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HYPOTHESIS

Is There a Maternally Induced Immunological Imprinting Phase à la Konrad Lorenz?

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In mammals, IgG antibodies are transferred from mothers to the offspring. Since these maternal antibodies result mainly from thymus-dependent immune responses which have undergone immune maturation through somatic hypermutations, they represent the highest quality of the collective maternal immunological experience. Maternal antibodies not only confer passive immunity as long as the newborn's immune system has not fully developed, but also exert an active stimulation as indicated by their regulatory influence on isotype expression, long-term idiotypic alterations, determination of the adult B and T cell repertoire, induction of antigen reactive IgM as well as an affinity enhancement of a proportion of early primary antibodies. The fact that several of these features can only be induced during limited sensitive periods shortly after birth is reminiscent of the behavioural imprinting as defined by Konrad Lorenz. We therefore propose that during early ontogeny there is an immunological imprinting phase with characteristics analogous to behavioural imprinting: (i) the internal imprinting effect is induced by external signals, (ii) in contrast to normal learning, immunological imprinting is also only possible during certain development phases and (iii) it is characterised by an (almost) irreversible result. Hence, if particular immunological experiences are only possible during such sensitive phases, maternal immunoglobulins and consequently the mother's immunological experience is of prime importance for the start of the ontogenetic development of the immune system.

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On the whole, IgG antibodies are the products of thymus-dependent immune responses and as such they mirror the successful interaction of the immune system with the world of external antigens. This process is characterized by an immune maturation which is brought about by somatic hypermutation in the immunoglobulin variable regions and in this way improves the quality of these humoral effector molecules. In mammals, IgG antibodies are transferred from the mother to the offspring either before birth via the placenta and/or after birth with the colostrum and the milk [1], and even in birds [2, 3] and fishes [4] antibodies are transferred to the next generation with the egg yolk. In mammals as well as in birds, there is overwhelming support for the view that these maternal antibodies provide passive protection to the newborns as long as their own immune system has not fully developed. Hence, maternal immunization can be utilized to increase the neonatal antibody titers which protect the offspring against environmental pathogens such as bacterial infections [5–7], bacterial intoxication [8–10] or a variety of viral diseases [11] caused for instance by respiratory syncytial virus (RSV) [12], rotavirus [13], influenza virus [14–16], haemorrhagic fever renal syndrome virus [17], reovirus [18] or poliovirus [19]. Moreover, even tumor immunity can be transferred from immunized female mice to the offspring [20–22]. Collectively, these observations provide the basis for a maternal vaccination which is already widely practiced in veterinary medicine [23, 24], and also in humans, mothers may be vaccinated with the aim to protect their babies against certain infectious diseases [7–9, 19, 25]. Other indirect observations also support the conception that maternal antibodies mediate passive immunity to the F1 generation, e.g. (i) an insufficient amount of maternal antibodies in preterm infants causes a higher risk of bacterial infections [26], (ii) the frequency and severity of infections with RSV is inversely correlated with the titer of the maternal anti-RSV antibodies [12, 27, 28], and (iii) when children suffer from severe streptococcus B infections it has been observed that their mothers had reduced IgG1, 2 and 3 serum levels [29].

MATERNAL IMMUNIZATION CONFERS MORE THAN PASSIVE PROTECTION ONLY

Maternal antibodies do not only confer passive protection, but may in addition influence the developing immune system of the newborn in such a way that antigen-induced immune responses may seemingly be suppressed or can be enhanced. Since the 1940s until present, it has been reported that antibody responses at an early age in the offspring of immunized mothers are suppressed and that this suppression is mediated by passively acquired maternal antibodies [30–36]. However, this suppression is transient in nature and affects apparently mainly the antibody response [31, 33, 37], while for instance the generation of delayed type hypersensitivity (DTH) effector cells and memory cells is not impaired, thus enabling normal secondary responses [38]. Consequently, this misleading suppression mediated by the maternal antibodies can be overcome by a second immunization [39] or by increasing the antigen dose of the primary vaccination [40].

