to the normal low or undetectable levels. Such SFA activity could be demonstrated both in irradiation-enhanced primary IgE responses (Tung *et al.*, 1978) and in adoptive secondary responses obtained following passive transfer of primed spleen cells to syngeneic, irradiated low responder recipients (Katz & Tung, 1978).

Extensive studies on the biological properties of SFA have revealed the following points. First, SFA predominates quantitatively in low IgE responder mice; it is also present, but in lesser amounts, in high IgE responders. Second, SFA appears to be present in varying amounts in normal serum, but can be greatly exaggerated in serum by Freund's complete adjuvant (FCA) immunization and in ascites fluids induced by repeated inoculations of FCA (Tung *et al.*, 1978; Katz & Tung, 1978). Another manoeuvre that is even more effective in inducing increased production of SFA is the generation of a transient allogeneic effect *in vivo* following transfusion of moderate numbers of histo-incompatible lymphocytes; likewise, SFA can be produced *in vivo* in mixed lymphocyte cultures (Katz, 1979b). As stated above, the activity of SFA is highly selective for IgE antibody responses and it exerts its effect in an antigen-non-specific fashion. Moreover, SFA is highly active in minute quantities in terms of suppressing *in vivo* IgE antibody responses. Finally, SFA acts across both strain and species barriers irrespective of whether the treated individual receiving SFA is of the low or high IgE responder phenotype (Katz, Bargatze, Bogowitz & Katz, 1980).

Physicochemical and immunochemical properties of SFA that are known thus far (Katz & Tung, 1979) include: (1) it is heat stable (56°, 1 h); (2) it is not lipoprotein or associated with lipoproteins; (3) it is precipitable by ammonium sulphate; (4) it has a molecular weight range of 150,000–200,000; (5) it does not express immunoglobulin determinants or MHC determinants (either H-2 or Ia); but (6) it does bear determinants identical or cross-reactive with those found on β_2-microglobulin.

The discovery of a regulatory factor with opposing enhancing activity (i.e. EFA) came about by serendipity (Katz, Bargatze, Bogowitz & Katz, 1979a). In any case, EFA, like SFA, exerts its activity in a selective fashion on IgE antibody production, is present in normal serum of both low and high responder mice, and also appears in increased amounts following inoculation with FCA. Interestingly, EFA production tends to rise very early after inoculation of Freund's adjuvant, peaking by day 3 or 4 and then subsiding; at the time that EFA subsides, SFA production begins to rise reaching a peak on days 7–10. This is of interest because IgE antibody responses of low responder mice can be enhanced by inoculation of FCA at the proper time relative to sensitization (indeed, resulting in conversion of low responder mice to the high responder phenotype without any other manipulation), whereas irradiation-enhanced IgE production by low responder mice can be suppressed by inoculation of FCA at the proper time as well (Katz *et al.*, 1979a). It becomes clear, therefore, that the net balance of SFA versus EFA in a given individual at any given time appears to determine the phenotype of IgE antibody production following antigen sensitization at that time. Not surprisingly, one of the earliest consequences of low dose irradiation is the abrogation of SFA production, hence explaining the mechanism by which low dose irradiation converts mice from the low-to-high responder phenotype (Tung *et al.*, 1978). It is also worth noting at this point that this inhibition of SFA production by low dose irradiation is short-lived, lasting only 36–48 h.

Since administration of Freund's adjuvant induces synthesis of both EFA and SFA, it soon became obvious that it would be advantageous to ascertain a method by which these two opposing factors could be easily separated from one another in a given serum or ascites fluid preparation. Fortunately, we found that affinity chromatography on concanavalin A–Sepharose is a convenient method to accomplish such separation since EFA tends to have greater affinity for concanavalin A than does SFA; hence, when ascites fluid is passed over such affinity columns, the pass-through effluent is enriched for SFA activity, while the material bound to the column and subsequently eluted from it by competitive sugar inhibition is substantially enriched in EFA activity (Katz *et al.*, 1979a). Indeed, the importance of separating these two factors from one another is underlined by the fact that unfractionated ascites fluids are *pseudo-restricted* in SFA activity, appearing to exert

suppressive effects on IgE antibody responses only on recipient mice of the same strain, and only if such recipient mice are of the low responder type (Katz & Tung, 1978). However, after fractionation on concanavalin A–Sepharose, an SFA-enriched fraction can exert suppressive effects on IgE responses across all strain barriers and irrespective of the recipient's IgE responder phenotype (Katz *et al.*, 1980). The conclusion from such results is that EFA must predominate in its biological effect when used across strain and species barriers, even when present in quantities insufficient to dominate over the activity of SFA when used in a homologous situation. Formal proof for this explanation should be forthcoming from studies currently in progress in the author's laboratory. In any case, the main point is that both SFA and EFA are produced by, and act on, experimental animals of both low and high IgE responder types (and also in man, see below). Furthermore, it cannot be overemphasized that since both factors are produced by living animals and are biologically active when passively transferred to living recipients, there can be no doubt about their physiological relevance.

General comments

The properties of the various factors that have been shown to exert regulatory effects on antibody responses are summarized in Table 1. These factors have one striking feature in common, namely, their biological effects are restricted to synthesis of IgE antibody molecules. A second common feature of all these factors is their ability to act in an antigen-non-specific manner, irrespective of whether specific antigen stimulation might be required to elicit their production. All except those studied in the Ishizaka laboratory have been shown to exert their effects on *in vivo* IgE antibody responses. There are, of course, some notable differences such as: (1) the apparent MHC-restricted activity of, and the presence of MHC determinants on, the factors studied in the Kishimoto laboratory, as contrasted to the absence of any strain or species barriers to the activity of, and the absence of MHC determinants on, the SFA studied in the author's laboratory (no definitive evidence on either of these points is yet available for EFA); (2) variations in the estimated sizes of certain of the factors where this has been analysed; and (3) the apparent direct action of IgE-potentiating factor on IgE-bearing B lymphocytes (Ishizaka laboratory) as contrasted with the apparent requirement for carrier-specific T cells for activity of the enhancing factor studied by the Ovary laboratory to manifest its effects. It should be noted, however, that these are not serious discrepancies and one could think of several plausible explanations to account for them. It will be interesting to learn, as time goes on, to what extent these various factors may overlap with, or even be identical to, one another.

The concept of 'allergic breakthrough' and its relevance to the pathogenesis of the allergic phenotype

As the pieces of information began to accumulate from the studies performed in the author's laboratory described above, they had a significant impact on conceptual perspectives concerning how at least certain of the manifestations of the allergic phenotype may develop. This evolved into a concept that was termed 'allergic breakthrough' (Katz, 1978b; Katz, Bargatze, Bogowitz & Katz, 1979b). The concept is actually quite simple and considers that IgE antibody production is normally maintained at a low, albeit effective, magnitude following sensitization because of the existence of a normal damping mechanism which exists precisely to limit the quantity of IgE antibodies produced in any given response. The normal damping mechanism would, of course, reflect the net balance of suppressive versus enhancing regulatory activities concerned with this antibody response. The fact that the system seems to be so designed as to limit IgE production is quite sensible since an inherent amplification mechanism makes it possible for small quantities of IgE molecules to exert their desired biological effect. This follows from the fact that IgE molecules become specifically and avidly bound to mast cells and basophils which are actually minute factories of potent pharmacological mediators. By tailoring the system with a normal damping mechanism to minimize quantities of IgE antibody molecules produced following sensitization, this would allow for IgE antibody responses that are sufficient to provide protection without resulting in undesirable and/or deleterious effects. However, if (1) any one of a number of possible perturbations disturb the damping mechanisms in such a way as to diminish the overall damping capabilities to a sufficiently low level, and if (2) at that point in time when the damping threshold is lowered, the individual becomes sensitized to one or more allergenic substances, this unfortunate juxtaposition in time can result in allergic breakthrough. This simply

