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REVIEW

THE ROLE OF ANTIBODY IN T-CELL RESPONSES

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SUMMARY

INTRODUCTION

The concept that mammalian and avian lymphocytes fall into two general domains, T and B, differing in site of differentiation, distribution, morphology, antigenicity and function (Mitchison, 1970; Playfair, 1971) initiated a new age in the fine study of the immune response. However, some of the original controversies that the resulting experiments might have been expected to settle are still as lively as ever, notably those concerning the function of the T cell in co-operation and the nature of its receptor. Added to these is the new enigma of the 'controlling' or 'suppressor' T cell. In the present paper, evidence will be marshalled for an overall hypothesis according to which many of these activities of the T cell can be explained in terms of passively acquired antibody.

I. THE T-CELL RECEPTOR

The ability of lymphocytes to bind specific antigens (Basten *et al.*, 1971) indicates the

presence of specific receptors. In the case of the B cell, all the evidence points to immunoglobulin (Ig) as the receptor (Raff, Feldmann & De Petris, 1973), but in the case of the T cell there are two rival candidates for the role: Ig and some other non-Ig receptor. In this section the pros and cons of each will be briefly summarized.

1. *Evidence in favour of Ig*

(a) *Demonstration of Ig on T cells.* It must be said at once that T cells do not appear to carry much Ig. The sensitive lactoperoxidase technique, by which surface proteins can be iodine-labelled *in situ*, has demonstrated IgM on thymus and thymus-derived cells in some hands (Marchalonis, Cone & Atwell, 1972; Cone, Sprent & Marchalonis, 1972) but not others (Vitetta *et al.*, 1972). It has also been claimed that some malignant cell lines of apparently T-cell origin carry surface Ig (Marchalonis *et al.*, 1972), the obvious objection being that malignant cells are not normal. Pure populations of 'activated' T cells from the thoracic duct (TTDL) have been found to carry Ig by immunofluorescence, but there is evidence that this may not be endogenous (Pernis *et al.*, 1973; see I, 4a), though not all workers agree, and in one experiment only antigen-induced and not mitogen-induced activation gave rise to Ig-positive T cells (Goldschneider & Cogen, 1973). The argument from specificity studies in T–B co-operation that T and B cells carry the same receptor (Schlossman, 1972) also amounts to an argument for T-cell Ig.

(b) *Blocking effects of anti-Ig.* More convincing evidence for T-cell Ig has come from the study of antigen binding by T cells, notably in the work of Greaves and his colleagues, who showed that some T cells could bind sheep red blood cells (SRBC) to form rosettes,which could be blocked by anti-Fab, anti-light chain, and occasional anti-μ chain sera (Greaves & Möller, 1970a,b). The same result has been obtained with soluble radio-labelled antigens (Roelants, Forni & Pernis, 1973a). There are claims that other expressions of T-cell recognition such as graft-versus-host (GVH) reactions (Mason & Warner, 1970; Greaves, Torrigiani & Roitt, 1969), mixed lymphocyte reactions (MLR) (Greaves, Torrigiani & Roitt, 1971), delayed hypersensitivity (DH) (Theis & Thorbecke, 1972), suicide by radioactive antigen (Basten *et al.*, 1971), and T–B cell co-operation (Lesley, Kettman & Dutton, 1971; Cheers *et al.*, 1971) can also be blocked by anti-Ig sera, but these have been contested, mainly on the grounds that anti-Ig heteroantisera may contain other anti-membrane antibodies (Nossal *et al.*, 1971), and in the case of alloantigen recognition the weight of evidence is against Ig being involved (see I, 2b).

2. *Evidence against Ig*

(a) *Failure to demonstrate Ig on T cells.* Immunofluorescent and other methods show less than 2% of Ig-positive cells in mouse thymus, and slightly more in the thymus of larger animals and birds (Vitetta, Uhr & Boyse, 1973), but these are strongly Ig-positive and are generally considered to be B cells, which might be either passing blood-borne contaminants or residing purposefully in the thymus. However their removal by passage through anti-Ig columns does not prevent the remaining cells, after subsequent 'education', being able to carry out cytotoxic reactions typical of T cells (Hudson *et al.*, 1973a), nor does removal of the Ig-positive cells alter the education (Hudson *et al.*, 1973b); thus both the precursor and the effector are not detectably Ig-positive. Moreover in the chicken, bursectomy, which does not impair T-cell responses, removes all the Ig-positive cells from blood and thymus

(Hudson, Thantrey & Roitt, 1973c). Following an immune response in mice, antibody-forming cells have been found in the thymus for many weeks (Anderson & Dresser, 1972). Taking all the above into consideration, it is hardly surprising that modest amounts of Ig are sometimes extractable from thymus-cell suspensions (Vitetta *et al.*, 1972).