More importantly, it has been observed that maternal immunization, e.g. with either pneumococcal polysaccharide [41], *Plasmodium berghei* [42] or DNA [43] can cause a significantly stronger response to the respective antigens in the offspring. The latter investigation led to the conclusion that the enhanced anti-DNA immune response in the offspring was most likely mediated by maternal antibodies, while the involvement of carrier protein, nucleoprotein and adjuvant transferred from the immunized dams could be excluded [44]. The authors even denied the possibility that immune complexes formed with residual undetectable maternal antibodies might have been responsible for the enhanced anti-DNA response [44]. Moreover, it has been observed that the postnatal transfer of a neutralizing monoclonal antibody which reacted with the F-glycoprotein (F-gp) of respiratory syncytial virus, sensitized the offspring in such a way that a *primary* immunization after weaning with the purified RSV F-gp resulted in a *secondary* type of immune response with the formation of virus-neutralizing antibodies [45]. This indicates that maternal antibodies are able to exert an active stimulatory influence on the nascent immune system of the newborns. Interestingly, even a *carrier*-priming of female mice with bovine serum albumin (BSA) mediated a typical secondary anti*hapten* immune response in the offspring when these were first primed with the hapten 2,4-dinitrophenyl (DNP) coupled to the *non*crossreactive carrier chicken gamma globulin (DNP-CGG) at an age of 3 months, and received a challenge with DNP-BSA 6 weeks later [46]. This allowed the conclusion that the carrier protein sensitivity was transferred from the mother to the fetus.

The observed immunomodulatory effects of a maternal immunization have mainly been attributed to an active pre- or neonatal immunization by maternally derived antigen [8, 9, 47]. However, this assumption is difficult to reconcile with the observations that firstly, the maternal effects are generally long-lasting and are still operative when maternal antibodies are not any longer detectable in the serum [46–48], secondly when an antigen-free, maternally derived monoclonal anti-F-gp antibody primed the young mice for a secondary immune response [45] and thirdly when maternal immunization may lead to the appearance of only immunoglobulin IgM antibodies without a switch to immunoglobulin IgG [49]. Hence, proceeding from the assumption that the maternal immune system is indeed able to influence the immunological capacity in the offspring, the question arises whether this can really only be achieved by maternally derived antigen itself. If so, any experimentally induced primary antigenic stimulus in the offspring of immunized dams will in fact give rise to a secondary immune response. Alternatively, one has to ask whether antigen-free maternal antibodies – like anti-F-gp [45] or anti-DNA [44] – can induce a preactivation in the nascent immune system of the newborn, altering thereby the starting conditions for the first encounter of external antigens. Evidently, this question can only be answered from experimental systems in which antigen is not involved.

MATERNAL ANTIBODIES PER SE CAN REGULATE THE ISOTYPE EXPRESSION DURING AN IMMUNE RESPONSE

Earlier investigations by Jarrett and coworkers in rats have shown that a maternal immunization with ovalbumin and the subsequent transfer of maternal antibodies to the offspring inhibited the induction of an immunoglobulin IgE immune response [48, 50] and circumstantial evidence suggested that this IgE-suppression was solely mediated by maternal IgG antibodies and *not* by transferred antigen [48, 51]. Again, this IgE-suppression lasted much longer than maternal IgG antibodies could be detected in the sera of the pups [48]. We have repeated such experiments in CBA/J mice with phospholipase A_2 (PLA_2) as antigen [52] and could confirm the main results obtained by Jarrett and coworkers. Moreover, it could be demonstrated that a mixture of 10 or even *one* single monoclonal maternally derived IgG–anti-PLA_2 antibody was equally effective in mediating an IgE-suppression. This formally proves that antigen is *not* involved in the process and that antibodies as such are able to influence the newborn's immune system and in this case to modulate the balance of expressed isotypes during the immune response in the offspring. These data seem to correlate with the finding that the transmission of atopy, as detected by high IgE serum levels, is linked to the marker D11S97 at chromosome 11q and is *only* detectable through the *maternal* line [53]. The authors concluded that this 'pattern of inheritance is consistent either with paternal genomic imprinting *or with maternal modification of developing immune responses*'.