Table 1. Regulatory factors selectively active on the IgE antibody system

Factor	Laboratory (Ref.†)	Species	Derivation	Properties			Cell Source	Cell Target
				Activity	Physicochemical	Immunological		
Cell-free supernatant	Ishizaka (1–3)	Rabbit	Antigen-primed mesenteric lymph node cells cultured with free carrier (24 h)	*in vitro*; enhancing	β-globulin; 150,000 mol. wt.	Antigen-non-specific; non-immunoglobulin	T cells?	ND*
Spleen extract	Ovary (4)	Mouse	Freeze–thaw extraction of normal spleen cells	*in vivo*; suppressive	heat-labile (56°, 2 h); protein; >300,000 mol. wt.	Antigen-non-specific; non-immunoglobulin	ND	ND
IgE class-specific suppressor factor	Kishimoto (5–7)	Mouse	DNP-Tbc-primed T cells cultured with antigen	*in vivo* and *in vitro*; suppressive	55,000–60,000 mol. wt.	Antigen-non-specific; non-immunoglobulin; MHC- restricted; bears H-2 and Ia determinants	T cells	IgE B cells
Potentiating factor	Ovary (8)	Mouse	Mesenteric lymph node and spleen cells from *N. brasiliensis*-infected mice cultured with Nb antigen	*in vivo*; enhancing	ND	Antigen-non-specific	ND	T cells
IgE B cell-generating factor	Ishizaka (9–12)	Rat	Mesenteric lymph node cells from *N. brasiliensis*-infected rats cultured alone or in presence of anti-IgE or anti-IgD	*in vitro*; enhances isotype switch to IgE B cells	10,000–20,000 mol. wt; sensitive to trypsin and ribonuclease A	Antigen-non-specific; non-immunoglobulin	IgE B cells	IgM B cells
IgE-potentiating factor	Ishizaka (13, 14)	Rat	Mesenteric lymph node cells from *N. brasiliensis*-infected rats cultured alone	*in vitro*; enhances development of IgE plasma cells in cultures of hapten-carrier primed mesenteric lymph node cells	10,000–20,000 mol. wt.	Antigen-non-specific; binds to IgE	FcR_ε^+ T cells	IgE B cells

IgE-binding factor	Ishizaka (15)	Rat	(1) Mesenteric lymph node cells from *N. brasiliensis*-infected rats cultured alone (2 week infected) or in presence of rat IgE (2 week and 8 day infected (2) Normal rat lymphocytes cultured in presence of rat IgE	*in vitro*; inhibits rosette-formation of IgE rosettes by FcR_ε^+ lymphocytes (? same as IgE-potentiating factor)	10,000–20,000 mol. wt.	Antigen-non-specific;	FcR_ε^+ T cells FcR_γ^+T	FcR_ε^+ cells
Suppressive factor of allergy (SFA)	Katz (16–21)	Mouse	(1) Serum or ascites fluids from Freund's complete adjuvant-primed mice; (2) Serum from mice injected with allogeneic cells; (3) Mixed lymphocyte culture supernatants	*in vivo*; suppressive for primary and secondary responses	150,000–200,000 not lipoprotein; heat stable (56 1 h) low affinity for concanavalin A; non-hydrophobic	Antigen-non-specific; non-immunoglobulin strain and species unrestricted; no H-2 or Ia determinants; bears β_2-microglobulin determinants	ND (not macrophages)	ND
Suppressive factor of allergy (SFA)	Katz (22, 23)	Human	Human two-way mixed lymphocyte culture supernatants	*in vitro* (human); suppressive *in vivo* (mouse); suppressive	ND	Antigen-non-specific; species unrestricted	ND	ND
Enhancing factor of allergy (EFA)	Katz (20)	Mouse	Serum or ascites fluids from Freund's complete adjuvant-primed mice	*in vivo* enhancing	high affinity for concanavalin A; hydrophobic	Antigen-non-specific; non-immunoglobulin	ND	ND

*ND—Not determined.

†References: 1 Kishimoto & Ishizaka, 1973c; 2 Kishimoto & Ishizaka, 1974; 3 Kishimoto & Ishizaka, 1975; 4 Watanabe & Ovary, 1977; 5 Suemura *et al.*, 1977; 6 Kishimoto *et al.*, 1978; 7 Watanabe *et al.*, 1978; 8 Kojima *et al.*, 1980; 9 Urban *et al.*, 1977b; 10 Urban *et al.*, 1978a; 11 Urban & Ishizaka, 1978; 12 Urban *et al.*, 1980; 13 Suemura & Ishizaka, 1979; 14 Suemura *et al.*, 1980; 15 Yodoi & Ishizaka, 1980b; 16 Tung *et al.*, 1978; 17 Katz & Tung, 1978; 18 Katz & Tung, 1979; 19 Katz, 1979b; 20 Katz *et al.*, 1979a; 21 Katz *et al.*, 1980; 22 Nonaka, Zuraw, O'Hair & Katz, in preparation; 23 Zuraw, Nonaka, O'Hair & Katz, in preparation.

means that the height of IgE antibody production to that given allergen rises to excessive quantities thereby leading to the possibility of allergic symptomatology.

The allergic breakthrough concept leads to three important, and testable, predictions. (1) Once 'breakthrough' has occurred, the height of IgE antibody production should remain elevated even though the damping mechanism has returned to its normal threshold level. (2) Any manipulation which either effectively re-establishes the damping mechanism (for example, SFA) or counteracts it (for example, EFA) should persist for long periods of time. (3) Allergic breakthrough should be highly specific for the antigen(s) to which the individual became sensitized coincident with disturbance in normal damping. All three of these predictions have been subjected to experimental analysis in the author's laboratory and have been borne out (Katz *et al.*, 1979b).

While such predictions can be tested in experimental animals, it is difficult, if not impossible, to either design or conduct suitable clinical studies that might address these issues in man. One of the difficulties in this regard stems from the fact that it appears that the balance of control of IgE synthesis is so delicate that it might become susceptible to very unsuspected perturbations that can upset this balance thereby resulting in production of higher than necessary quantities of IgE. Some useful information comes out of those circumstances where clinically evident allergic symptomatology developed, for the first time, in some patients subjected to immunosuppressive drug therapy associated with tissue transplantation (Lakin *et al.*, 1975a, b). Such cases may represent easily definable examples of 'allergic breakthrough' since the responsible perturbations (i.e. immunosuppressive drugs) were obvious.

In general, one might feel that things more subtle pose the more common perturbations that may underlie allergic breakthrough in real life. One good candidate might be upper respiratory viral infections, first because they occur so commonly, and second because the systemic symptoms associated with such illnesses can be sufficiently stressful to pose a disturbing effect (albeit transient) on the normal damping mechanism controlling IgE. Into the equation, of course, one must consider the genetic predisposition of each individual to (1) be subject to disturbances in the normal damping mechanism, (2) be capable of responding to the particular sensitizing allergen(s) to which he/she may become exposed, and (3) perhaps display increased target organ sensitivities to the vasoactive mediators of immediate hypersensitivity reactions. In point of fact, in a prospective study on the development of allergic symptomatology in children born of two allergic parents, Frick, German & Mills (1979) observed that the onset of clinical and immunological evidence of allergy (which developed in 11 of 13 children studied) usually coincided with, or followed within weeks of an upper respiratory infection most commonly with parainfluenza or respiratory syncytial virus. Indeed, experimental studies in dogs and mice have indicated that deliberate infection with upper respiratory viruses in these experimental animals leads to enhanced IgE antibody synthesis to unrelated antigens in a manner analogous to low dose irradiation (O. L. Frick, personal communication).

Clearly, further studies of this type in man are both warranted and necessary to sort this out. As stated above, however, this will not be easy by any means because of the potentially large number of influences, both exogenous and endogenous, that may contribute to perturbations of regulatory control mechanisms associated with the IgE antibody system. As an example of how unsuspected endogenous influences can affect IgE antibody production, we have recently obtained evidence that low responder SJL mice can display striking variations in the magnitude of IgE antibody synthesis following antigen sensitization either alone or in conjunction with exposure to the optimal enhancing dose of whole body irradiation (Bargatze & Katz, 1980). Faced with these observations, we were prompted to evaluate the magnitudes of IgE antibody synthesis in relation to the normal diurnal curve of endogenous corticosteroid production.