(b) *Failure to block T-cell responses with anti-Ig.* Probably the most thorough of the unsuccessful attempts to block a T-cell function with anti-Ig sera is the work on GVH reactions in chickens by Simonsen's group, who discussed the problem very fully and concluded that Ig was not the receptor for this type of recognition (Crone, Koch & Simonsen, 1972). What appears to be a related finding is that cytotoxic T cells, derived from thymus and sensitized on target cell monolayers, could not be blocked in either the sensitization or the effector stage by anti-Ig sera, whilst alloantisera were highly effective (Feldmann, Cohen & Wekerle, 1972). Because of the unavoidable involvement of B cells, systems for studying the effect of antisera on T–B co-operation can never be quite so conclusive (but see I, 1b).

(c) *The Ir gene alternative.* A valuable by-product of the T–B concept has been the realization that genetic restrictions in the immune response can occur at more than one level, and there is a class of strain difference where it looks as if antibody and DH responsiveness is dictated purely by the major histocompatibility genotype of the T cells (Benacerraf & McDevitt, 1972). Whether this is a reflection of cross-reaction with self-antigens combined with T-cell tolerance (Ebringer & Davies, 1973) or a true manifestation of the T-cell receptor (Livnat, Klein & Bach, 1973) is not settled, but the latter possibility is under very active scrutiny and, if upheld, would suggest that, at least where T–B co-operation and DH are concerned, the T-cell receptor is not Ig, but rather some other structure related to H-2. Genetic mapping actually places the Immune Response (Ir) gene within the H-2 pseudolocus (Livnat *et al.*, 1973), and there is the added finding that another recognition unit, that concerned in the MLR, is also in this general region, and separate from H-2 (Festenstein *et al.*, 1972). One problem is that T-cell recognition shows definite signs of restriction at the cell level (tolerance, etc.) and no 'variable region' has yet been identified for the above-mentioned receptors; perhaps the Ir genes, like Ig, will turn out to be clonally expressed.

3. *Can the conflict be resolved?*

Accepting for the moment that the proponents of both the Ir gene concept and of T-cell Ig are right, there are two ways in which their views could be reconciled. First, there might be two separate populations of T cells, one using each type of receptor. Those involved in cytotoxic and GVH responses (see I, 2b) would be non-Ig and therefore Ir. Co-operating T cells would also be Ir (see I, 2c), leaving to the Ig receptor only the phenomena of antigen binding (see I, 1b) and conceivably some forms of DH (Theis & Thorbecke, 1972).

But there is a second possibility, namely that the basic T-cell receptor is the 'Ir gene product' and that under some circumstances T cells can acquire Ig—and therefore a second receptor—passively. This idea is far from new, but has not hitherto, to my knowledge, been followed up to its logical conclusion.

4. *Evidence for passive uptake of Ig by T cells*

(a) *Demonstration of binding of Ig to T cells.* It has been asserted that B cells carry a receptor for the Fc region of Ig while T cells do not (Basten *et al.*, 1972). However Yoshida & Andersson (1972) found binding of Ig-coated RBC to resting and cortisone-resistant thymus

cells, and especially to T cells activated against H-2 antigens. Here the numbers of positive cells were far too high to be explained by contamination with non-T cells. Aggregated Ig blocked the binding but free Ig did not, suggesting that the T cell has a receptor for altered or complexed Ig. Hudson and his colleagues have confirmed this result with H-2 activated T cells, and shown that strict depletion of B cells from the original thymus inoculum markedly reduces the number of TTDL derived from them which carry specific anti-H-2 IgM. The same group have further shown that these TTDL carry IgG of both donor and recipient allotype (Hudson *et al.*, 1973a). Thus there is good evidence that at least some of the Ig on these activated T cells is not endogenous but passively acquired. Somewhat different experiments by Lee & Paraskevas (1972) have shown binding to T cells of an IgG2a–antibody–antigen complex present 6 hr after immunization. A θ-positive lymphoma has also been shown to have a receptor for IgG (Grey, Kubo & Cerottini, 1972). The notion that T cells do not bind Ig under any circumstances must therefore be revised and cannot be used as evidence that T-cell Ig is a T-cell product.

(b) *Antigen binding by passive Ig on T cells.* Since the best evidence for T-cell Ig comes from studies of antigen binding (Greaves & Möller, 1970a,b), the idea of passive T-cell Ig logically should be tested in this system. The prediction would be that animals with T cells but no antibody would have no antigen-binding T cells, but would develop them if given passive antibody. Experiments of this kind have not always succeeded (Greaves & Möller, 1970b), but exactly the predicted result has been obtained in the agammaglobulinaemic chicken by Webb & Cooper (1973). Moreover in related experiments (Gyöngyössy & Playfair, in preparation), it was found that the presence of rosette-forming T cells (TRFC) in mice correlated precisely with that of antibody—TRFC being notably absent following the injection of glutaraldehyde-fixed SRBC, which prime T cells but stimulate little or no antibody (Dennert & Tucker, 1972)—and also that T cells incubated at 37°C no longer made rosettes, suggesting the irreversible loss of receptors (Giustino, Hudson & Roitt, 1973). The opposite result has however been obtained by Roelants and colleagues, who found that after antigen-induced loss of T-cell receptors, they spontaneously reappeared. (Roelants *et al.*, 1973b). Until this important result is confirmed in the strict absence of B cells or antibody, it cannot be considered really conclusive; moreover the technical problems involved are considerable.

Another prediction from the idea of passive T-cell Ig is that TRFC should not necessarily be restricted to a single antigen. Unfortunately the detection of double antigen binding by one cell is not always easy, even when the cell is entitled to carry Ig of more than one specificity—a macrophage, for instance (Kapp & Benacerraf, 1972). None the less, double RFC have been demonstrated, especially early in the immune response (Liacopoulos, Amstutz & Gille, 1971), and it is probable that these are T cells (Bach, personal communication). Another reservation is that some antigen binding by T cells, even of RBC, might be non-Ig-mediated, like the binding to H-2 antigens (Feldmann *et al.*, 1972), and yet go undetected in the relatively insensitive estimation of anti-Ig blocking effects, particularly as these are usually performed against the gradual fall of TRFC due to incubation alone (see above).

In summing up this section, one might say that there is ample evidence for the possibility that in many cases where T cells behave as if they carried Ig, it may have been passively acquired. The same, however, might equally well be said of RBC (Nossal *et al.*, 1971), and it remains to be shown whether the Ig is involved in any T-cell function.

II. CONTROL OF THE IMMUNE RESPONSE

Innumerable publications have been devoted to the striking effect of T cells in enhancing antibody responses and of (passive feedback) antibody in suppressing them. Indeed 5 years ago or so it was reasonable to visualize T cells and antibody as the basic 'positive and negative poles' in the homeostatic control of antibody production. However, more and more attention is now being drawn to the reverse state of this polarization—that is, the enhancement of antibody responses by antibody itself and their suppression by T cells. In this section all four situations will be appraised, with emphasis on the more recent work.

5. *Enhancement of the immune response*

(a) *Enhancement by T cells.* The detailed evidence is given in many reviews (Mitchison, 1970; Playfair, 1971; Miller *et al.*, 1971). Briefly, T-cell 'help' is needed for most IgG and some IgM antibody responses, and possibly also for memory and the increase in affinity (Gershon & Paul, 1971). Experiments carried out *in vitro* have detected the presence of several 'soluble factors', some antigen-specific and others not (Feldmann & Basten, 1972). The outstanding studies in the former category have been those of Feldmann, showing that when T cells and B cells are cultured, with antigen, in separate compartments, a co-operative response between them can be mediated by a soluble (mol. wt. 180,000) product from the T-cell compartment, acting via the surface of the macrophages, where its binding can be blocked by anti-κ and anti-μ sera (Feldmann, 1972). In view of what has been said earlier (see I, 4a) it will be appreciated that there is no proof yet that this co-operating monomeric IgM is made by the T cells rather than passively liberated from them. Elimination of all the B cells from the T cells before education would be highly desirable, but is possibly unattainable, since some IgM B-cell precursors apparently carry too little surface Ig to be removed by columns or killed by anti-Ig sera and complement (Hudson & Playfair, unpublished). Moreover it cannot be excluded that some IgM antibody is made by the lethally irradiated mice used to 'educate' the T cells.

As regards the non-antigen specific factors, they are almost embarassingly profuse, especially when tested for *in vitro*. Perhaps the most thought-provoking effects are those of allogeneic T cells, which appear to be able to override the usual need for carrier-primed T cells in carrier–hapten co-operation (Katz, 1972); these can perhaps be grouped with those of other T-cell and/or B-cell stimulants, and explained by postulating the need for a second stimulus (antigen being the first) to the B cell, of which the T cell is the usual, but not the only possible source.

(b) *Enhancement by antibody.* It is quite obvious that antibody cannot regularly increase its own production, since this would be a case of positive feedback with disastrous consequences. However in certain situations antibody does have an enhancing effect. Henry & Jerne (1968) found that a suboptimal PFC response by mice to SRBC could be enhanced ten-fold by an immediately prior injection of anti-SRBC IgM. Dennert found the same effect and showed that it coincided with an improvement in antigen localization in the spleen (Dennert, 1971). Wason also concluded that antigen localization was the key to enhancement, and showed that it did not occur *in vitro* nor in rats (Wason, 1973). Dennert however (personal communication) finds enhancement by IgM *in vitro* too. There is one report of enhancement by mouse IgG2 antibodies (Murgita & Vas, 1972), but IgG1 has uniformly produced only suppression (see II, 6a, below).

Experiments with better defined antigens have been more revealing. Pearlman showed that anti-SRBC antibody could have several effects on the response of rabbits to a hapten coupled to the SRBC; given with the antigen, IgM and to a slight extent IgG, especially in antibody excess, could enhance the anti-hapten response, though usually suppressing the response to the carrier (Pearlman, 1967). Like the other authors cited, he found small doses better at enhancing than large. The most intensive studies of anti-carrier antibodies are those of Schierman & McBride (Schierman & McBride, 1967; Schierman, Leckband & McBride, 1969), working in the chicken, where certain RBC blood group isoantigens (B locus) have the convenient property of acting as carriers for other isoantigens (A locus, etc.). Injection of allogeneic RBC incompatible at both A and B loci, in the presence of anti-B (i.e. anti-carrier antibodies) leads to suppression of the anti-B response and enhancement of that to the A isoantigen (i.e. the hapten). McBride & Schierman made the interesting proposal that a hapten is, by definition, a determinant to which no antibody has yet been formed, but can be converted into a carrier by antibody (McBride & Schierman, 1970). Enhancing effects of anti-carrier antibody have also been obtained by Pincus and colleagues to haptenic parts of Ig molecules and to DNP (Pincus, Lamm & Nussenzweig, 1971; Pincus, Miller & Nussenzweig, 1973), and by Janeway & Paul (1973) in the response to an IgG2a idiotype. However Haughton & Makela (1973) could not enhance an anti-NIP response with hyperimmune anti-carrier serum, though they did so with a supposedly anti-hapten serum which, curiously, could not be deprived of its enhancing activity by absorption with the hapten, and may therefore have been directed against 'new', and potentially 'carrier-like' determinants. Other negative results with hyperimmune serum have also been reported.

An entirely new twist has been given to the problem with the almost simultaneous discovery by McBride & Schierman (1973) and by Dennert (1973), working in their above-mentioned systems, that the enhancing effect of anti-carrier antibodies required the presence of T cells. As both authors point out, this greatly weakens the argument that the antibody merely acts to concentrate the antigen, since this concentration is apparently normal, or even increased, in thymectomized animals (Dennert, 1971; Miller & Howard, 1964). There remain two kinds of explanation: first, that the (unknown) enhancing mechanism of anti-carrier antibodies acts only on the T-cell-dependent part of the antibody response, and secondly, that it acts through the T cells. For reasons already hinted at in section I (3, 4), I believe that this latter possibility deserves serious consideration (see Sections III, IV).

(c) *Enhancement of T-cell responses.* One would like to know how far the enhancing effects discussed above for the antibody response also exert themselves on 'pure' T-cell responses. The trouble is that there is no measure of the latter remotely as clear-cut and sensitive as the PFC assay for the B-cell response, and effects of antibody such as the accelerated rejection of skin grafts (Baldamus *et al.*, 1973) or an increase in GVH splenomegaly (Batchelor & Howard, 1965) could be explained as simply additive. An effect of one kind of T cell on another, producing together a GVH response that looks more than additive, has been fully explored by Cantor and colleagues (Cantor, 1972), but the rewards so far have been chiefly in the delineation of T-cell subpopulations.

6. *Suppression of the immune response*

(a) *Suppression by antibody.* The early literature has been admirably reviewed by Uhr & Moller (1968), and there is undoubted evidence for a general homeostatic role of antibody in the antibody response; sometimes even a state resembling tolerance can be induced by the

injection of the appropriate antibody (Terman, Minden & Crowle, 1973; Thomson & Jutila, 1972). However the original belief that antibody (usually IgG) feeds back specifically (usually on IgM) purely by virtue of covering up antigenic determinants (Britton & Moller, 1968) has been undermined by more recent work. Controversy has always surrounded the question whether the whole Ig molecule or only the antigen-combining (Fab) regions are needed. Experiments *in vivo* favour the idea that the Fc region is also required. For example Sinclair has shown that whole IgG is 100–1000 times as potent in suppressing the response to SRBC as a F(ab)2 preparation of equal antigen-binding power (Sinclair, 1969), and that the difference is not simply due to a shorter half-life for the smaller fragment (Chan & Sinclair, 1971). Moreover passive antibody in suppressive doses need not prevent T-cell activation (Kappler, Hoffman & Dutton, 1971) nor antigenic competition of presumed T-cell origin (Gershon & Kondo, 1971a), and suppressive activity can be removed by absorption with spleen cells, suggesting a cytophilic role for the Fc portion (Ivanyi, 1970). In one case the suppressive antibody was IgG2, and appeared to act through macrophages, since normal peritoneal cells overcame its effect *in vivo* (Thomson & Jutila, 1972). Though the thymus-dependence of antibody-mediated suppression has not been tested for, the possibility has nevertheless been advanced that suppressive Ig requires its Fc region to bind to a T cell, and that only the much weaker effect of F(ab)2 fragments is due to antigen masking (Chan & Sinclair, 1971; Vuagnat, Neveu & Voisin, 1973). A similar result, and the same conclusion, have been arrived at with an *in vitro* model (Watson & Fitch, 1973). Other workers *in vitro*, however, have found F(ab)2 to be superior to Fab, but not inferior to whole Ig (Feldmann & Diener, 1972), but since the antigen in question (POL) is apparently non-thymus-dependent, this may be the exception that proves the rule—namely that T cells are involved in the Fc-requiring type of antibody-mediated suppression. There is a report of the suppression of IgE in rats by IgG, which did not require a full complement of T cells, since it operated after adult thymectomy (Okumura & Tada, 1971a; see II, 6b below).

Experiments with defined carrier–hapten complexes have confirmed that anti-carrier antibodies can suppress anti-hapten responses (Haughton & Makela, 1973; Vuagnat *et al.*, 1973; Hamaoka, Takatsu & Kitagawa, 1971; Tada & Okumura, 1971), which further implicates the T cell but does not distinguish between blocking of determinants on the antigen, conformational change, or 'arming' of the T cell via the Fc region. However in view of the evidence from the SRBC model (above) the latter explanation seems quite likely.