CLONAL SELECTION BY MATERNALLY DERIVED IDIOTYPES OR ANTI-IDIOTYPES

Immunoglobulins as antigen receptors of B cells form a network of interacting idiotypes [54] which is functionally connected to the T cell compartment [55]. Hence, in the context of the idiotypic network, immunoglobulins are information-bearing molecules which function as internal network antigens and, in

this context, it had to be expected that maternal antibodies *per se* will influence the clonal development of the nascent immune system of the newborn. Indeed, the regulation of idiotype or anti-idiotype expression by maternal influence has extensively been investigated.

The induction of an anti-idiotypic response or the administration of preformed anti-idiotypic antibodies mostly leads to suppression of that idiotype and such a suppression may especially be long-lasting when the anti-idiotypic response is induced in newborns shortly after birth [56–58] or the corresponding idiotype may even be permanently lost [59, 60]. When anti-idiotypic antibodies are actively induced or injected into pregnant mothers and reach the fetus via the maternal route before and/or after birth, they also suppress the corresponding idiotype in the offspring [61, 62]. Interestingly, if an anti-idiotypic manipulation either by direct immunization of the neonate or via the mother is directed towards a highly connected idiotype expressed by multispecific, cross-reactive IgM antibodies, a long-lasting severe disturbance of the *entire* repertoire of that animal may occur [60, 63].

Moreover, several experiments have shown that even the transfer of idiotypes or anti-idiotypes solely *after* birth with the colostrum and milk is sufficient to mediate idiotypic interaction and/or protection against microbial infection from the mother to the offspring [5, 15, 61, 64, 65] demonstrating thereby the importance of natural postnatal rearing. From such experiments it has been concluded that not only the experimentally induced but also naturally occurring antibodies of the mother can influence the development of the newborns' immune system and the generation of the antibody repertoire [60, 63, 65–69]. In the present context, it is important to stress that these earlier experiments have demonstrated that not only a particular immune response, but also the development of the whole B cell repertoire can be influenced by maternally derived antibodies *without the participation of antigen*. The only sensible way to explain these data is the acknowledgement of idiotypic-anti–idiotypic interactions, outlined as the idiotypic network theory [54], despite the appraisal of a senior immunologist that 'there isn't any pay dirt' in that concept and the promise of another colleague that 'there are about 10 other ways' for an explanation which 'make more sense' [70]. To our knowledge, these alternative explanations have not been presented so far. Admittedly, however, the biological relevance/significance of those maternally induced clonal alterations induced by various idiotypic manipulations remained unclear.

MATERNAL IMMUNOLOGICAL EXPERIENCE IMPROVES THE QUALITY OF THE PREIMMUNE REPERTOIRE

The validity of the idiotypic network theory can best be demonstrated by the fact that even vaccinations with anti-idiotypic antisera [71] or monoclonal anti-idiotypic antibodies [72, 73] or by maternal vaccination with recombinant anti-idiotypes [74] (see also [75]), i.e. without the involvement of antigen or antigen-binding antibodies, are able to confer protection against microbial infections or tumor formation. The first hint for us that the maternally induced idiotypic activation in the newborn's immune system causes more than a clonal alteration of unknown relevance was provided by the findings of Okamoto and colleagues mentioned above [45], by showing that the postnatal transfer of an idiotype caused an immune response with secondary kinetics when the young mice were challenged with the corresponding antigen for the first time. These data clearly exemplify that the offspring can derive a benefit from the maternal immunological experience. Hence, we hypothesized that first, antibodies which are generated by somatic mutations during antigen-induced immune responses in the course of ontogeny can be regarded as single steps of an environmentally induced immunological learning process of the mother, secondly that this accumulated maternal immunological knowledge is passed on to the next generation resulting in an education of the nascent immune system of the newborn and thirdly that maternal antibodies will not only bring about an irrelevant alteration of the idiotypic composition of the immune response in the offspring, but will induce advantageous effects, e.g. with respect to immunity against infectious diseases.