As shown in Fig. 1, when individual groups of SJL mice were both irradiated and immunized at the same time, but at 2 h intervals during the day between 6:00 a.m. and 6:00 p.m., the IgE responses obtained varied from undetectable levels in groups irradiated and immunized in the early morning, showing significant rises at mid-day and thereafter, reaching a peak titre of 2560 at 4:00 p.m., before falling rapidly again to undetectable levels at 6:00 p.m. When this IgE response curve is superimposed on a curve depicting normal variation in the plasma levels of corticosterone, an interesting relation becomes evident. Thus, it appears that low responses occur when plasma steroid levels are low, IgE synthesis begins to heighten as the steroid level gradually

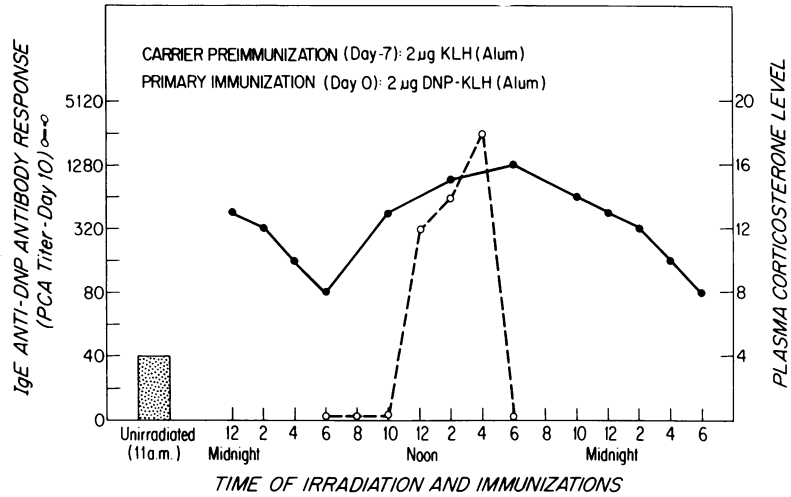

Figure 1. The magnitude of irradiation-enhanced IgE responses of low responder SJL mice varies in relation to the time of day mice are exposed to irradiation and sensitization. Groups of SJL female mice (five per group) were irradiated and immunized at the same time, but at 2 h intervals during the day between 6 a.m. and 6 p.m. Mice in a control group not exposed to irradiation were immunized at 11 a.m. (vertical bar). Carrier pre-immunization with 2 µg of DNP-KLH in alum on day 0. The day 10 DNP-specific IgE antibody responses (PCA titres) of these various groups of mice are depicted by the open circles and dashed line, while the diurnal curve of plasma corticosterone levels of mice are depicted by the closed circles and solid lines. (Taken from Bargatze & Katz, 1980, with permission.)

rises at mid-day until steroid production reaches its peak level at which time the capacity to synthesize IgE antibodies appears to be depressed once again.

This apparent effect of endogenous steroid production on IgE antibody synthesis was supported by experiments demonstrating that the normal IgE pattern in both unirradiated and irradiated mice could be perturbed by administration of cortisone at the proper time of day (Bargatze & Katz, 1980). Such results indicate that IgE antibody synthesis displays unique sensitivity to fluctuations in plasma steroid levels and, therefore, may have significant implications for the role of steroids in the pathogenesis and management of allergic diseases.

Prospects for future immunological control of allergic diseases

In addition to satisfying our curiosities about immunological control mechanisms, one obvious goal of investigations on the IgE antibody system is to hasten the time when it will become possible effectively and reproducibly to manage clinical allergies by judicious and safe manipulations of the immune system. The idea of desensitizing mast cells and basophils by administration of an analogue of the pertinent domain of the Fc region of IgE (Hamburger, 1979), while attractive in concept, probably will have practical disadvantages that will limit its clinical usefulness. Improvements on standard procedures for immunotherapy, such as the use of polymerized allergens (Bacal, Zeiss, Susko, Levitz & Patterson, 1978) are important advances that may have wide applications in the treatment of antigenically defined allergies, although there still remains the bothersome aspect of the possible development of deleterious circulating immune complexes during the course of therapy of this type, at least in some patients (Yang, Dorval, Osterland & Gilmore, 1979; Kohler, 1979). The notion of manipulating IgE synthesis by induction of auto-anti-idiotypic antibodies has been shown to be experimentally feasible by de Weck and colleagues (de Weck, Geczy & Toffler, 1977; Geczy, de Weck, Geczy & Toffler, 1978; Blaser, Geiser & de Weck, 1980), but such an approach in man would require individual, tailor-made therapy which could also be impractical.

What, then, can we hope to offer as alternative modes of immunological control of allergic diseases at some time in the future? Based on much recent

work in experimental animals, this author sees three areas of promise that can be summarized as follows.

First, a major category of promise concerns the use of appropriate substances that are effective in inducing specific immunological tolerance. This derives from experimental work which has shown the ability to synthesize compounds comprised of allergenic determinants covalently linked to non-immunogenic backbone carriers whose properties impart to the compound tolerogenic characteristics. The prototype carriers of this type are the synthetic copolymer of D-glutamic acid, D-lysine (D-GL) which has been studied extensively in the author's laboratory for some years (Katz, Davie, Paul & Benacerraf, 1971; reviewed in Katz, 1974; Katz & Benacerraf, 1974), and isologous gamma-globulin which has been studied by Borel and his colleagues during the same period of time (reviewed in Borel, 1976).

While the bulk of such work concentrated on the ability to induce specific immunological tolerance to haptenic determinants, studies conducted more recently have shown that protein allergens (such as ragweed antigen E) coupled by appropriate methodology to backbones such as D-GL (Liu, Zinnecker, Hamaoka & Katz, 1979a) can induce highly specific tolerance to the protein determinants which, interestingly, is selective for antibody responses of the IgE class (Liu & Katz, 1979; Liu, Bogowitz, Bargatze, Zinnecker, Katz & Katz, 1979b). Similar success has been reported by others using various protein allergens and different types of carrier backbones (Lee & Sehon, 1977, 1978a, b; Usui & Matuhasi, 1979).

The ability to induce specific immunological tolerance by administration of either small haptenic determinants (relevant to certain drug sensitivities) or to more complex protein allergens promises to provide a highly specific immunotherapeutic approach to at least certain allergic diseases where the relevant allergen involved has been defined. Whether this approach will be as effective in humans as it has been in experimental animal systems should be known in the not-too-distant future from results of limited clinical trials with certain compounds of this type. If successful, such compounds would clearly have clinical usefulness for those allergic disorders in which the allergen is well known, and, at the very least, could provide therapy for those patients until a more universal form of therapy becomes available.

Another major category of promise concerns the induction of suppressor mechanisms capable of damping IgE antibody production. These may be sub-classified as *antigen-specific* and *antigen-non-specific*. Experimental studies have clearly shown that ongoing IgE antibody responses can be specifically diminished or abolished by administration of chemically modified antigens (Bach & Brashler, 1975). Studies by Ishizaka and colleagues have demonstrated that administration of certain chemically denatured antigens tends to preferentially induce antigen-specific suppressor T cells capable of effectively diminishing IgE antibody responses specific for the antigen employed (Ishizaka, Okudaira & King, 1975; Takatsu, Ishizaka & King, 1975; Takatsu & Ishizaka, 1975, 1976a, b). As in the case of the antigen-specific tolerance approach described above, the practical drawbacks to an approach based on induction of antigen-specific suppressor T cells pertain to the necessity for (1) accurately defining the specific allergen concerned in any given patient's allergic disorder, and (2) tailoring such therapy on a more or less individual basis from one patient to the next. These limitations become particularly significant in considering therapy for those individuals manifesting multiple systemic allergies or in those individuals for which the specific offending allergen cannot be accurately defined.

For these reasons, it seems essential that effective methodology for inducing *non-specific* suppressor mechanisms be developed. Particularly if the non-specific suppressor mechanism displays selectivity for IgE antibody production, such an approach might offer a more universal therapeutic tool for IgE-mediated allergic disorders. For example, it is conceivable that it will be possible to administer substances, such as SFA, as a means for heightening the damping mechanism such that it would be sufficient to diminish IgE antibody synthesis to the offending allergen(s) responsible for a given individual's allergic disorder. Alternatively, one can consider the feasibility of developing proper manipulations that would result in stimulation of endogenous production of sufficient quantities of SFA, or SFA-like activity, that would have the same heightened damping effect on the IgE antibody system. The latter possibility might be accomplished by administration of appropriate pharmacological agents that would have a similar effect to that observed in experimental animals following the administration of Freund's complete adjuvant.

The validity of these considerations depends, of

course, upon the demonstration that humans, like mice, are capable of synthesizing and secreting suppressor molecules similar (or identical) to SFA, and that man, like mice, responds to the action of SFA in terms of its selective damping effect on IgE antibody responses. Studies from the author's laboratory that have already been published have shown the existence of an SFA-like activity in culture supernatants of two-way human mixed lymphocyte cultures which displayed IgE-selective suppressive activity that could be assayed biologically in mice (Katz *et al.*, 1980).

