Autoantibodies in infertility: current opinion

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Historical notes

The concept of autoimmune-related infertility has remained controversial. Traditionally, abnormal autoimmune function has been implicated as a contributing factor to female as well as male infertility. In the female, abnormal autoimmunity primarily relates to autoantibody activity against ovarian tissue components, whereas in the male, abnormal autoimmunity, believed to be clinically relevant, is mostly directed against the spermatozoon itself.

Historically, abnormal autoimmune function has been seen as a rather organ-specific process in both female and male infertility, with either ovarian or testicular antigens as the primary targets. In recent years it has, however, also been recognized that additional, and possibly less organ-specific, processes of autoimmune nature may play a role. For example, female infertility patients have demonstrated a significantly higher incidence of non-organ-specific autoantibody abnormalities. The incidence of such autoantibody abnormalities appears to be positively correlated to increasing intractability of infertility (Gleicher et al., 1993). On the other hand, there is doubt as to whether such non-organ-specific autoantibodies themselves cause disease or only serve as epiphenomena for a still undefined immunological defect which causes infertility (Gleicher, 1994).

Lastly, the newly evolving field of neuroimmunology needs to be considered here. Since reproductive function is under neuroendocrine control, autoimmune processes that affect the hypothalamic–pituitary–gonadal axis at the central nervous system (CNS) level will have considerable impact on infertility.

This review will therefore report on autoimmune abnormalities at CNS and gonadal levels and on non-organ-specific abnormalities systemically. It will also separate female from male findings since they are usually distinct, though both can often be found in a single couple presenting with an infertility problem.

The autoantigens and autoantibodies

In the female

Premature ovarian failure

The most clearly defined condition of autoimmune-associated infertility is premature ovarian failure, defined as the cessation of menses due to failing ovaries before the age of 40 years and consequently increased peripheral gonadotrophin levels (Blumenfeld et al., 1993). Its incidence is poorly defined but it has been estimated to occur in 2–10% of women with amenorrhoea and in 1–3% of females in the general population, with autoimmune abnormalities being detectable in up to 66% of cases (Cohen and Speroff, 1991). This observation formed the basis for the current understanding that a large percentage of premature ovarian failure cases are due to an autoimmune aetiology. Premature ovarian failure has thus been associated with rheumatoid arthritis, myasthenia gravis, candida endocrinopathy, pseudoparathyroidism, Addison’s disease and, especially, thyroid disorders (Cohen and Speroff, 1991). Antithyroid antibodies can be found in approximately one-third of premature ovarian failure patients, based on rather dated studies (Coulam, 1982). One can therefore assume that with current assay techniques, which have significantly greater sensitivity, an even greater percentage of premature ovarian failure patients would be positive for antithyroid antibodies. Premature ovarian failure can also be part of the multiple autoimmune endocrine deficiency syndrome. It is therefore not surprising that Addison’s disease can be...
diagnosed in up to 20% of premature ovarian failure patients (Cohen and Speroff, 1991).

Specific autoantigens which elicit abnormal autoimmune responses within the ovary have so far not been identified in the human. Circulating antibodies in ovarian tissue have been widely reported (Cohen and Speroff, 1991). Detection methods, however, also vary widely. The alleged association of premature ovarian failure with a variety of non-specific antiovigain antibodies therefore needs to be viewed with some caution. Especially the validity of an alleged association with generic antibodies to zona pellucida seems questionable. More interesting observations suggest that the observed antiovigain activity may be geared at gonadotrophin receptors (Chiauzzi et al., 1982; Tang and Farman, 1983). This was also suggested by Moncayo et al. (1989) who reported antibody activity against the unoccupied luteinizing hormone (LH)/human chorionic gonadotrophin (HCG) receptor as well as the hormone–receptor complex of the bovine corpus luteum. Such antiovigain activity was especially prevalent in infertile women and in women with polyendocrinopathy. Unfortunately, the authors did not investigate women with premature ovarian failure.

The investigation of autoantibodies may be severely hampered by the fact that premature ovarian failure represents an end-stage of disease. By the time a woman is diagnosed, she has by definition exhausted her follicular supply and, presumably, also the target antigen for the autoimmune attack on her ovary. Attempts to identify target autoantigens may therefore be futile and investigations may have to focus on disease stages that precede premature ovarian failure.