To address this possibility, we studied the immunomodulatory impact of maternal antibodies. We suspected that maternal effects could best be studied in the well characterized primary immune response to the hapten 2-phenyloxazolone (phOx) coupled to the carrier chicken serum albumen (CSA) when this response is induced at an age when maternal antibodies were not any longer detectable in the sera of the young mice plus a further waiting-period of 4–8 weeks. During the analysis of the influence of a primary, secondary or tertiary immune response of BALB/c females to phOx-CSA on the primary humoral immune response to the same antigen in the offspring, an alteration of the *kinetics*, the *quantity* and the *quality* of the antiphOx antibody production was observed [76, 77].

The first striking result was the production of IgM-antiphOx antibodies in the offspring of secondarily immunized dams even when the F1 animals themselves were *not* immunized [76]. This observation has been confirmed by others [78].

A small amount of tertiary antiphOx antibodies could also be transferred via the F1 females to the F2 generation. When these F2 mice, which obtained antiphOx antibodies from their grandmothers, received a primary immunization with phOx-CSA, half of them developed an immune response as normal mice, but in the other half maximal antibody titers of about 7×10^5 were reached which in normal mice (born to nonimmunized dams) can only be observed in the course of a secondary immune response [76].

When high affinity tertiary or quaternary antiphOx antibodies, either as a result of an active immunization or injected as antigen-free monoclonal antibodies, were transferred from the mother or even the grandmother, the expression of the normally dominant Id_{Ox1} was rendered exceedingly variable, i.e. in most mice the amount of Id_{Ox1} was reduced, but in some mice the proportion of the Id_{Ox1} was even increased to 90–95%. This is in

contrast to normal mice, in which the Id_{Ox1} is dominant and constitutes about 75% of the day 7 primary antibodies with little deviation between different animals [77].

Among the early primary antiphOx antibodies in normal mice, those of the Id_{Ox1} are of highest affinity [79]. In contrast, in the offspring of tertiary immunized dams, half of the non-Id_{Ox1} antibodies exhibited a strong increase in affinity, being either identical (60%) or even 7–25 times higher (40%) than Id_{Ox1} antibodies [77].

This affinity enhancement of half of the non-Id_{Ox1} antibodies seemed to results from (i) the expression of new and nonmutated V_L genes (ii) V_H/V_L gene combinations which have so far not been observed in the antiphOx immune response, and (iii) the expression of nonmutated V_H/V_L gene products which normally occur during immune maturation of the secondary or tertiary immune response.

These results demonstrated for the first time that maternal immunological experience in the form of *high affinity*, *tertiary* antibodies is not only able to cause an alteration of the antigen-inducible B cell repertoire of unknown relevance, but can influence the nascent immune system in a *biologically meaningful* way by enhancing the *quality* of the early primary antibodies, thus *improving the starting conditions* of the immune system in the offspring. This is reminiscent of observations which described the transfer/inheritance to the next generation of phenotypic characters which are not encoded in the germline, but induced through environmental factors and thus prove a '*maternal guidance of nongenetic contributions*' [80]. Furthermore, our experiments showed that maternal factors can be regarded as the first encounter initiating a life-long educational process of the immune system [81].