What emerges then is a picture of both specific enhancement (by IgM) and specific suppression (by IgG) with the T cell playing a central but vaguely defined role. Critical experiments are lacking at present, but an obvious one would be to study the need for the Fc region, or for cytophilic antibody, for passive suppression in mice lacking T cells.

There is also some evidence suggesting that antibody can suppress T-cell reactions, examples being the 'enhancement' of tumour or organ graft survival by antibody, or antigen–antibody complexes (Feldman, 1972) and the stimulatory effect of B-cell depletion on contact sensitivity (Turk, 1973). However in these cases the point of action of the antibody, requirement of the Fc region, etc. (see above), have not been worked out yet.

(b) *Suppression by T cells.* This new field of interest was ushered in and vigorously championed by Gershon (Gershon & Kondo, 1970) and reactions have varied from enthusiasm (Allison, Denman & Barnes, 1971) to mild scepticism (Basten & Howard, 1973; Playfair, 1973). The favourable evidence has been fully reviewed (Gershon, 1973) and will only be summarized here.

It is vital to distinguish at the outset between specific and non-specific effects. Much of the data is of the kind where removal of T cells leads to an increased antibody response or addition of T cells to a reduced one, the effect being easier to detect when there is not concomitant T-cell help. For instance, anti-thymocyte serum can cause an increased PFC response to Type 3 *Pneumococcus* polysaccharide (S3), a T-independent antigen (Baker *et al.*, 1970); the argument that this is a direct effect of the antiserum on B cells is weakened by the demonstration that it fails to work in the T-cell-less 'nude' mouse (Baker *et al.*, 1973). Similarly, adult thymectomy increases many T-cell-independent antibody responses (Kerbel & Eidinger, 1971), and also the thymus-dependent IgE response of rats to DNP coupled to *Ascaris* extracts (Okumura & Tada, 1971b). Some cases of antigenic competition appear to be due to a suppressive factor produced by, or under the influence of, T cells (Gershon & Kondo, 1971a). In GVH reactions by parental T cells in F1 hosts, addition of F1 thymocytes can reduce the GVH, suggesting a 'shut-off' action of T cells on other T cells (Gershon *et al.*, 1972). Droege has found a bursa-dependent thymus cell population in chickens with immunosuppressive effects upon transfer to normal birds (Droege, 1971). Despite some failures to repeat them (Basten & Howard, 1973), these and similar experiments do suggest that T cells can be responsible, either directly or indirectly, for the non-specific inhibition of various stages of the immune response, which is not too surprising when one thinks of their cytotoxic powers or the many soluble factors ('lymphokines') they are thought to produce (Dumonde *et al.*, 1969).

In a quite different category however, are the cases in which the suppressive effect of T cells is claimed to be antigen-specific, since these, if true, cannot be shrugged off by invoking lymphokines or toxic factors. In retrospect, the first such claim dates from 1968, when Horiuchi & Waksman (1968) found that injection of antigen into the thymus of rats led to 'whole-animal' tolerance. Ha and Waksman (1973) have recently shown that thymus cells from tolerant animals can transfer specific tolerance to normal rats, not due to antigen carry-over; only the delayed and Arthus reactions were affected, and not PCA reactions (IgG1 and IgE). Shortly afterwards, Gershon introduced the term 'infectious tolerance' to describe the phenomenon of tolerant T-cell populations inhibiting normal populations, in his case in the IgG response to SRBC (Gershon & Kondo, 1971b). In the IgE anti-DNP–*Ascaris* model mentioned above, *Ascaris* (carrier) primed thymocytes were able to counteract the increase in the IgE response caused by X-irradiation or splenectomy, but BSA–DNP-(hapten)-primed thymocytes were not (Okumura & Tada, 1971b). And Droege's suppressive chicken thymus cells (see above) can also transfer specific unresponsiveness if antigen is given with them (Droege, 1973). Another example of T cells specifically inhibiting DH has been reported by Asherson and his colleagues. Mice can be prevented from mounting a DH skin response to picryl chloride by prior injection of picryl sulphonic acid, and θ-positive cells from the lymph nodes of these suppressed mice can overcome the response of simultaneously transferred normal cells in irradiated recipients (Zembala & Asherson, 1973). Three special cases where T cells also appear to inhibit the production of particular antibodies are the allotype-suppression model (Herzenberg *et al.*, 1973), and the suppression of autoantibody in NZB (Allison *et al.*, 1971) and A/Jax mice (Teague & Friou, 1969).

Thus there is plenty of evidence for suppression associated with T cells though little agreement as to which subclass is most readily suppressed—unlike the situation with passive antibody, where IgM is apparently the easiest. Nevertheless, one objection often raised is that suppressive antibody, being predominantly IgG1 (see II, 6a) and therefore T cell-dependent,

could be mistaken for an actual T-cell product. Special attention is therefore merited by those models where serum antibody is either absent (Gershon *et al.*, 1972) or ineffective. However, the possibility of cell-bound antibody (Ivanyi, 1970; see II, 6a) being transferred with, or on, the T cells has not generally been gone into. One experimental approach that has given preliminary but promising results is the injection of specific antibody to the donors of 'educated' T spleen cells, just before transferring the cells and testing their helper effect on a SRBC by normal bone marrow cells. When early (IgM ?) antibody is used, there is an increase in the IgM response (Playfair, Marshall-Clarke & Hudson, 1974), but with later antibody (IgG) there is a decrease; both effects need the presence of T cells in the transferred spleen (Playfair, in preparation). The IgG response is much less affected and it may be that the mechanism of enhancement and suppression is different for IgM and IgG. Alternatively the right conditions for antibody-mediated suppression of IgG responses via T cells may not yet have been found.

III. SUMMARY

Before attempting to interpret them, I will summarize what seem to me the essential points from the previous two sections. In the present very incomplete state of the evidence, it is profitless to try and fit every single observation neatly into an overall scheme, but any such scheme, to be valid, would probably have to accommodate the following facts: (1) binding of some antigens by T cells involves Ig (I, 1b); (2) T cells need not carry detectable Ig in order to respond to some antigens, such as alloantigens (I, 2a and 2b); (3) T cells, especially if activated, can bind Ig, and through this, antigen (I, 4a and 4b); (4) antibody production can be enhanced both by T cells and by IgM antibodies in the presence of T cells (II, 5a and 5b); (5) antibody production can be specifically suppressed both by T cells and by IgG antibodies which may be cytophilic (II, 6a and 6b); (6) some T-cell responses can themselves be enhanced or suppressed by antibody (II, 6a) and by T cells (II, 5c, 6b).

IV. HYPOTHESIS

Listed in the above form, the facts tempt one towards a simple hypothesis: namely that antigen binding, enhancement of antibody production, and suppression of antibody production, can all be mediated by passively-acquired Ig on the surface of T cells. Ig need not therefore be made by T cells but only by B cells. In this section, some of the possibilities and limitations of such a hypothesis are briefly explored.

7. *Some implications and predictions*

(a) *Carriers and haptens.* In most cases of T–B-cell co-operation, the T cell recognizes the carrier and the B cell the hapten. If the T-cell recognition is via passive Ig, this must be made by a B cell, and if the T cell cannot get started until this Ig is made, it must be made by a non-T cell-dependent B cell. There is some evidence for such cells (Playfair & Purves, 1971) and I would predict that, in general, antigens that can stimulate these IgM-only 'B1' cells—for instance antigens that nude mice respond to—should turn out to be good carriers, since they should induce useful amounts of T-cell IgM 'enhancing' antibody. A hapten, by definition, would be a determinant that could not do this, unless the antibody is provided from elsewhere, which is virtually a restatement of McBride & Schierman's proposal (see II, 5b).

Fig. 1 gives an outline of the hypothesis as it relates to carrier and hapten and the two kinds of B cell.

(b) *T-cell activation and specificity.* An important reservation to the previous statement is that T cells may need to be activated in order to utilize the anti-carrier antibody (see I, 4a). Thus a good B1-cell-stimulating antigen that failed to stimulate T cells would not be a good carrier (S3 may be an example); nor would an antigen that stimulated T cells but no antibody; in this case one might expect a brief effect, provided antibody was made available in time. In other words, the production of fully-fledged carrier-primed T cells may be a two-step process (Fig. 2). It is certainly true that one of the best carriers in mice, KLH, is a potent T-cell stimulator and a good T-cell independent antigen. It would obviously be easy to check whether this correlation held for other carriers.

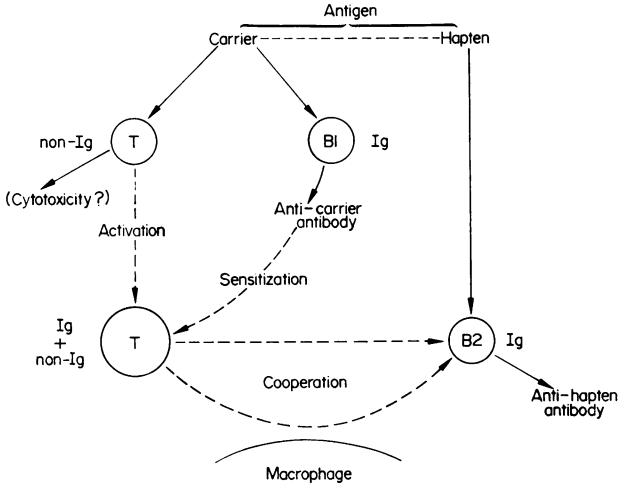

FIG. 1. T–B-cell co-operation by cytophilic anti-carrier antibody.

If T cells do need prior activation, a vital question is whether they need to be activated by the same antigen (i.e. the carrier), or whether any kind of activation will do. In the latter case, the better the activation, presumably, the better the uptake of Ig and the better the co-operation. The very potent effect of allogenic T cells—the 'allogeneic effect' (Katz, 1972)—could be cited in favour of this idea. However, many experiments of T-cell activation for co-operation show that, though not as antigen-specific as might be expected (but see I, 1a), it is not completely non-specific either (Playfair & Marshall-Clarke, 1973; Falkoff & Kettman, 1972). This might mean that not every activated T cell can make use of a particular specificity of anti-carrier antibody. This is very hard to explain purely in terms of an Fc receptor, and would imply a role for antigen—that is, complexes—as well, with a recognition of antigenic determinants (like that postulated for the non-Ig receptor in the H-2 system, see I, 2b) and another recognition of the Fc portion of the antibody. Alternatively, antigen could first be bound by the non-Ig receptor, binding antibody and, in turn, further antigen (Fig. 3). This 'multiplication of entities' may offend Occam, but there is some vague evidence in its favour; for instance the enhancing effect of anti-carrier antibody in chickens is said not to work in carrier-tolerant birds (McBride & Schierman, 1973), and mouse T cells tolerant

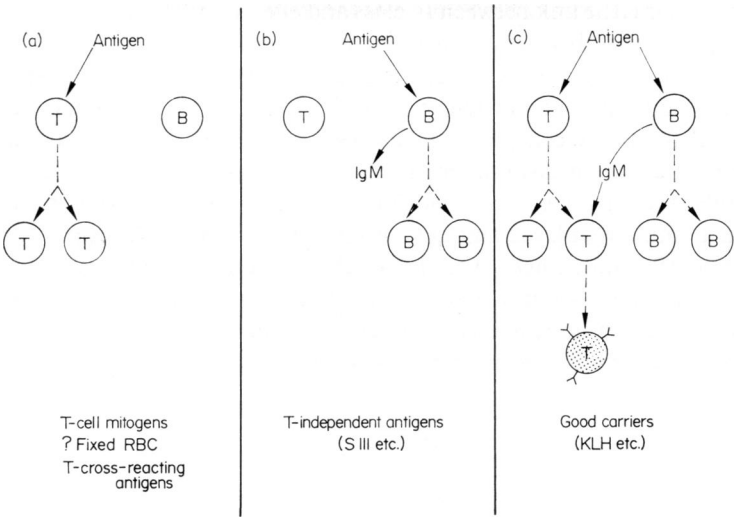

FIG. 2. Generation of carrier-primed T cells as a two-step process (c), involving both T-cell activation (a) and antibody production (b). Some typical stimulants are listed under each type of response.

to chicken globulin but coated with this antigen in the form of anti-lymphocyte antibodies do not act as carrier-primed cells (Miller *et al.*, 1971). It would be interesting to know whether the complexes described by Lee & Paraskevas (1972) bind equally well to tolerant T cells.

(c) *Ig classes and feedback*. It is only in the case of IgM that the situation is anywhere near clear enough to construct a tentative model. Fig. 4 illustrates the concept that passive feedback by IgG and by T cells are aspects of the same mechanism, as are enhancement by IgM and by T cells. It could be, of course, that despite their similarities these twin pairs of phenomena are really quite unrelated. The suppression of IgE may resemble that for IgM, but it is not clear what suppresses IgG. Perhaps there is a special final 'shut off' subclass (Thomson & Jutila, 1972), or it may not be so much a question of subclass as of affinity.

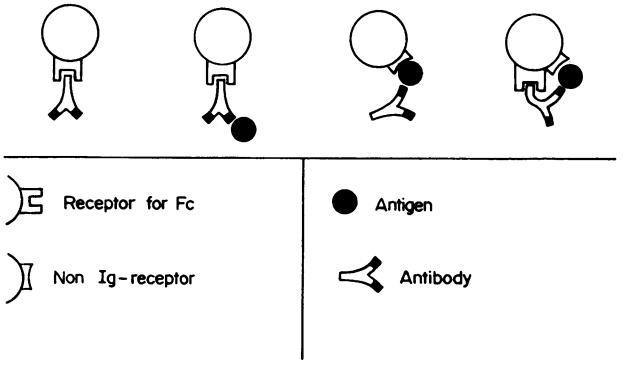

FIG. 3. Possible configurations for antibody and antigen passively bound to T cells.

But if the Fc receptor is the link between Ig class and effector cell (as in the case of mast cells), there is the further question whether all activated T cells express the same Fc receptors, or whether the effector activity of the T cell is linked to its Fc receptor: IgM-recognizing T cells being mainly stimulators and IgG-recognizing ones mainly suppressors. This kind of 'clonal selection' for the T-cell product has been suggested, for quite other reasons, by Talmage (personal communication). One might even go as far as to visualize mast cells and basophils as IgE-recognizing cells atavistically related to T cells (Burnet & Holmes, 1964).

If it is borne in mind that large amounts of IgG can suppress IgM even without the need for the Fc region (Sinclair, 1969)—i.e. presumably by acting directly on the antigen or the B cell—and also that the number of activated T cells available at various times in the immune response may not be constant, it will be realised that even the control of IgM production must be vastly more complicated than Fig. 4 suggests.

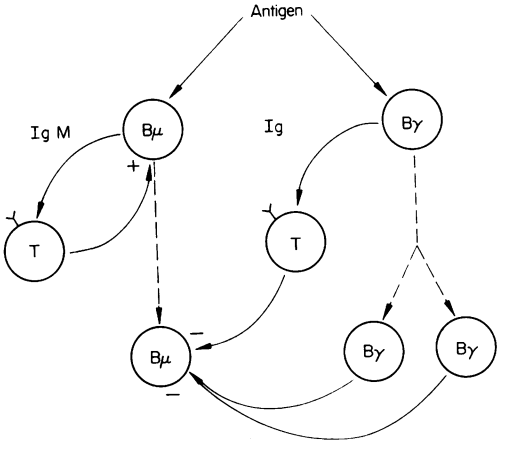

FIG. 4. A scheme for the enhancement and suppression of IgM production by antibody and T cells. The passage of time is from top to bottom. In the secondary response there would be more T and Bγ cells. In this figure the distinction between anti-carrier and anti-hapten antibodies is not shown (but see Fig 1).

8. *Some objections*

Though I do not know of any data that flatly contradicts the whole hypothesis, there are a number of observations that certainly do not fit in.

(a) Antigen-activated TDL can become Ig-positive *in vitro*, but not only by picking up Ig from the serum used in the culture, though they do this too (Goldschneider & Cogen, 1973). However unless all B cells are removed beforehand, they remain a possible source of Ig; indeed, the failure of the T cells to develop Ig after mitogen stimulation rather suggests that it is the activation of the B cells that is the essential step.

(b) Secondary DH responses in bursectomized agammaglobulinaemic chickens are inhibited by rabbit-anti-chicken Ig sera given to the birds before the antigen (Theis & Thorbecke, 1972). Here the major reservation is probably the specificity of the antiserum; the demonstration that chicken serum absorbs out the inhibitory factor does not entirely rule out its being directed against non-Ig membrane antigens that also circulate free in the

serum. Another possibility is that the special Ig responsible for DH is not completely bursa-dependent, and if it is cytophilic it might not normally be detectable in the serum.

(c) T-cell education for co-operation *in vitro* is not prevented by removal of Ig-positive B cells (Kontianen & Feldmann, 1973) nor by the use of T cells from agammaglobulinaemic chickens (Weinbaum, Gilmour & Thorbecke, 1973). One explanation is given in section II, 5a; another is that only the non-Ig activation step may be achieved at this stage (Fig. 2a), the anti-carrier antibody being made by the same B-cell population that makes the anti-hapten antibody. Use of a carrier-tolerant B-cell population would be the correct control here.

(d) After antigen-induced loss of Ig receptors on T cells, they spontaneously re-appear on incubation (Roelants *et al.*, 1973). My objection is mentioned in section I, 4b.

(e) IgE in rats is specifically suppressed by IgG even in the absence of 'suppressor' T cells (Okumura & Tada, 1971a). However this was not only anti-carrier but also anti-hapten antibody, and the requirement for the Fc region was not tested. It may therefore be due to one of the non-T cell-mediated feedback mechanisms (section II, 6a).

(f) Judged by the concentrations of free hapten required to inhibit rosette formation by hapten-coated RBC, the affinity of spleen B-cell receptors increases with time after immunization, while that of spleen T-cell receptors does not (Moller & Makela, 1972). This certainly suggests that T cells do not continually refurnish themselves with Ig from the B cells. However, after a second immunization, T-cell receptor affinity is substantially increased, indicating a possible relationship to antibody affinity. As the authors point out, a change in receptor density can cause confusion in this system.

(g) Low-zone tolerance to BSA in mice can be accompanied by apparently normal anti-BSA antibodies, yet it is apparently as specific as antibody (Rajewsky, Brenig & Melchers, 1972). The implication is that the missing receptor in tolerance is T-cell Ig only, suggesting that it is not automatically acquired from B cells. It is crucial in this case to be sure that the tolerant T cells are absent, and not merely blocked by a particular kind of specific antibody. There is also the remote possibility that there is also low-zone tolerance of a special class of Ig whose absence goes undetected in this experiment (Taussig, 1973). None the less, this finding, if confirmed, is difficult to reconcile with the present hypothesis.

(h) The IgM response to S3 is apparently suppressible by T cells (Section II, 6b). Yet S3 does not activate T cells (Kruger & Gershon, 1972) nor does it usually induce IgG (Basten & Howard, 1973). Therefore suppression by IgG on activated T cells seems doubly improbable. At first sight this is a serious objection to the model shown in Fig. 4. However three points are worth making. Firstly, the T-cell suppression of S3 IgM has not yet been shown to be antigen-specific, and therefore need not involve Ig at all; conversely its antibody-mediated suppression may not involve the T cells (section II, 6a). Secondly, there is the curious observation that S3 as a carrier is able to inhibit IgG responses to a hapten (Basten & Howard, 1973); that is, the opposite way round to the usual Ig class effect. In other ways, too, individual T-independent antigens seem to be a law unto themselves (Basten & Howard, 1973). Thirdly, in the preliminary experiments with educated T cells and passive antibody mentioned above (Section II, 6b), I have found that T cells not activated with antigen, but passively sensitized with IgM antibody, seem to specifically inhibit IgG. Perhaps this is somehow analogous to the situation with S3, but at present speculation beyond this point would be rather perilous, and the possibility is raised in the spirit of the whole hypothesis outlined in this paper—that is, to suggest where further experimental attention might be directed.

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