Is there any evidence that SFA or SFA-like molecules can be produced by human cells and exert IgE-selective suppressive effects on human IgE responses? In order to ascertain whether regulatory mechanisms governing IgE antibody synthesis in man follow certain of the same patterns observed in mice, we have been working to establish a system of *in vitro* IgE antibody synthesis by human peripheral blood lymphocytes. Recent studies in other laboratories have been successful in demonstrating biosynthesis of IgE antibody molecules by human lymphocytes *in vitro*, both spontaneously and following stimulation by suitable polyclonal mitogenic substances (Buckley & Becker, 1978; Saxon & Stevens, 1979; Tjio, Hull & Gleich, 1979; Pryjma, Munoz, Virella & Fundenberg, 1980); one study reported the ability to stimulate production of IgE antibodies with specific antigens in cultures of sensitized human lymphocytes (Urena, Garcia, Vela, Ortiz & Lahoz, 1979). Our aim was to develop a system whereby human lymphocytes could be stimulated by specific antigens to develop primary IgE responses *in vitro* without the *absolute* requirement for incorporation of polyclonal mitogens into such cultures. In such studies, we have successfully established a system that allows us to elicit primary *in vitro* IgE antibody responses of human peripheral lymphocytes stimulated with DNP-protein conjugates either alone or together with pokeweed mitogen (Nonaka *et al.*, in preparation; Zuraw *et al.*, in preparation). With this system, we have shown the ability to inhibit specifically these responses to DNP-protein conjugates by prior exposure of the human lymphocyte population to a DNP derivative of D-GL. GL.

More importantly, this system has allowed us to verify that, indeed, human SFA exists and is capable of selectively inhibiting IgE antibody synthesis. A representative experiment demonstrating this is summarized in Table 2. In this particular experiment peripheral blood lymphocytes of a normal donor were plated in microcultures (3×10^5 cells/well) either alone (cultures I and II) or in the presence of varying dilutions of culture supernatant taken from 8 day two-way mixed lymphocyte cultures (III-V). One day later, cultures II–V were exposed to a mixture of pokeweed mitogen and DNP-KLH, at concentrations found to be optimal for generating IgE and IgG responses to these agents; control culture I was left unstimulated. Two days later, all cultures were harvested, washed thoroughly and the cells replated in microwells with fresh medium devoid of any MLC supernatant, antigen or mitogen, and then allowed to incubate for 6 additional days. At the end of this period, culture supernatants from individual wells were harvested and assayed for IgE and IgG antibodies by a new, highly sensitive solid-phase radio-

Table 2. Human suppressive factor of allergy (SFA) suppresses *in vitro* IgE antibody production but not IgG

Culture	Conc. of MLR Supernatant* (Day −3)	Stimulation† (Day −2)	IgE synthesized (pg/ml) (Day 6)	IgG synthesized (ng/ml) (Day 6)
I	None	None	430	116
II	None	PWM + DNP-KLH‡	974	2936
III	1:4	PWM + DNP-KLH	228	3282
IV	1:32	PWM + DNP-KLH	1215	2292
V	1:256	PWM + DNP-KLH	1072	2601

*1×10^6 PBL of each of two unrelated individuals in 2 ml/well were co-cultured in RPMI-1640 + 10% FCS for 8 days and supernatants were harvested and used at appropriate dilutions.

†3×10^5 cells were stimulated with antigen plus mitogen for 2 days and washed on Day 0.

‡PWM, 1 μ/ml; DNP-KLH, 10 μg/ml.

immunoassay procedure (Nonaka *et al.*, in preparation; Zuraw *et al.*, in preparation).

As shown in Table 2, exposure of cultured cells to a mixture of pokeweed mitogen and DNP-KLH stimulated synthesis of IgE and IgG antibodies (culture II) over baseline antibody synthesis in unstimulated cultures (culture I). Exposure of such lymphocytes for 1 day prior to stimulation to an appropriate concentration of human SFA totally inhibited the *in vitro* IgE antibody response. This is clearly illustrated by culture III, where the IgE antibody response was inhibited but the IgG response was not diminished; moreover, the inhibitory effects of SFA were, as expected, dose dependent.

Studies currently underway are designed to (1) characterize the target cell(s) of SFA activity in this human *in vitro* system; (2) purify the relevant molecule(s); and (3) produce monoclonal antibodies reactive with human SFA. Once the latter reagents are available, we should be in a position to begin to investigate whether SFA circulates normally in the serum of man and, if so, whether there is a correlation in quantities of such molecules with the existence (or not) of atopic disease. Moreover, if circulating human SFA can be readily quantified this would provide a potential prognostic tool for evaluating the effectiveness of therapeutic manoeuvres aimed at controlling the IgE antibody system in allergic diseases.

Concluding remarks

It would be a relatively fair and safe conclusion to state that out of fundamental basic research concerned with regulation of the immune system in general, and regulation of IgE synthesis in particular, have come several new insights in recent years that promise to have substantial implications in terms of directing us along more fruitful avenues for successful therapy of IgE-mediated disorders. This optimism is supported by the evolution of new findings, some of which have been summarized in this review. Obviously, many gaps in our knowledge still exist; nevertheless, much information obtained in recent experimental work provides useful guidelines to shape our subsequent approaches in applying some of this knowledge to the management of clinical allergic diseases. While it is judicious to be conservative in extrapolating findings in experimental animals to what may be taking place in man, it must be borne in mind that there has been an encouraging concordance between mouse and man in terms of what has been previously learned about immunoregulation of cell-mediated immunity and humoral responses of other antibody classes. It seems very likely, therefore, that a similar concordance will ultimately be demonstrated in the case of regulation of IgE antibody synthesis. Indeed, the fact that IgE-selective suppressor molecules can be obtained from human cells and be shown to act in a selective fashion on IgE responses of human lymphocytes in culture, as described herein, represents a significant step in the proper direction.

Acknowledgments

The author is grateful for the expert assistance of Cherie Dichter, Anthea Hugus, Lucy Gunnill and Keith Dunn in the preparation of this manuscript. This is publication number 174 from the Department of Cellular and Developmental Immunology and publication number 2137 from the Immunology Departments, Research Institute of Scripps Clinic, La Jolla, CA. The author's work cited herein was supported by NIH grants AI-13874 and AI-10386 and by a grant from Miles Laboratories, Inc.

References

ALCASID M.L.S., CHIARAMONTE L.T., KIM H.J., ZOHN. G., BONGIORNO J.R. & MULLIN W. (1973) Bronchial asthma and intestinal parasites. *N. Y. St. J. Med.* **73,** 1786.

ANDERSON H.R., (1974) The epidemiological and allergic features of asthma in the New Guinea Highlands. *Clin. Allergy*, **4,** 171.

BACAL E., ZEISS C.R., SUSZKO I., LEVITZ D. & PATTERSON R. (1978) Polymerized whole ragweed: an improved method of immunotherapy. *J. Allery Clin. Immunol.* **62,** 289.

BACH M.K. & BRASHLER J.R. (1975) IgE antibody-specific abrogation of an established immune response in mice by modified antigens. *J. Immunol.* **114,** 1799.

BARGATZE R.F. & KATZ D.H. (1980) 'Allergic breakthrough' following antigen sensitization: height of IgE synthesis is temporally related to diurnal variation in endogenous steroid production. *J. Immunol.* (in press.)

BINAGHI R.A. & BENACERRAF B. (1964) The production of anaphylactic antibody in the rat. *J. Immunol.* **92,** 920.

BLASER K., GEISER M. & DE WECK A.L. (1980) Suppression of phosphorylcholine-specific IgE antibody formation in BALB/c mice by isologous anti-T15 antiserum. *Europ. J. Immunol.* **9,** 1017.

BLOCH K.J. (1967) The anaphylactic antibodies of mammals including man. *Progr. Allergy*, **10,** 84.

BLOCH K.J. (1973) Reaginic and other homocytotropic antibodies. Diverse immunoglobulins with common function. In: *Mechanisms in Allergy* (Ed. by L. Goodfriend, A. H. Sehon and R. P. Orange), p. 11. Marcel Dekker, New York.

BLOCH K.J., OHMAN J.L., WALTIN J. & CYGAN R.W. (1973) Potentiated reagin response: initiation with minute doses of antigen and alum followed by infection with *Nippostrongylus brasiliensis*. *J. Immunol.* **110,** 197.

BOREL Y. (1976) Isologous IgG-induced immunologic tolerance to haptens: a model of self versus non-self recognition. *Transplant. Rev.* **31,** 3.