EARLY ONTOGENY IS ALSO FOR THE IMMUNE SYSTEM AN EXCEPTIONALLY SENSITIVE PHASE

The early phases of ontogeny are of great importance for all aspects of the development of an individual. This can be examplified by the learning of a language. While children can easily learn one or more languages during the first years of life, the capacity of the central nervous system in this respect rapidly declines and ends with puberty [82]. The same principle seems to hold true for the development of the immune system. There are a few reports which help to evaluate the importance of the early ontogeny as an exceptionally sensitive phase. First it has repeatedly been shown, that idiotypic-anti–idiotypic interactions have long-lasting or permanent influences when induced around birth, but are transient in nature when activated during adulthood [56–60]. Second, moreover, since particular idiotypic interactions are only operative during certain fixed periods early in life, but exert a determinative influence on the composition of the *adult* repertoire, the concept of 'developmental windows' has been put forward [68, 83, 84]. Third, similar conclusions have been reached from the work of Coutinho and his group by showing that an immunoglobulin-dependent selection of the T-cell repertoire *only* operates during the first 3 weeks on life [85]. In analogy to our results [77], they also observed that this effect could be passed on to the F2 generation. Fourth, Haba and Nisonoff have studied the conditions for the induction of IgE immune responses and found that a long-term suppression of IgE synthesis could *only* be achieved when syngeneic IgE was administered during a short period from 2 to 11 days of life [86, 87]. Fifth, these results are in line with the conception that influences in early life are important for the appearance of allergic diseases in later life [88, 89] and that the transmission of atopy is *only* detectable through the *maternal* line (see above and [53]).

These immunological characteristics are reminiscent of experiments which have demonstrated a behavioral imprinting as defined by Konrad Lorenz [90]. In connection with his findings and the general concept of imprinting [91] we would like to propose that during the early ontogenetic development of the immune system, there is an imprinting phase à la Konrad Lorenz, so to speak. In full analogy to the behavioral imprinting, this *immunological imprinting* seems to be characterized by the following features: first, the internal imprinting effect is induced by external signals, second, in contrast to normal learning, immunological imprinting is also only possible during certain developmental phases and third, it is characterized by an (almost) irreversible result. This means that particular immunological experiences must be made during appropriate sensitive phases and can not be made up leeway. Hence, maternal immunoglobulins as well as a variety of growth factors present in colostrum and milk provide the first immunologically relevant environment for the fetus and this environment is of particular importance for the start of the ontogenetic development of the immune system.

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REFERENCES

1 Nevard CHF, Gaunt M, Ockleford CD. The transfer of active and passive immunity. In: Chaouat G, ed. The Immunology of the Fetus. Boca Raton, Florida: CRC Press, 1990:193–214.
2 Klemperer F. Über die natürliche Immunität und ihre Verwertung für die Immunisierungstherapie. Arch Exp Pathol Pharmacol 1893;31: 356–82.
3 Bartz CR, Conklin RH, Tunstall CB, Steele JH. Prevention of murine rotavirus infection with chicken egg yolk immunoglobulins. J Infect Dis 1980;142:439–41.
4 Hayman JR, Lobb CJ. Immunoglobulin in the eggs of the channel catfish (*Ictalurus punctatus*). Dev Comp Immunol 1993;17:241–8.
5 Heiman HS, Weisman LE. Transplacental or enteral transfer of maternal immunization-induced antibody protects suckling rats from type III group B streptococcal infection. Pediatr Res 1989;26:629–32.
6 Lee CJ, Ching ED, Vickers JH. Maternal immunity and antibody response of neonatal mice to pneumococcal type 19F polysaccharide. J Clin Microbiol 1991;29:1904–9.

7 Mulholland K, Suara RO, Siber G *et al.* Maternal immunization with Haemophilus influenzae type b polysaccharide-tetanus protein conjugate vaccine in The Gambia. Jama 1996;275:1182–8.

8 Gill TJd, Repetti CF, Metlay LA *et al.* Transplacental immunization of the human fetus to tetanus by immunization of the mother. J Clin Invest 1983;72:987–96.

9 Vanderbeeken Y, Sarfati M, Bose R, Delespesse G. In utero immunization of the fetus to tetanus by maternal vaccination during pregnancy. Am J Reprod Immunol Microbiol 1985;8:39–42.

10 Dastur FD, Awatramani VP, Chitre SK, D'Sa JA. A single dose vaccine to prevent neonatal tetanus. J Assoc Physicians India 1993;41:97–9.