Unfortunately, only relatively little is known on the precursor stages to autoimmune-induced premature ovarian failure. Some authors have suggested that the so-called resistant ovary syndrome represents such a precursor stage. In resistant ovary syndrome, the ovary still contains follicles, though they are highly resistant to stimulation by gonadotrophins (Blumenfeld et al., 1993). Whether antibody activity to gonadotrophin receptor-related epitopes is present in women with resistant ovary syndrome is at best questionable. Since we were unable to demonstrate autoimmune differences between women with and without resistance to stimulation in a well-defined infertility population (Gleicher et al., 1994), we doubt the concept of resistant ovary syndrome as a precursor stage to premature ovarian failure. Von Weissenbruch et al. (1991) suggested that an immunoglobulin (lg)G fraction can block ovarian granulosa cell growth in vitro and thus potentially in vivo contribute to the occurrence of resistant ovary syndrome. Blumenfeld et al. (1993) reported an astonishing 40% conception rate in premature ovarian failure patients treated with routine ovulation induction and non-specific immunosuppression with corticosteroids. They suggested that their treatment rescued follicles in immunologically induced resistant ovary syndrome patients on the way to premature ovarian failure.

Autoimmune oophoritis has quite clearly been established as a precursor lesion to premature ovarian failure (Biscotti et al., 1989). Unfortunately, this condition, at least in its clinical manifestation, is rare and therefore cannot be seen as the universal precursor. In mouse models, thymectomy has been shown to induce an autoimmune oophoritis (Miyake et al., 1988; Smith et al., 1991). Moreover, oophoritis can be transferred to young mouse recipients and the disease can be prevented by reconstitution with normal adult spleen cells. The effector cells are CD4+, and transfer of oophoritis can be abrogated by an antibody to CD4 (but not a CD8 antibody). Smith et al. (1991) speculated that an endogenous ovarian antigen may be required to activate effector T-cells; however, they were unable to substantiate the claim of others that suppressor cells are normally specific for ovarian antigen. Miyake et al. (1988) reported in their mouse model that oophoritis was characterized by the presence of circulating antibodies to ooplasm, zona pellucida and/or steroid-producing cells within the ovary. Interestingly, mice in this model also developed gastritis with accompanying antibodies. Kenneth Tung’s group (Smith et al., 1992) also demonstrated the connection between oophoritis and gastric autoimmune disease (gastritis) by showing that neonatal splenocytes, neonatal thymocytes, or phenotypically mature adult thymocytes, transferred from normal BALB/c mice to syngeneic athymic nu/nu (or SCID) mice, caused autoimmune oophoritis and gastritis with corresponding serum autoantibodies in the recipient in 73% of animals. CD4+ neonatal spleen cells and CD4+CD8− adult thymocytes were required for the induction of autoimmune disease.

Rhim et al. (1992), from the same research group, were also able to induce ovarian autoimmunity with a 15 amino acid ZP3 peptide (Cys-Ser-Asn-Ser-Ser-Ser-Ser-Glu-Phe-Ile-Gly-Pro-Arg). ZP3 is the sperm-binding site of the zona pellucida. The peptide induced T-cell as well as antibody responses. However, adoptive transfer of CD4+ T-cells in this mouse model caused oophoritis without an antibody response to the zona. This observation suggests that the T-cell response, rather than the autoantibody response, may have primacy in this model, a fact further suggested by the finding that peptides of as little as eight amino acids (Asn-Ser-Ser-Ser-Ser-Glu-Phe-Glu) caused oophoritis but not an antibody response. These
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investigations also suggested that, due to the similarity of the ZP3 protein in mouse and human (67% homology) a similar process may be involved in human premature ovarian failure.

Histological findings compatible with oophoritis, changes in total T-cell counts, as well as autoantibody abnormalities have been widely reported in women afflicted by premature ovarian failure (Cohen and Speroff, 1991; Nelson et al., 1991). Hill et al. (1990) suggested that the induction of class II major histocompatibility complex antigen expression in human granulosa cells by interferon-γ may contribute to the process of premature ovarian failure. Coulam and Stern (1991) concluded that all of the immunological findings described above and the increased prevalence of HLA DR3 in women with premature ovarian failure strongly support a cytokine-mediated autoimmune aetiology for at least some cases.