BUCKLEY R.H. & BECKER W.G. (1978) Abnormalities in the regulation of human IgE synthesis. *Immunol. Rev.* **41,** 288.

CAPRON A., DESSAINT J.-P., CAPRON M. & BAZIN H. (1975) Specific IgE antibodies in immune adherence of normal macrophages to *Schistosoma mansoni* schistosomules. *Nature (Lond.)*, **253,** 474.

CAPRON A., DESSAINT J.P., JOSEPH M., ROUSSEAUX R., CAPRON M. & BAZIN H. (1977) Interaction between IgE complexes and macrophages in the rat: a new mechanism of macrophage activation. *Europ. J. Immunol.* **7.** 315.

CARSON D., METZGER H. & BLOCH K.J. (1975) Serum IgE levels during the potentiated reagin response to egg albumin in rats infected with *Nippostrongylus brasiliensis*. *J. Immunol.* **114,** 521.

CHACKO D.D. (1970) Intestinal parasites and asthma. *New Eng. J. Med.* **283,** 101.

CHEAH J.S. & KAHN S.P. (1972) Lack of association between helminthic infestations and bronchial asthma in Singapore. *Aust, N.Z. J. Med.* **4,** 383.

CHIORAZZI N., FOX D.A. & KATZ D.H. (1976) Hapten-specific IgE antibody responses in mice. VI. Selective enhancement of IgE antibody production by doses of X-irradiation and by cyclophosphamide. *J. Immunol.* **117,** 1629.

CHIORAZZI N., FOX D.A. & KATZ D.H. (1977a) Hapten-specific IgE antibody responses in mice. VII. Conversion of IgE 'non-responder' strains to IgE 'responders' by elimination of suppressor T cell activity. *J. Immunol.* **118,** 48.

CHIORAZZI N., TUNG A.S., ESHHAR N. KATZ D.H. (1977b) Hapten-specific IgE antibody responses in mice. VIII. A possible new mechanism by which antilymphocyte serum enhances IgE antibody synthesis *in vivo*. *J. Immunol.* **119,** 685.

CHIORAZZI N., TUNG A.S. & KATZ D.H. (1977c) Induction of a ragweed-specific allergic state in Ir gene-restricted non-responder mice. *J. exp. Med.* **146,** 302.

DESSAINT J.-P., CAPRON A., JOSEPH M. & BAZIN. H. (1979a) Cytophilic binding of IgE to the macrophage. II. Immunologic release of lysosomal enzyme from macrophages by IgE and anti-IgE in the rat: a new mechanism of macrophage activation. *Cell. Immunol.* **46,** 24.

DESSAINT J.-P., TORPIER G., CAPRON M., BAZIN H. & CAPRON A. (1979b) Cytophilic binding of IgE to the macrophage. I. Binding characteristics of IgE on the surface of macrophages in the rat. *Cell. Immunol.* **46,** 12.

DORF M.E., NEWBURGER P.E., HAMAOKA T., KATZ D.H. & BENACERRAF B. (1974) Characterization of an immune response gene in mice controlling IgE and IgG antibody responses to ragweed pollen extract and its 2,4-dinitrophenylated derivative. *Europ. J. Immunol.* **4,** 346.

FRICK O.L., GERMAN D.F. & MILLS J. (1979) Development of allergy in children. I. Association with virus infections. *J. Allergy clin. Immunol.* **63,** 228.

FRIDMAN W.H. & GOLSTEIN P. (1974) Immunoglobulin-binding factor present on and produced by thymus-processed lymphocytes (T cells). *Cell. Immunol.* **11,** 442.

FRIDMAN W.H., GUIMEZANES A. & GISLER. R.H. (1977) Characterization of suppressive immunoglobulin-binding factor (IBF). I. Production of IBF by a θ-positive lymphoma (L-5178-Y). *J. Immunol.* **119,** 1266.

FRITSCHE R. & SPIEGELBERG H.L. (1978) Fc receptors for IgE on normal rat lymphocytes. *J. Immunol.* **121,** 471.

GECZY A.F., DE WECK A.L., GECZY C.L. & TOFFLER O. (1978) Suppression of reaginic antibody formation in guinea pigs by anti-idiotypic antibodies. *J. Allergy clin. Immunol.* **62,** 261.

GISLER R.H. & FRIDMAN W.H. (1976) Inhibition of the *in vitro* 19S and 7S antibody response by immunoglobulin-binding factor (IBF) from alloantigen-activated T cells. *Cell. Immunol.* **23,** 99.

GODREY R.C. (1975) Asthma and IgE levels in rural and urban communities of the Gambia. *Clin. Allergy*, **25,** 201.

GONZALEX-MOLINA A. & SPIEGELBERG H.L. (1976) Binding of IgE myeloma proteins to human cultured lymphoblastoid cells. *J. Immunol.* **117,** 1838.

GONZALEZ-MOLINA A. & SPIEGELBERG H.L. (1977) A subpopulation of normal human peripheral B lymphocytes that bind IgE. *J. clin. Invest.* **59,** 616.

GROSSI C.E., WEBB S.R., ZICCA A., LYDYARD P.M., MORETTA L., MINGARI M.C. & COOPER M. (1978) Morphological and histochemical analyses of two human T-cell subpopulations bearing receptors for IgM or IgG. *J. exp. Med.* **147,** 1405.

HAMAOKA T., KATZ D.H. & BENACERRAF B. (1973a) Hapten-specific IgE antibody responses in mice. II. Cooperative interactions between adoptively transferred T and B lymphocytes in the development of IgE responses. *J. exp. Med.* **138,** 538.

HAMAOKA T., KATZ D.H., BLOCH K.J. BENACERRAF B. (1973b) Hapten-specific IgE antibody responses in mice. I. Secondary IgE responses in irradiated recipients of syngeneic primed spleen cells. *J. exp. Med.* **138,** 306.

HAMBURGER R.N. (1979) Inhibition of IgE binding to tissue culture cells and leucocytes by pentapeptide. *Immunology*, **38,** 781.

HAYWARD A.R., LAYWARD L., LYDYARD P., MORETTA L., DAGG M. & LAWTON A.R. (1978) Fc-receptor heterogeneity of human suppressor T cells. *J. Immunol.* **121,** 1.

HELLSTRÖM U. & SPIEGELBERG H.L. (1979) Characterization of human lymphocytes bearing Fc receptors for IgE isolated from blood and lymphoid organs. *Scand. J. Immunol.* **9,** 75.

HOGARTH-SCOTT R.S., JOHANSSON S.G.O. & BENNICH H. (1969) Antibodies to toxocara in the sera of visceral *Larva migrans* patients: the significance of raised levels of IgE. *Clin. exp. Immunol.* **5,** 619.

ISHIZAKA K. (1975) Immunoglobulin E and reaginic hypersensitivity. *Johns Hopkins med. J.* **135,** 67.

ISHIZAKA K. (1976) Cellular events in the IgE antibody response. *Adv. Immunol.* **23,** 1.

ISHIZAKA K. & ISHIZAKA T. (1978) Mechanisms of reaginic hypersensitivity and IgE antibody response. *Immunol.*

Rev. **41,** 109.

ISHIZAKA K. & KISHIMOTO T. (1972) Regulation of antibody response *in vitro*. II. Formation of rabbit reaginic antibody. *J. Immunol.* **109,** 65.

ISHIZAKA K. & OKUDAIRA H. (1973) Reaginic antibody formation in the mouse. II. Enhancement and suppression of anti-hapten antibody formation by priming with carrier. *J. Immunol.* **110,** 1067.

ISHIZAKA K., ISHIZAKA T., OKUDAIRA H. & BAZIN H. (1978) Ontogeny of IgE-bearing lymphocytes in the rat. *J. Immunol.* **120,** 655.

ISHIZAKA K., OKUDAIRA H. & KING T.P. (1975) Immunogenic properties of modified antigen E. II. Ability of urea-denatured antigen and α-polypeptide chain to prime T cells specific for antigen E. *J. Immunol.* **114,** 110.

ISHIZAKA T., URBAN J.F. Jr & ISHIZAKA K. (1976) IgE formation in the rat following infection with *Nippostrongylus brasiliensis*. I. Proliferation and differentiation of IgE-bearing cells. *Cell. Immunol.* **22,** 248.

JARRETT E.E.E. (1978) Stimuli for the production and control of IgE in rats. *Immunol. Rev.* **41,** 52.

JARRETT E. & BAZIN H. (1974) Elevation of total serum IgE in rats following helminth parasite infection. *Nature (Lond.)*, **251,** 613.

JARRETT E.E.E. & BAZIN H. (1977) Serum immunoglobulin levels in *N. brasiliensis* infection. *Clin. exp. Immunol.* **30,** 330.

JARRETT E. & FERGUSON A. (1974) Effect of T cell depletion on the potentiated reagin response. *Nature (Lond.)*, **250,** 420.

JARRETT E.E.E. & STEWART D.C. (1972) Potentiation of rat reaginic (IgE) antibody by Helminth infection. Simultaneous potentiation of separate reagins. *Immunology*, **23,** 749.

JARRETT E., MACKENZIE S. & BENNICH H. (1980) Parasite-induced 'non-specific' IgE does not protect against allergic reactions. *Nature (Lond.)*, **283,** 302.

JARRETT E.E.E., HENDERSON D., RILEY P. & WHITE R.G. (1972) The effect of various adjuvant regimens and of nematode infection on the reaginic antibody response to egg-albumin in the rat. *Int. Archs Allergy*, **42,** 775.

JOSKOWICZ M., RABOURDIN-COMBE C., NEAUPORT-SAUTES C. FRIDMAN W.H. (1978) Characterization of suppressive immunoglobulin-binding factor (IBF). III. Biochemical and immunochemical characteristics of IBF produced by activated T cells. *J. Immunol.* **121,** 777.

KATZ D.H. (1974) Hapten-specific tolerance induced by the DNP derivative of D-glutamic acid and D-lysine (D-GL) copolymer. In: *Immunological Tolerance: Mechanisms and Potential Therapeutic Applications* (Ed. by D. H. Katz and B. Benacerraf), p. 189. Academic Press, New York.

KATZ D.H. (1977a) *Lymphocyte Differentiation, Recognition and Regulation*, p. 429. Academic Press, New York.

KATZ D.H. (1977b) *Lymphocyte Differentiation, Recognition and Regulation*, p. 89. Academic Press, New York.

KATZ D.H. (1977c) *Lymphocyte Differentiation, Recognition and Regulation*, p. 344. Academic Press, New York.

KATZ D.H. (1978a) Control of IgE antibody production by suppressor substances. *J. Allergy clin. Immunol.* **62,** 44.

KATZ D.H. (1978b) The allergic phenotype: manifestation of 'allergic breakthrough' and imbalance in normal 'damping' of IgE antibody production. *Immunol. Rev.* **41,** 77.

KATZ D.H. (1979a) New concepts concering the clinical control of IgE synthesis. *Clin. Allergy*, **9,** 609.

KATZ. D.H. 1979b) Regulation of IgE antibody production by serum molecules. III. Induction of suppressive activity of allogeneic lymphoid cell interactions and suppression of IgE synthesis by the allogeneic effect. *J. exp. Med.* **149,** 539.

KATZ D.H. (1980) Prospects for the clinical control of IgE synthesis. In: *Progress in Clinical Immunology*, vol. 4 (Ed. by R. S. Schwartz), p. 127. Grune and Stratton, Inc., N.Y.

KATZ D.H. & BENACERRAF. B. (1974) Reversible and irreversible B cell tolerance: distinguishing properties and mechanisms. In: *Immunological Tolerance: Mechanisms and Potential Therapeutic Applications* (Ed. by D. H. Katz and B. Benacerraf), p. 249. Academic Press, New York.

KATZ TUNG A.S. (1978) Regulation of IgE antibody production by serum molecules. II. Strain-specificity of the suppressive activity of serum from complete Freund's adjuvant-immune low responder mouse donors. *J. Immunol.* **120,** 2060.

KATZ D.H. & TUNG. A.S. (1979) Regulation of IgE antibody production by serum molecules. VI. Preliminary biochemical and immunological characterization of serum molecules active in suppressing IgE antibody production. *Immunopharmacology*, **1,** 103.

KATZ D.H., BARGATZE R.F., BOGOWITZ C.A. & KATZ L.R. (1979a) Regulation of IgE antibody production by serum molecules. IV. Complete Freund's adjuvant induces both enhancing and suppressive activities detectable in the serum of low and high responder mice. *J. Immunol.* **122,** 2184.

KATZ D.H., BARGATZE R.F., BOGOWITZ C.A. & KATZ L.R. (1979b) Regulation of IgE antibody production by serum molecules. V. Evidence that coincidental sensitization and imbalance in the normal damping mechanism results in 'allergic breakthrough'. *J. Immunol.* **122,** 2191.

KATZ D.H., BARGATZE R.F., BOGOWITZ C.A. & L.R. (1980) Regulation of IgE antibody production by serum molecules. VII. The IgE-selective damping activity of suppressive factor of allergy (SFA) is exerted across both strain and species restriction barriers. *J. Immunol.* **124,** 819.

KATZ D.H., DAVIE J.M., PAUL W.E. & BENACERRAF B. (1971) Carrier function in anti-hapten antibody responses. IV. Experimental conditions for the induction of hapten-specific tolerance or for the stimulation of anti-hapten anamnestic responses by 'non-immunogenic' hapten–polypeptide conjugates. *J. exp. Med.* **134,** 201.

KING T.P., KOCHOUMIAN L. & CHIORAZZI N. (1979) Immunological properties of conjugates of ragweed pollen antigen E with methoxypolyethylene glycol or a copolymer of D-glutamic acid and D-lysine. *J. exp Med.* **149,** 424.

KISHIMOTO T. & ISHIZAKA K. (1972) Regulation of antibody response *in vitro*. III. Role of hapten-specific memory cells and carrier-specific helper cells on the distribution of anti-hapten antibodies in IgG, IgM and IgE classes. *J. Immunol.* **109,** 612.

KISHIMOTO T. & ISHIZAKA K. (1973a) Regulation of antibody response *in vitro*. V. Effect of carrier-specific helper cells on generation of hapten-specific memory cells of different immunoglobulin classes. *J. Immunol.* **111,** 1.

Kishimoto T. & Ishizaka K. (1973b) Regulation of antibody response *in vitro*. VI. Carrier-specific helper cells for IgG and IgE antibody response. *J. Immunol.* **111,** 720.

KISHIMOTO T. & ISHIZAKA K. (1973c) Regulation of antibody response *in vitro*. VII. Enhancing soluble factors for IgG and IgE antibody response. *J. Immunol.* **111,** 1194.

KISHIMOTO T. & ISHIZAKA K. (1974) Regulation of antibody response *in vitro*. VIII. Multiplicity of soluble factors released from carrier-specific cells. *J. Immunol.* **112,** 1685.

KISHIMOTO T. & ISHIZAKA K. (1975) Immunologic and physiocochemical properties of enchancing soluble factors for IgG and IgE antibody responses. *J. Immunol.* **114,** 1177.

KISHIMOTO T., HIRAI Y., SUEMURA M. & YAMAMURA Y. (1976) Regulation of antibody response in different immunoglobulin classes. I. Selective suppression of anti-DNP IgE antibody response by preadministration of DNP-coupled mycobacterium. *J. Immunol.* **117,** 396.

KISHIMOTO T., HIRAI Y., SUEMURA M., NAKANISHI K. & YAMAMURA Y. (1978) Regulation of antibody response in different immunoglobulin classes. IV. Properties and functions of 'IgE class-specific' suppressor factor(s) released from DNP-Mycobacterium-primed T cells. *J. Immunol.* **121,** 2106.

KOHLER P.F. (1979) Circulating immune complexes and the practising allergist. *J. Allergy clin. Immunol.* **63,** 297.

KOJIMA S. & OVARY Z. (1975a) Effect of *Nippostrongylus brasiliensis* infection on anti-hapten IgE antibody response in the mouse. I. Induction of carrier specific helper cell. *Cell. Immunol.* **15,** 274.

KOJIMA S. & OVARY Z. (1975b) Effect of *Nippostrongylus brasiliensis* infection on anti-hapten IgE antibody response in the mouse. II. Mechanism of potentiation of the IgE antibody response to a heterologous hapten–carrier conjugate. *Cell. Immunol.* **17,** 383.

KOJIMA S., KAMIJO T. & OVARY Z. (1980) Nonspecific enhancement of mouse anti-hapten IgE antibody response: Involvement of a T-cell subpopulation and its product for the potentiation. *Cell. Immunol.* **50,** 327.

LAKIN J.D., GRACE W.R. & SELL K.W. (1975a) IgE anti-polymyxin B antibody formation in a T-cell-depleted bone marrow transplant patient. *J. Allergy clin. Immunol.* **56,** 94.

LAKIN J.D., STRONG D.M. & SELL K.W. (1975b) Polymixin B reactions, IgE antibody and T cell deficiency: immunoonemical studies in a patient after bone marrow transplantation. *Ann. int. Med.* **83,** 204.

LEE W.Y. & SEHON A.H. (1977) Abrogation of reaginic antibodies with modified allergens. *Nature (Lond.),* **267,** 618.

LEE W.Y. & SEHON A.H. (1978a) Suppression of reaginic antibodies with modified allergens. I. Reduction in allergenicity of protein allergens by conjugation to polyethylene glycol. *Int. Archs. Allergy appl. Immun.* **56,** 159.

LEE W.Y. & SEHON A.H. (1978b) Suppression of reaginic antibodies with modified allergens. II. Abrogation of reaginic antibodies with allergens conjugated to polyethylene glycol. *Int. Archs. Allergy appl. Immun.* **56,** 193.

LEVINE B.B. & VAZ N.M. (1970) Effect of combinations of inbred strain, antigen and antigen dose on immune responsiveness and reagin production in the mouse. A potential mouse model for immune aspects of human atopic allergy. *Int. Archs. Allergy appl. Immun.* **39,** 156.

LEVINE B.B., STEMBER R.H. & FOTINO M. (1972) Ragweed hay fever: genetic control and linkage to HL-A haplotypes. *Science,* **178,** 1201.

LIU F.-T. & KATZ D.H. (1979) Immunological tolerance to allergenic protein determinants: a therapeutic approach for selective inhibition of IgE antibody production. *Proc. natn. Acad. Sci. (U.S.A.),* **76,** 1430.

LIU F.-T., ZINNECKER M., HAMAOKA T. & KATZ D.H. (1979a) New procedures for preparation and isolation of conjugates of proteins and a synthetic copolymer of D-amino acids and immunochemical characterization of such conjugates. *Biochemistry,* **18,** 690.

LIU F.-T., BOGOWITZ C.A., BARGATZE R.F., ZINNECKER M., KATZ L.R. & KATZ D.H. (1979b) Immunological tolerance to allergenic protein determinants: properties of tolerance induced in mice treated with conjugates of protein and a synthetic copolymer of D-glutamic acid and D-lysine (D-GL). *J. Immunol.* **123,** 2456.

LUM L.G., MUCHMORE A.V., KEREN D., DECKER J., KOSKI I., STROBER W. & BLAESE R.M. (1979) A receptor for IgA on human T lymphocytes. *J. Immunol.* **122,** 65.

MARSH D.G. & BIAS W.B. (1977) Basal serum IgE levels HLA antigen frequencies in allergic subjects. II. Studies in people sensitive to rye grass group I and ragweed antigen E and of postulated immune response (Ir) loci in the HLA region. *Immunogenetics,* **5,** 235.

MARSH D.G., GOODFRIEND L. & BIAS W.B. (1977) Basal serum IgE levels and HLA antigen frequencies in allergic subjects. I. Studies with ragweed allergen Ra3. *Immunogenetics,* **5,** 217.

MARSH D.G., BIAS W.B., HSU S.H. & GOODFRIEND L. (1973) Association of the HL-A7 cross-reacting group with a specific reaginic antibody response in allergic man. *Science,* **179,** 691.

MARSH D.G., CHASE G.A., FREIDHOFF L.R., MEYERS D.A. & BIAS W.B. (1979) Association of HLA antigens and total serum immunoglobulin E level with allergic response and failure to respond to ragweed allergen Ra_3. *Proc. natn. Acad. Sci. (U.S.A.),* **76,** 2903.

MAYRHOFER G., BAZIN H. & GOWANS J.L. (1976) Nature of cells binding anti-IgE in rats immunized with *Nippostrongylus brasiliensis*: IgE synthesis in regional nodes and concentration in mucosal mast cells. *Europ. J. Immunol.* **6,** 537.

MEACOCK S.C.R. & MARSDEN C.H. (1976) The production of IgE and IgG1 antibodies in mormal rats and rats infected with *Nippostrongylus brasiliensis*. *Immunology,* **30,** 491.

MÖLLER G. (1978) Immunoglobulin E. *Immunol. Rev.* **41,** 3.

MORETTA L., MINGARI M.C. & MORETTA A. (1979a) Human T cell subpopulations in normal and pathologic conditions. *Immunol. Rev.* **45,** 163.

MORETTA L., MINGARI M.C., MORETTA A. & COOPER M.D. (1979b) Human T lymphocyte subpopulations: studies of the mechanism by which T cells bearing Fc receptors for IgG suppress T-dependent B cell differentiation induced by pokeweed mitogen. *J. Immunol.* **122,** 984.

MOTA I. (1964) The mechanism of anaphylaxis. I. Production and biological properties of 'mast cell sensitizing' antibody. *Immunology*, **7,** 681.

MUSOKE A.J., WILLIAMS J.F. & LEID R.W. (1978) Immunological response of the rat to infection with *Taenia taeniaeformis*. VI. The role of immediate hypersensitivity in resistance to reinfection. *Immunology*, **34,** 565.

NEAUPORT-SAUTES C. & FRIDMAN W.H. (1977) Characterization of suppressive immunoglobulin-binding factor (IBF). II. Purification and molecular weight determination of IBF produced by L-5178-Y θ-positive lymphoma. *J. Immunol.* **119,** 1269.

OGILVIE B.M. (1967) Reagin-like antibodies in rats infected with the nematode parasite *Nippostrongylus brasiliensis*. *Immunology*, **12,** 13.

OGILVIE B.M. JONES V.E. (1971) *Nippostrongylus brasiliensis*. A review of immunity and the host/parasite relationship in the rat. *Exptl. Parasitol.* **29,** 138.

OKUDAIRA H. & ISHIZAKA K. (1973) Reaginic antibody formation in the mouse. III. Collaboration between hapten-specific memory cells and carrier-specific helpers cells for secondary anti-hapten antibody formation. *J. Immunol.* **111,** 1420.

OKUMURA K. & TADA. T. (1971a) Regulation of homocytotropic antibody formation in the rat. III. Effect of thymectomy and splenectomy. *J. Immunol.* **106,** 1019.

OKUMURA K. & TADA T. (1971b) Regulation of homocytotropic antibody formation in the rat. VI. Inhibitory effect of thymocytes on the homocytotropic antibody response. *J. Immunol.* **107,** 1682.

ORR T.S.C. & BLAIR A.M.J.N. (1969) Potentiated reagin response to egg albumin and conalbumin in *Nippostrongylus brasiliensis* infected rats. *Life Sci.* **8,** 1073.

ORR T.S.C., RILEY P.A. & DOE J.E. (1972) Potentiated reagin response to egg albumin in *Nippostrongylus brasiliensis* infected rats. III. Further studies on the time course of the reagin response. *Immunology*, **22,** 211.

PRYJMA J., MUNOZ J., VIRELLA G. & FUNDENBERG H.H. (1980) Evaluation of IgM, IgG, IgA, IgD and IgE secretion by human peripheral blood lymphocytes in cultures stimulated with pokeweed mitogen and *Staphylococcus aureus* cowan I. *Cell. Immunol.* **50,** 115.

REVOLTELLA R. & OVARY Z. (1969) Reaginic antibody production in different mouse strains. *Immunology*, **17,** 45.

ROUSSEAUX-PREVOST R., CAPRON M., BAZIN H. & CAPRON A. (1978) IgE in experimental schistosomiasis. II. Quantitative determination of specific IgE antibodies against *S. mansoni*: a follow-up study of two strains of infected rats. Correlation with protective immunity. *Immunology*, **35,** 33.

SADUN E.H. & GORE R.W. (1970) *Schistosoma mansoni* and *S. haematobium*: homocytotropic reagin-like antibodies in infections of man and experimental animals. *Exp. Parasitol.* **28,** 435.

SAXON A. & STEVENS R.H. (1979) Stimulation and regulation of human IgE production *in vitro* using peripheral blood lymphocytes. *Clin. Immunol. Immunopath.* **14,** 474.

SPIEGELBERG H.L., O'CONNOR R.D., SIMON R.A. & MATHISON D.A. (1979) Lymphocytes with immunoglobulin E Fc receptors in patients with atopic disorders. *J. clin. Invest.* **64,** 714.

SUEMURA M. & ISHIZAKA K. (1979) Potential of IgE response *in vitro* by T cells from rats infected with *Nippostrongylus brasiliensis*. *J. Immunol.* **123,** 918.

SUEMURA M., KISHIMOTO T., HIRAI Y. & YAMAMURA Y. (1977) Regulation of antibody responses in different immunoglobulin classes. III. *In vitro* demonstration of 'IgE class-specific' suppressor functions of DNP-mycobacterium-primed T cells and the soluble factor released from these cells. *J. Immunol.* **119,** 149.

SUEMURA M., YODOI J., HIRASHIMA M. & ISHIZAKA K. (1980) Regulatory role of IgE-binding factors from rat T lymphocytes. I. Mechanisms of enhancement of IgE response by IgE-potentiating factor. *J. Immunol.* (in press).

TADA T. (1975) Regulation of reaginic antibody formation in animals. *Progr. Allergy*, **19,** 122.

TADA T., TANIGUCHI M. & OKUMURA K. (1971) Regulation of homocytotropic antibody formation in the rat. II. Effect of X-irradiation. *J. Immunol.* **106,** 1012.

TAKATSU K. & ISHIZAKA K. (1975) Reaginic antibody formation in the mouse. VI. Suppression of IgE and IgG antibody responses to ovalbumin following the administration of high dose urea-denatured antigen. *Cell. Immunol.* **20,** 276.

TAKATSU K. & ISHIZAKA K. (1976a) Reaginic antibody formation in the mouse. VII. Induction of suppressor T cells for IgE and IgG antibody responses. *J. Immunol.* **116,** 1257.

TAKATSU K. & ISHIZAKA K. (1976b) Reaginic antibody formation in the mouse. VIII. Depression of the ongoing IgE antibody formation by suppressor T cells. *J. Immunol.* **117,** 1211.

TAKATSU K., ISHIZAKA K. & KING T.P. (1975) Immunogenic properties of modified natigen E. III. Effect of repeated injections of modified antigen on immunocompetent cells specific for native antigen. *J. Immunol.* **115,** 1469.

TANUGUCHI M. & TADA (1971) Regulation and homocytotropic antibody formation in the rat. IV. Effects of varous immunosuppressive drugs. *J. Immunol.* **107,** 579.

TANIGUCHI M. & TADA T. (1974) Regulation of homocytotropic antibody formation in the rat. X. IgT-like molecule for the induction of homocytotropic antibody response. *J. Immunol.* **113,** 1757.

TJIO A.H., HULL W.M. & GLEICH G.J. (1979) Production of human immunoglobulin E antibody *in vitro*. *J. Immunol.* **122,** 2131.

TULLIS D.C.H. (1970) Bronchial asthma associated with intestinal parasites. *New Eng. J. Med.* **282,** 370.

TUNG A.S., CHIORAZZI N. & KATZ D.H. (1978) Regulation

of IgE antibody production by serum molecules. I. Serum from complete Freund's adjuvant-immune donors suppresses irradiation-enhanced IgE production in low responder mouse strains. *J. Immunol.* **120,** 2050.

TURNER K.J., BALDO B.A. & ANDERSON H.R. (1975) Asthma in the Highlands of New Guinea. Total IgE levels and incidence of IgE antibodies to house dust mite and *Ascaris lumbricoides*. *Int. Archs. Allergy appl. Immun.* **48,** 784.

TURNER K.J., QUINN E.H. & ANDERSON H.R. (1978) Regulation of asthma by intestinal parasites. Investigation of possible mechanisms. *Immunology*, **35,** 281.

TURNER K.J., ROSMAN D.L. & O'MAHONEY J. (1974) Prevalence and familial association of atopic disease and its relationship to serum IgE levels in 1,061 school children and their families. *Int. Archs. Allergy appl. Immun.* **47,** 650.

URBAN J.F., JR. & ISHIZAKA K. (1978) IgE-B cell-generating factor from lymph node cells of rats infected with *Nippostrongylus brasiliensis*. II. Effector mechanisms of IgE-B cell-generating factor. J. Immunol. **121,** 199.

URBAN J.F., JR, ISHIZAKA T. & ISHIZAKA K. (1977a) IgE formation in the rat following infection with *Nippostrongylus brasiliensis*. II. Proliferation of IgE-bearing cells in neonatally thymectomized animals. *J. Immunol.* **118,** 1982.

URBAN J.F., JR. ISHIZAKA T & ISHIZAKA K. (1977b) IgE formation in the rat following infection with *Nippostrongylus brasiliensis*. III. Soluble factor for the generation of IgE-bearing lymphocytes. *J. Immunol.* **119,** 583.

URBAN J.F., JR, ISHIZAKA T. & ISHIZAKA K. (1978) IgE-B cell-generating factor from lymph node cells of rats infected with *Nippostrongylus brasiliensis*. I. Source of IgE-B cell-generating factor. *J. Immunol.* **121,** 192.

URBAN J.F., JR, ISHIZAKA K. & BAZIN H. (1980) IgE-B cell generating factor from lymph node cells of rats infected with *Nippostrongylus brasiliensis*. III. Regulation of factor formation by anti-immunoglobulin. *J. Immunol.* **124,** 527.

URENA V., GARCIA R., VELA C., ORTIZ F. & LAHOZ C. (1979) *In vitro* production of IgE and IgG by sensitized human peripheral lymphocytes. *Int. Archs. Allergy appl. Immun.* **59,** 135.

USUI M. & MATUHASI T. (1979) IgE-selective and antigen-specific unresponsiveness in mice. I. Induction of the unresponsiveness by administration of ovalbumin-pullulan conjugate. *J. Immunol.* **122,** 1266.

VAN DELLEN R.G. & THOMPSON J.H. (1971) Absence of intestinal parasites in asthma. *New Eng. J. Med.* **285,** 146.

VAZ E.M., VAZ N.M. & LEVINE B.B. (1971) Persistent formation of reagins in mice injected with low doses of ovalbumin. *Immunology*, **21,** 11.

WATANABE N. & OVARY Z. (1977) Suppression of IgE antibody production in SJL mice. III. Characterization of a suppressor substance extracted from normal SJL spleen cells. *J. exp. Med.* **145,** 1501.

WATANABE N. KOJIMA S. & OVARY Z. (1976) Suppression of IgE antibody production in SJL mice. I. Nonspecific suppressor T cells. *J. exp. Med.* **143,** 833.

WATANABE N., KOJIMA S., SHEN F.W. & OVARY Z. (1977) Suppression of IgE antibody production in SJL mice. II. Expression of Ly-1 antigen on helper and non-specific suppressor T cells. *J. Immunol.* **118,** 485.

WATANABE T., KIMOTO M., MARUYAMA S., KISHIMOTO T. & YAMAMURA Y. (1978) Regulation of antibody response in different immunoglobulin classes. V. Establishment of T hybrid cell line secreting IgE class-specific suppressor factor. *J. Immunol.* **121,** 2113.

DE WECK A.L., GECZY A.F. & TOFFLER O. (1977) Regulation of IgE antibody synthesis by autoanti-idiotype immunization in guinea pigs. In: *Immune System: Genetics and Regulation* (Ed. by E. E. Sercarz, L. A. Herzenberg and C. F. Fox), p. 209. Academic Press, New York.

YANG W.H., DORVAL G., OSTERLAND C.K. & GILMORE N.J. (1979) Circulating immune complexes during immunotherapy. *J. Allergy clin. Immunol.* **63,** 300.

YODOI J. & ISHIZAKA K. (1979a) Lymphocytes bearing Fc receptors for IgE. I. Presence of human and rat T lymphocytes with Fcε-receptors. *J. Immunol.* **122,** 2577.

YODOI J. & ISHIZAKA K. (1979b) Lymphocytes bearing receptors for IgE. III. Transition of FcγR(+) cells to FcεR(+) cells by IgE. *J. Immunol.* **123,** 2004.

YODOI J. & ISHIZAKA K. (1980a) Induction of Fcε-receptor bearing cells *in vitro* in human peripheral lymphocytes. *J. Immunol.* **124,** 934.

YODOI J. & ISHIZAKA K. (1980b) Lymphocytes bearing Fc-receptors for IgE. IV. Formation of IgE-binding factor by rat T lymphocytes. *J. Immunol.* **124,** 1322.

YODOI J., ISHIZAKA T. & ISHIZAKA K. (1979) Lymphocytes bearing Fc-receptors for IgE. II. Induction of Fc-receptor-bearing rat lymphocytes by IgE. *J. Immunol.* **123,** 455.