11 Englund J, Glezen WP, Piedra PA. Maternal immunization against viral disease. Vaccine 1998;16:1456–63.

12 Cranage MP, Gardner PS. Systemic cell-mediated and antibody responses in infants with respiratory syncytial virus infections. J Med Virol 1980;5:161–70.

13 Offit PA, Clark HF. Maternal antibody-mediated protection against gastroenteritis due to rotavirus in newborn mice is dependent on both serotype and titer of antibody. J Infect Dis 1985;152:1152–8.

14 Reuman PD, Paganini CM, Ayoub EM, Small PA Jr Maternal-infant transfer of influenza-specific immunity in the mouse. J Immunol 1983;130:932–6.

15 Ali HM, Scott R, Toms GL. The susceptibility of breast-fed and cow's milk formula-fed infant guinea pigs to upper respiratory tract infection with influenza virus. Br J Exp Pathol 1988;69:563–75.

16 Mbawuike IN, Six HR, Cate TR, Couch RB. Vaccination with inactivated influenza A virus during pregnancy protects neonatal mice against lethal challenge by influenza A viruses representing three subtypes. J Virol 1990;64:1370–4.

17 Zhang XK, Takashima I, Hashimoto N. Role of maternal antibody in protection from hemorrhagic fever with renal syndrome virus infection in rats. Arch Virol 1988;103:253–65.

18 Gaulton GN, Sharpe AH, Chang DW, Fields BN, Greene MI. Syngeneic monoclonal internal image anti-idiotopes as prophylactic vaccines. J Immunol 1986;137:2930–6.

19 Linder N, Handsher R, Fruman O *et al.* Effect of maternal immunization with oral poliovirus vaccine on neonatal immunity. Pediatr Infect Dis J 1994;13:959–62.

20 Chieco-Bianchi L, Collavo D, Biasi G, Colombatti A. Prevention of murine sarcoma virus oncogenesis in offspring of immunized female mice. Br J Cancer 1973;28:238–44.

21 Buffett RF. Prevention of 334C murine virus-induced leukemia by transmission of maternal immunity to offspring. Cancer Res 1974;34:559–63.

22 Sakamoto I, Kawakatsu H, Kidowaki T, Matumura T, Sugimoto T, Sawada T. Experimental study of the maternal effects on tumor immunity of infant mice with C1300 mouse neuroblastoma. J Pediatr Surg 1988;23:350–3.

23 Fenner F, Bachmann PA, Gibbs EPJ, Murphy FA, Studdert MJ, White DO. Veterinary Virology. New York: Academic Press, 1987.

24 Smith NC, Wallach M, Miller CM, Morgenstern R, Braun R, Eckert J. Maternal transmission of immunity to Eimeria maxima: enzyme-linked immunosorbent assay analysis of protective antibodies induced by infection. Infect Immun 1994;62:1348–57.

25 Ada GL. Vaccines. In: Paul WE, ed. Fundamental Immunology. 3rd edn. New York: Raven Press, 1993:1309–52.

26 Whitelaw A, Parkin J. Development of immunity. Br Med Bull 1988;44:1037–51.

27 Parrott RH, Kim HW, Arrobio JO *et al.* Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease with respect to age, immunologic status, race and sex. Am J Epidemiol 1973;98:289–300.

28 Prince GA, Horswood RL, Chanock RM. Quantitative aspects of passive immunity to respiratory syncytial virus infection in infant cotton rats. J Virol 1985;55:517–20.

29 Oxelius VA, Linden V, Christensen KK, Christensen P. Deficiency of IgG subclasses in mothers of infants with group B streptococcal septicemia. Int Arch Allergy Appl Immunol 1983;72:249–52.

30 Vahlquist B. Response of infants to diphtheria immunisation. Lancet 1949;I:16–8.

31 Muscoplat CC, Setcavage TM, Kim YB. Regulation of the immune response in neonatal piglets by maternal antibody. