

edited by S. ISOJIMA
& W. D. BILLINGTON

**REPRODUCTIVE
IMMUNOLOGY
1983**

REPRODUCTIVE IMMUNOLOGY 1983

Proceedings of the 2nd International Congress of Reproductive
Immunology held in Kyoto, Japan, on 17-20 August, 1983

Editors

S. Isojima

and

W.D. Billington



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FOREWORD

This volume documents the invited lectures, symposium presentations, round-table discussion themes and workshop topics that constituted the 2nd International Congress of Reproductive Immunology held as the 2nd Congress of the International Society for Immunology of Reproduction. The abstracts of the papers presented in all sessions and workshops have been published separately in a special supplement of the Journal of Reproductive Immunology (1983).

We believe that the Congress marked a turning point in this fertile field of scientific and clinical endeavour. Representatives from 23 nations made up a total of over 350 participants who met at the Kyoto International Conference Hall from 17-20 August, 1983, to present and discuss their work on all the different aspects of the subject. The overall level of debate was high and much of the current dogma was aggressively questioned, in some cases for the first time. The result was a clearer appreciation of what can be accepted and what needs to be pursued further. There should now be optimism that the next few years will see significant advances in several important areas of reproductive immunology, perhaps especially in the dissection of spermatozoal antigens and anti-sperm antibody responses using monoclonal antibody probes, the biochemistry of zona pellucida and trophoblast membrane antigens, the immunoregulatory agents in pregnancy, the aetiology of pregnancy disorders and the use of hormone analogues and antibodies for regulation of reproductive processes, with genetic engineering being applied in at least some of these areas.

The newly-elected Executive Council of the I.S.I.R. under the presidency of Professor R.E. Billingham have undertaken a commitment to stimulate and co-ordinate the efforts of reproductive immunologists world-wide by continuing the series of triennial International Congresses, advising and assisting national societies in the organization of meetings, disseminating information by regular circulation of Newsletters and by monitoring the publication of the Proceedings of relevant Symposia. A number of sub-committees chaired by members of the Executive Council have been established for this purpose.

The Local Organizing Committee of the Kyoto Congress (Y. Nishikawa, S. Isojima, T. Hamaoka, A. Iritani, J. Ishigami and H. Mohri) wish to take this opportunity to express their gratitude to the councillors of the I.S.I.R. for their valuable advice and help and to the Japan World Exposition Commemorative Fund, Japan Pharmaceutical Association, Research Foundation of Hyogo

Medical College and the numerous pharmaceutical companies and personal contributors for their generous financial support. It was their understanding and interest that made the organization of the Congress possible.

Finally, we would like to record our appreciation of Dr. Koji Koyama, Miss Maki Yoshida and Miss Fusako Tamaki for their devoted and tireless support in the organization of the Congress and in the compilation of material for these Proceedings.

Shinzo Isojima
David Billington

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OPENING ADDRESS

REPRODUCTIVE IMMUNOLOGY - HISTORICAL ROOTS, ACHIEVEMENTS AND PROSPECTS

KIRIL BRATANOV* (Sofia, Bulgaria)

President of the International Society of Immunology of
Reproduction and of the International Coordination Committee
for Immunology of Reproduction

Mr. Chairman, Dear Colleagues,
Ladies and Gentlemen,

On behalf of the Executive Council of the International Society of Immunology of Reproduction and of the International Coordination Committee for Immunology of Reproduction I have the high privilege and the honor of extending heartfelt greetings to all participants and guests and particularly to the organizers of the 2nd International Congress of Reproductive Immunology, taking place in the ancient capital of Japan - Kyoto, worldknown for her splendid cultural monuments built throughout many ages. We are happy to enjoy the warm hospitality of the people of Japan - the Land of the Rising Sun, the country of Shibasabiro Kitasato (1852-1931) who discovered (jointly with Behring) the antitetanus and antidiphtheria antitoxins and laid the foundations of sero-immunotherapy, giving a mighty impetus also to the further development of fundamental immunology.

After these words of salute I shall proceed with a brief survey of the more significant moments in the development of Reproductive Immunology - the fascinating marginal field of medico-biological sciences which deals with the immunological factors in reproduction of animals and man and with the immunological means that could keep up and control this most important life-sustaining process. This field of experimental and clinical

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research emerged from the non-infectious immunology and is closely associated with immunoembryology, transplantation immunology, oncoimmunology and immunogenetics.

IMMUNOGENICITY AND ANTIGENIC STRUCTURE OF GAMETES AND OTHER COMPONENTS OF THE REPRODUCTIVE TRACT

The fact of the immunogenicity of the male gamete came to be known in the process of the experimental verification of Metchnikoff's teaching on cytotoxins. In 1899, studying the role of macrophages in the resorption of spermatozoa introduced in the peritoneal cavity of test-animals, Metchnikoff established that the injection of xenogenic sperm into rabbits and guinea pigs renders their serum and peritoneal fluid "spermotoxic", i.e. sperm-agglutinating and sperm-immobilizing. At the very same time Landsteiner (1899) communicates that the peritoneal fluid of guinea pigs, injected repeatedly with bull sperm, immobilized spermatozoa of the same species. The consequent exhaustive work of Metchnikoff (1900) on the spermotoxin and antispermotoxin and especially of Metalnikoff (1900) who developed fundamentally the ideas of his teacher, stimulated other authors' research on this topic. Moxter (1900) from the Laboratory of Robert Koch studied the species-specificity of spermotoxins; Farnum (1901), Straube (1902), Pfeiffer (1903) and others encountered spermoprecipitins in rabbits immunized with heterogenic or allogenic testis tissue or sperm. And Adler (1909) demonstrated in guinea pigs the formation of autospermotoxins.

It was the detection of the ABO iso-group antigens in spermatozoa (Landsteiner & Levine, 1926) that revived the interest to the immunological behavior to the male gamete, and for a long time thereafter many investigators were inclined to seek correlation between the "unexplained" (idiopathic) infertility and the ABO-incompatibility among partners in married couples. This proved to be true as regards the Rh-system, but had no connection with spermatozoa since the presence of the D antigen on these cells was not confirmed. Yet, blood group antigens, as well as histocompatibility antigens on human spermatozoa, discovered later, continued to be a focus of attention with respect to their significance as genetic markers (Edwards et al., 1964; Boettcher, 1965, 1967). It was found that the A and B antigens of AB-men

were situated in different spermatozoa (Gullbring, 1957; Shahani & Southam, 1962), and a method for the separation of the two spermatozoal population from AB ejaculates was demonstrated (Popivanov & Vulchanov, 1962).

Here it should be specially emphasized that the further work on the identification, purification and characterization of spermatozoal antigens would have been impossible without the pioneer contributions of Voisin et al. who elaborated the first model of autoimmune aspermatogenic orchitis as early as 1951. And in the late sixties the first in-vitro model for continuous study of the immunological interaction between human spermatozoa and somatic cells in culture was introduced (Tribulev et al., 1967). Detailed studies were made on the species- and organ-specificity of human spermatozoa (Popivanov & Vulchanov, 1961; Vulchanov & Popivanov, 1967) including their immunological cross-reactivity with other body's antigenic components, parasites and microorganisms. The results of these and other fundamental and laboratory clinical studies on sperm immunization proved their worth later in the assay of spermatozoal antigens looked upon as candidates for anticonceptive immunogens.

Quite different and considerably more recent is the record of our knowledge of the antigenic structure of the female gamete. And no need of stating special reasons for that: while sperm cells are available in enormous quantities outside the male organism, the oocytes (in higher vertebrates) are inaccessible unless artificially detached from the female organism. The earlier studies on the antigenicity and specificity of the total ovary or its components (Lewis, 1934; Victorov, 1936; Isojima et al., 1959; and others) were a good orientation for the further fundamental research on the very oocyte (Shivers et al., 1964; Matoušek, 1965; Edwards, 1969; Oikawa et al., 1973; Jilek & Pavlock, 1975; Lopata et al., 1976, and others) that laid the solid basis for extensive work on the identification and characterization of the antigens associated with the ovum: the antigens in the follicular fluid, in the cumulus and corona cells, in the zona pellucida and on the egg surface. Of utmost interest proved to be the zona antigens (Hartman & Gwatkin, 1971; Oikawa et al., 1974) in connection with the attempts at developing an anticonceptive vaccine (Shivers, 1976). And lately a model of autoimmune oophoritis was elaborated (Jancović et al., 1980).