Unexplained infertility and endometriosis

Unexplained infertility and endometriosis, generally considered distinct clinical entities, in our opinion represent a continuum of disease, classically associated with a significant level of autoantibody abnormalities. It would exceed the framework of this review to explain in detail all the scientific data in support of our statement. For this purpose the reader is referred to another review (Gleicher et al., 1993). A multitude of immunological studies strongly suggest that a broadly based activation of the immune system is responsible for both of these clinical conditions. As also previously described in conjunction with premature ovarian failure, this immunological profile is characterized by autoantibody abnormalities, especially in naturally occurring non-organ-specific autoantibody groupings. We have therefore raised the question whether endometriosis does not represent a classical autoimmune disease (Gleicher et al., 1987).

Concomitantly, both patient groups also demonstrate (similar to premature ovarian failure patients) a remarkably broad spectrum of T-cell abnormalities. Moreover, antibody and cellular abnormalities can be seen in both conditions locally within the peritoneum as well as systemically (Gleicher et al., 1989; Hill and Anderson, 1989; Confino et al., 1990).

The incidence of such immunological abnormalities increases in infertile women in direct correlation to the intractability of their condition. Since in-vitro fertilization (IVF) generally represents the final treatment option, one could expect the highest incidence of immunological abnormalities amongst IVF patients. This is, in fact, the case, as reported by us and confirmed by a variety of other investigators (El Roeiy et al., 1987; Fisch et al., 1991; Birkenfeld et al., 1994; Gleicher et al., 1994). Therefore a considerable percentage of women with intractable infertility demonstrate an abnormal immunological profile which, at least in part, is characterized by autoantibody abnormalities. In a recent study we demonstrated that infertile women also exhibit a high incidence of other immunological abnormalities, usually associated with classical autoimmune diseases, such as monoclonal and polyclonal gammapathies, IgA deficiency and abnormalities in IgG subclasses (N.Gleicher et al., unpublished observations).

Whether these abnormalities of immune function are causally related to infertility has not yet been determined. We have been able to demonstrate that a reduction in abnormal autoantibody levels in women with endometriosis appears to improve fecundity (El Roeiy et al., 1988). A similar observation has been reported in IVF patients (Dmowski et al., 1995). Lastly, while traditional textbooks do not associate classical autoimmune diseases with infertility, a recent study of women with rheumatoid arthritis does exactly that (Lee Nelson et al., 1993). Older studies, which failed to demonstrate such an association, are of exceedingly poor quality; thus at this point abnormal (auto)immune function may be (causally) associated with decreased fecundity in females.

Pregnancy loss

Immunological pregnancy loss also represents a form of infertility, and recurrent pregnancy loss was the first clinical condition to be associated with abnormal autoimmune function. An initial association was made with the presence of lupus anticoagulant, which was later expanded to phospholipid antibodies, and especially anticardiolipin antibody (Gleicher et al., 1993). Our understanding differs from that of many of our colleagues working in this area.

Considerable evidence suggests that the presence of certain non-organ- and organ-specific autoantibodies is predictive of an increased miscarriage risk. As noted before, antiphospholipid antibodies, and especially antibodies to cardiolipin, were initially implicated amongst non-organ-specific antibodies. Since then, some authors have argued that cardiolipin, as a primarily intracellular epitope, may not be the best target for an immune response and that some cell membrane-based phospholipids may, at least on a theoretical basis, be better candidates as epitopes that initiate an antibody response. Amongst those, antibodies to phosphatidylycerine have been most often mentioned (Rote et al., 1990).
A number of published studies have exclusively investigated anticardiolipin responses in patients who repeatedly abort or are at risk of doing so. However, even those investigators who have argued against cardiolipin as the ‘ideal’ epitope for investigation, have usually only concentrated on one additional antiphospholipid, namely antiphosphatidylserine. A few researchers, and ourselves, have argued that the arbitrary selection of one or two antiphospholipid specificities simply does not make sense, neither clinically nor from a conceptual immunological viewpoint. Such an approach could be equated to attempts to diagnose systemic lupus erythematosus (SLE) simply through one single antibody test (Gleicher et al., 1993).

Most rheumatologists would argue that such an approach to SLE would be clinically naive and immunologically unsound since SLE, similar to most other autoimmune conditions, does not represent a monoclonal event. Yet those same investigators pursue exactly such a course of action in autoimmune-associated reproductive failure.

In contrast, we have advocated for many years the concept of autoimmune-associated pregnancy loss as a polyclonal event, which therefore requires a much more broadly based immunological evaluation. The reader may have noticed that this review only refers to autoimmune-associated pregnancy loss, rather than autoimmune-caused pregnancy loss. Our opinion represents that of a minority insofar as we have reached the conclusion that a direct autoantibody-mediated process is probably not the cause of repeated pregnancy loss (Gleicher, 1994). This view is based on many conflicting observations that have been reported in the literature. On the one hand Shoenfeld’s group has been able to develop an animal model for cardiolipin antibody-induced pregnancy loss (and, incidentally, infertility), an observation that potentially suggests a direct antibody effect (Bakimer et al., 1992). On the other hand, it is very difficult to understand, at least on a theoretical basis, how such vastly different autoantibody specificities such as non-organ-specific antiphospholipid antibodies and organ-specific antithyroid antibodies, both independent risk markers for pregnancy loss, can be responsible for basically the same processes that lead to pregnancy loss (Gleicher et al., 1989; Pratt et al., 1993).

Recent data, moreover, also suggested that the clinical activity of antiphospholipid antibodies was largely restricted to those specificities that were only detectable with a co-factor (B2-glycoprotein I)-dependent assay system (Matsuura et al., 1992). We have demonstrated that, although a co-factor-dependent single assay was superior to a co-factor-independent single assay, a broadly based panel of co-factor-independent assays is at least as sensitive in detecting the immunological abnormality associated with reproductive failure. Once again, these non-specific findings suggest that autoantibodies serve as an epiphenomenon rather than as a direct pathogen (Aoki et al., 1995a).

Christiansen (1996) in a recent review came to similar conclusions. He suggests that the frequent occurrence of autoantibodies in women with recurrent pregnancy loss is due to a T_{H1} response against the trophoblast. Lim et al. (1996), in a recent review, remain without an opinion about the mechanism by which autoantibodies contribute to pregnancy loss. However, their paper represented a wide-ranging survey of the various theories of immunological pregnancy loss rather than a focused description of a possible pathophysiology.

An all-encompassing hypothesis might conclude that the presence of autoantibody abnormalities represents only an epiphenomenon, characteristic of an overall activation of the immune function (Gleicher, 1994). Such a generalized activation of the immune system is not uncommon in patients with classical autoimmune diseases and has been repeatedly described in women with immunologically associated infertility as well as pregnancy loss (Gleicher et al., 1993). We demonstrated that women who present for infertility treatment demonstrate the same increased incidence of monoclonal and polyclonal gammapathies, selective IgA deficiency and IgG subclass abnormalities as patients with classical autoimmune diseases (N. Gleicher et al., unpublished observations). Moreover, we were able to demonstrate that habitually aborting women, even prior to their miscarriage, demonstrate an elevated level of natural killer (NK) cell activity (Aoki et al., 1995b). All of these observations point toward an immunological defect at the T-cell level which, as is also postulated in classical autoimmune diseases, may manifest itself in abnormal autoantibody production in addition to many other epiphenomena.

We thus currently postulate that autoimmune-associated reproductive failure in the female, whether in conjunction with infertility or repeated pregnancy loss, represents a likelihood of a T-cell defect, the nature of which has so far not been determined. Since some of the previously noted infertility-associated conditions, such as endometriosis, are familial and may be linked to the presence of certain HLA loci, a contributing genetic factor is likely (Gleicher et al., 1993). What triggers the expression of such a genetic predisposition and its manifestation as reproductive failure is undetermined. Considering an apparent increase in this phenomenon, it would be tempting to speculate that an infectious agent may be the culprit.
**In the male**

Autoimmune reproductive failure in the male is even more controversial. The classically defined autoimmune aetiology of male reproductive failure is the presence of antibodies to spermatozoa. However, as in the female, autoimmune processes can also affect the gonads and in this case cause orchitis.

Autoimmune orchitis has been comprehensively reviewed by Mahi-Brown (1994). Various animal models and limited human experience have led to the current opinion that this condition, in analogy to female oophoritis, is a T-cell-mediated condition regulated by immunological factors under genetic control.

As with oophoritis, CD4+ positive T-cells appear to play a crucial role in inducing and suppressing the disease, at least in animal models. Since in men the antigen causing the initial insult is usually unknown, little is also known about the aetiology and pathophysiology of this condition in humans. Not even the presence of antibodies to testicular components in the circulation is informative. These antibodies may represent a response to severe tissue injury rather than be a cause of disease, since orchitis is (similar to oophoritis) usually only diagnosed in advanced stages. It has been suggested that molecular mimicry, with an infectious agent, carrying shared epitopes with testicular tissues, could be a contributing factor. However, as with autoimmune oophoritis, no significant progress in our understanding of the condition in the human seems likely unless the disease-inducing antigens can be identified (Mahi-Brown, 1994).

Even though autoimmune orchitis is clearly a cause of male infertility, it is often overlooked, even in authoritative reviews (Howard, 1995; Skakkebaek, 1994). This is at least partially due to the fact that the true incidence of the condition in men is not known (Mahi-Brown, 1994). Histological examination of affected testes reveal immunoglobulin deposits which correlate in density to the severity of the disease. Orchitis can also be focal in nature, demonstrating considerable infiltrates by monocytes, thus resembling animal models actively immunized with testis homogenates (Mahi-Brown, 1994).

Orchitis not infrequently follows viral infection, with mumps representing the most frequent and best investigated association. A cross-reactivity between salivary gland and testicular antigens has been suggested (Mahi-Brown, 1994), not dissimilar to the proposed cross-reactivity between thyroid and ovarian antigens in females, resulting in a high degree of antithyroid antibodies in women with premature ovarian failure (Cohen and Speroff, 1991; Coulam and Stern, 1991). However, the majority of orchitis cases have no known aetiology and, in contrast to animals, vasectomy in men does not lead to orchitis (Mahi-Brown, 1994).

**Sperm antibodies**

Antisperm antibodies represent an autoimmune response against a variety of tissue-specific sperm antigens which are not present during embryonic life, when self-tolerance develops, since spermatogenesis is not initiated until puberty. Autoimmunity to sperm antigens is therefore avoided through the prevention of their exposure to immunoreactive cell populations. As comprehensively reviewed by Bronson and Fusi (1994), antisperm autoimmunity will be generated if the blood–testis barrier between Sertoli cells is breached. Such an event can take place as a consequence of a variety of traumatic, infectious or unknown insults.

To what extent antisperm antibodies cause infertility has remained controversial. Antibody activity to spermatozoa has been demonstrated in males and in females. In females it obviously does not represent an autoimmune event. The clinical significance of antisperm antibodies has, however, remained controversial in both genders. There appears to be a consensus that antisperm activity in males has to reach higher titres than in the female to be considered clinically significant. Since this review addresses only autoantibodies, further discussion of antisperm immunity will concentrate on the male.

Considerable data from both human and animal experiences suggest that antisperm antibodies can affect fertility in a variety of ways. Mechanisms that can affect the fertility potential of a male include a effect on sperm transport, sperm capacitation and acrosome reaction, sperm–egg interaction and, lastly, a possible systemic effect under which the presence of antisperm antibodies is only reflective of a general immune activation and thus represents only one amongst many, possibly non-specific, responses.

With regard to sperm transport, investigations have suggested that the spermatozoa’s capability to pass through the cervical mucus is affected if spermatozoa are coated by sperm antibodies. Both IgA and IgG antibody isotypes appear capable of this inhibition. Complement-mediated sperm immobilization, in contrast, appears to be mediated by IgG and IgM antisperm antibodies (Bronson and Fusi, 1994).

Spermatozoa must undergo capacitation and acrosome reaction before being able to fuse with the zona pellucida of the oocyte in the first step of the fertilization process. It has been suggested that some antisperm antibodies can induce a premature acrosome reaction, thus shortening the life
span of available spermatozoa for fertilization. In contrast, other antisperm antibodies, especially in various animal models, have been shown to block the acrosome reaction and thus prevent fertilization.

Sperm–egg interaction has in recent years been quite well investigated. In various animal models sperm antibodies have been able to prevent sperm binding to zona pellucida-based receptors. In the human model the data have remained controversial. While some authors have suggested that fertilization is impaired in the presence of antisperm antibodies, many have demonstrated exactly the opposite. Human data are primarily derived from clinical IVF experiences which cannot always be equated with in-vivo conditions.

Polyclonal autoimmune activation may also result in production of sperm antibodies. We were able to demonstrate this indirectly by showing that individuals with significant sperm antibody levels concomitantly demonstrated a significant degree of non-organ-specific autoantibody abnormalities. More importantly, however, we were also able to demonstrate that mouse antisperm antibodies which were able to inhibit fertilization, were completely cross-reactive with some nonorgan-specific autoantibodies. This observation has led to the conclusion that some antisperm antibodies and at least some classical non-organ-specific autoantibodies can inhibit the fertilization process in identical fashion (Gleicher et al., 1993; Saling et al., 1985).

Neuroimmunology

Increasingly, immune and endocrine systems are seen as an intertwined web of signals and responses, mediated by often identical messengers of information. Nowhere is this more apparent than in the fields of neuroendocrinology and neuroimmunology. Reichlin (1993) exhaustively reviewed the topic. Without being able to address all those interactions in detail within the framework presented here, the following will be a brief summary of the most salient points.

Hyperprolactinaemia

Prolactin, produced by lactotrope cells within the anterior pituitary, is a hormone of major importance for reproductive processes of both female and male. Hyperprolactinaemia in the female can directly affect ovulation and probably also implantation. In the male, semen quality can be affected. Hyperprolactinaemia represents an extremely common finding in women but is seen much less frequently in males with infertility problems. Its effect on immune function in general and on autoimmune function in particular has been reviewed (Rabin, 1994). Prolactin enhances antibody production and, as expected, hypophysectomy equally suppresses the production of antibodies. Bromocriptine, which effectively suppresses prolactin production, exerts a similar effect on antibodies as does a hypophysectomy, while either prolactin or the administration of growth hormone appears able to induce antibody production. Treatment with bromocriptine also ameliorates experimental autoimmune encephalitis (Riskind et al., 1992).

The high incidence of hyperprolactinaemia in women with infertility problems, which mimics the presence of significant autoimmune abnormalities in this population (Gleicher 1993), suggests that hyperprolactinaemia may affect fecundity not only by affecting ovulation and implantation through hormonal but also through immunological processes. This hypothesis obviously requires a scientific confirmation.

Gonadotrophins

Autoimmunity to gonadotrophins has been suggested by a number of authors, though the whole concept has remained controversial. As previously noted in this review, gonadal failure in the female could be caused by antigonadotrophic activity by autoantibodies. This issue has also repeatedly entered the literature in reference to the exogenous administration of gonadotrophic drugs, which represents standard therapy for most infertility couples (Jones and Toner, 1993). Observational studies in treated patients have suggested that with increasing numbers of stimulation cycles, increasing dosages of medication may be required. This increasing resistance to stimulation by gonadotrophins has been attributed to the development of autoantibodies to gonadotrophins. Convincing evidence that such autoantibodies do exist is lacking.

Autoimmunity to gonadal hormones was suggested ~15 years ago when some authors reported the induction of anti-oestrogenic autoantibodies after oral contraceptive use. The presence of such antibodies has never been confirmed.

A recent symposium on microcontraception also failed to report on the occurrence of any significant autoimmune responses with newer generations of contraceptives (Anank Kumar, 1997).

Gonadal hormones do, however, exert considerable effects on the immune system and can greatly affect autoimmune conditions. It would exceed the framework of this review to describe those any further. The interested reader is therefore referred to the recent review by Reichlin (1993).
Clinical utility and conclusions

Autoantibodies that have been associated with infertility are often non-specific to the disease state, and, if specific, are often unidentified and are never produced in response to a presently known antigen. The clinical utilization of autoantibodies for diagnostic purposes is currently very limited and restricted to a number of research centres. This should be considered when clinical decisions are made based on antibody data reviewed here or reported elsewhere in the literature. Furthermore, antibody assay systems are often laboratory-produced, and inter-assay variability between laboratories can be considerable (Peaceman et al., 1992). It is therefore important to be familiar with the individual techniques utilized by laboratories that supply autoantibody results to clinical practitioners and it is crucial to choose reputable laboratories. A very detailed critical review on this topic has been published (Gleicher, 1993).

References


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