The immunology and immunochemistry of reproductive hormones, emerging with the studies of Bussard (1948), was introduced in relation to fertility control mainly through the work of Shanta Rao (1958, 1964, 1968). Hayashida (1963) demonstrated inhibition of spermiogenesis, prostate and seminal vesicle development in normal animals with antigonadotropic hormone serum. The antigenicity of the luteinizing hormone, the trophoblast chorionic gonadotropin and the chorionic somato-mammo-gonadotropin acquired considerable importance in the search of endocrine fertility-regulation agents after the late sixties (Laurence & Ishikawa, 1968; Stevens et al., 1970-73; Mougdal et al., 1971; Talwar, 1974; and other more recent authors).

Besides hormone proteins, other defined proteins of human placenta, namely the pregnancy-specific β 1-glycoprotein (SP₁) and the placental protein (PP₅) as well as the placental proteins functioning as enzymes, were characterized (Bohn, 1971, 1972, 1975). The "embryonic placenta-specific antigens" - ESPA₁₋₃ (Kehayov et al., 1978) are also being under assay.

In the immunology of adnexory sexual glands, following the pioneer exhaustive studies of Shulman et al. 1963, 1965, 1967; Chernishov, 1969, 1970; Ablin et al., 1970 and others) there appeared recently data on the identification of a "prostatic specific antigen in human cancer" (Kuryama et al., 1980; Papsidero et al., 1980) and of an "adenoma prostatae specific antigen" (Bratanov et al., 1980; Vulchanov et al., 1982).

THE ROLE OF IMMUNOLOGICAL FACTORS IN REPRODUCTION

It is remarkable, indeed, that the first experimental evidence about the significance of spermotoxins in reproduction was communicated in 1901 by a lady - Miss C. de Leslie, working under the guidance of Metchnikoff in Paris. She established that the injecting of mice with guinea pig spermotoxic serum induced infertility lasting 20 days. Savini (1911), Venema (1916), Dittler (1920) and other investigators succeeded in inducing reversible infertility (up to 29 weeks) in female rabbits by repeated injections with homologous sperm. Guyer (1922), McCartney (1923), Kennedy (1926), Fogelson (1926) and others produced sperm-antibody and testicular necrosis in male rabbits, guinea pigs and rats by injecting them with homologous or heterologous testis homogenates

or spermatozoa. Pomeranke (1926) demonstrated that under such conditions of immunization the vaginal secretion of rabbits acquires also spermotoxicity. Ten years later the detection of spermoantibodies in the sera of infertile women (Szanto, 1936) marks the first speculation on the eventual clinical importance of iso-sperm-immunization in women. There are no data of the fate of the "non-specific spermotoxic vaccine" to induce temporary sterility in women, as patented by Baskin (1937), which lacked experimental grounding.

In 1948 we investigated the effect of immune speroagglutinins on the reproduction capacity of farm animals (cattle, sheep, goats, horses, dogs). In cows it was found that sperm-agglutinating titres in the oestral uterine secretions were much higher in those animals which had to be inseminated or mated by the sire several times in comparison with the titres on non-inseminated or such which had been inseminated (mated) 1-2 times. The conception rate of sexually mature animals (cows, sheep and rabbits) which were preliminarily immunized with homologous sperm was considerably reduced. For the first time low-titre natural spermoagglutinins were demonstrated in the sera of heifers and in male animals of the above-mentioned species (Bratanov et al., 1949).

And, five years later, the demonstration of auto-spermoagglutinins in the sera of infertile men with extreme oligospermia or azoospermia or with induced spermostasis by ligation of vas deferens (Rümke, 1954; Wilson, 1954) emphasized the casual connection between testis lesions - penetration of spermatozoa in blood circulation - and the resulting autosperm-antigenicity. This discovery and the exhaustive subsequent studies of Rümke et coll. and other authors on the incidence of sperm-antibodies in infertile men and women, mark the era of the suddenly increased clinical interest to reproductive immunology.

Meanwhile, a number of experimental studies elucidated the phenomena observed in humans. Menge et al. (1962) obtained decreased fertility of cattle and rabbits inseminated with semen treated with antibodies produced against semen, spermatozoa and erythrocytes. Mancini et al. (1965) induced immune aspermatogenesis by treatment of the testis with various non-immune factors. Eyquem et al. (1967) demonstrated the prevention of pregnancy in baboons (up to 3 years) by s.c. and intracervical immunization with human

semen, following up the antisperm response by several tests. Isojima et al. (1968) made a detailed analysis of the sperm-immobilizing factor in the sera of women with unexplained sterility and recommended a method for its detection.

It is not the object of this brief historical overview to cover all the further steps of experimental and laboratory-clinical studies which elucidated the humoral and cellular iso-/allo-/ or autoimmune reactivity of the male and female organism to the antigens of the reproductive tract. An amazing circumstance has to be noted, however. In the late sixties reproductive immunology suddenly entered a phase of intensive and extensive development. It was not only the new methodology of immunochemistry, cytoimmunology and molecular genetics that had been recently introduced. There was something far more substantial: the acute demands of life were calling forth and imposing definite problematics of reproductive immunology. It had been globally realized that in some parts of our planet human fertility was progressively decreasing, despite the favourable life conditions, while in other parts the immensely increasing rate of reproduction was leading to overpopulation with all its consequences. In economics the problem of lowering fertility or infertility in farm animals (considered in association with the environmental pollution by industrialization) was looked upon with deep concern, especially with regards to the growing demands for protein sources. So, reproductive immunology had to take two firm directions of development:

1. elaboration of methods for efficient immunodiagnostics, immunoprophylaxis and immunotherapy of the etiologically "unexplained" (but in fact immunologically-conditioned) infertility in humans and in farm animals, as well as development of immunological techniques for increasing animal productivity;

2. finding of approaches to safe and effective fertility-regulation based on specifically directed (selective) action of the immune mechanisms within the reproductive system, and developing of harmless longlasting vaccines which could be used in humans on the principle of individual free choice accorded with medical indications.

With time it appeared that the screening of the immunological consequences of contraception achieved by other methods, e.g.

vasectomy (Zappi et al., 1970; Alexander, 1975; Tung, 1976) or tubectomy, oral anticonceptives and various other devices (see Edwards, 1976), also demanded the methodology and the interpretative competence of reproductive immunology.

Along with the pursue of these practical goals, fundamental research in reproductive immunology revealed a number of problems as the immunogenetics of gametes (Boettcher, 1967; Vojtiškova, 1969, 1972; Erickson, 1972; and others), the intimate mechanism of the local immune response in the genital tract, the possibilities for sex ratio modulation, and others.

IMMUNOLOGICAL MOTHER /FOETUS INTERACTION AND IMMUNOREGULATION OF THE REPRODUCTIVE PROCESS

Immunology is immensely indebted to Owen (1945) for his unique observation on the immunogenetical consequences of vascular anastomoses between the placentae of dizygotic bovine twins. Erythrocyte himerism, detected later also in humans by Dunsford et al. (1953), and the phenomena of tolerance were brilliantly interpreted and elucidated experimentally in two independent and simultaneously published investigations on different species' models. Billingham, Brent and Medawar (1953) obtained actively acquired tolerance of foreign /A/ cells in CBA mice by injecting (intrauterinely) CBA embryos with A splenocytes, achieving survival of A-skin grafts in the mice grown from the same embryos. Hašek (1953), on the other hand, working with his model of parabiosis between embryos of two different chicken breeds (with experimental sinchorial anastomoses of the blood circulations of the two embryos) also induced specific tolerance in the grown-partners of the parabiont couple.

Many aspects of the immunological mother / placenta / foetus interrelations were elucidated. Sokolovskaya (1953) established the selective permeability of zona pellucida and emphasized its immunological function in the system of hemato-genital barriers. Volkova (1955, 1958, 1968) experimentally focussed the immunological problem of tissue rejection and parturition, elaborating later a model (jointly with Vyazov) of the hemolytic disease of the newborn in *Papio hamadryas*. Billingham (1964), considering full-term placenta as a type of homograft that has remained healthy and intact for approximately nine months, suggested that a great deal could be

learned about transplantation if the mechanism responsible for the successful placental graft were understood. With the deepening of our knowledge of the immunology of pregnancy and the hematomplacental barrier; of the antigenic topography of the trophoblast and the interaction of antibodies and cells with surface antigens; of the immunological privilege resulting from the endocrine activity of trophoblast in-vivo; of the lymphocytes' participation in immune reactions during pregnancy; and of many other facets of mother/foetus interrelations, the concept of the foetus as a semiallogenic graft finds more and more confirmations. Here specially should be mentioned the brilliant contributions of Kirby (1964, 1968) who passed away so early, and the exhaustive research of Billington (1964) and Faulk (1971) on postimplantation placental antigens, and the model studies of Voisin (1978) on the types of immune responses of the mother to the foetus.

Here it would not be possible to hint at another aspects of mother/foetus interrelations, i.e. the immunology of the intrauterine differentiation and development of the foetus itself. This is rather the object of immunoembryology. We have to mention, however the detection and the study of the so called "stage-specific antigens" in the embryo (Vyazov, 1951, 1962), of the carcino-embryonic antigen (Abelev, 1963) and of the phase-specificity and expression of certain enzymes (Holleman & Palmer, 1972) which exhibited broad biological and immunopathological validity. Taken in their connection with the classical finding of Hirschfeld & Halber (1932) that in the species limits embryonic tissues are antigenically more related with tumour tissues than with tissues of adults, these data represent another link between reproductive immunology and immunooncology

The immuno-regulatory (modulating) mechanisms in pregnancy have been and still are the object of multifacets experimental and clinical research. Speaking of immuno-modulation, I am quite tempted to mention here how we proceeded in the era before the immunological mother/foetus relations were understood. In our sheep x goat hybridization (Bratanov & Dikov, 1952, 1959), attributing the constant embryonic mortality to the strong interspecies incompatibility, after many fruitless efforts, we succeeded in obtaining hybrids (ovides and caprides, depending on the mother) by changing the donor species' spermatozoal coating with such of the recipient

species, e.g. before inseminating the sheep, goat spermatozoa were exhaustively washed and then treated with ram seminal plasma (see also Bratanov, 1968). When one thinks of today's vast progress in overcoming immunological incompatibility, the new horizons seem quite optimistic. Concerning immunosuppression applied in the cases of early abortions, as well as in immunologically-conditioned infecundability, good results have been obtained with corticosteroids. Lately, attention is being attracted by the so called "natural immunosuppressive molecules" - still incompletely defined structures or compounds isolated from various parts of the genital tract - uteroglobin, transglutaminase, pregnancy-zone protein and others, acting as modulators on different levels. Besides in the obstetrics-gynecological clinic, immunosuppressive agents are especially needed in the practice of embryo-transfer in farm animals, the survival rate being at present still under 50% despite the impeccable surgical or non-surgical implantation technique.

The other arm of the immunoregulation curve - the immunostimulation - being aimed at activating the immune mechanisms, especially those acting locally within the reproductive tract, is achieved by various immunogens derived from gametes (spermatozoa fractions, zona pellucida) and different components of the reproductive tract, including reproductive hormones. Still, it cannot be stated with certainty that an anticonceptive immunogen has been found to be completely devoid of crossed immunoreactivity with some of the body's antigenic or haptenic determinants. In this respect the experimental work on the possible use of artificial (synthetic) immunogens with no analogues in nature (Petrov, 1980) is looked upon with hopes. The durability of anticonceptive vaccines is also a matter of further research.

Very closely related to the immunological mother/foetus interaction is the subsequent early post-natal phase of lactation. The phenomena of transmission of immune protection from the mother to offspring through colostrum and milk, which contain concentrated secretory IgA and milkborn T-lymphocytes; the autoimmunization of the mother against her own lacto-proteins in cases of nipple lesions; the cases of allergization of the suckling infant with respect to cow milk proteins; the approaches to desensitization in milk allergy - all these items outline a new chapter of reproductive immunology with both clinical and theoretical importance. I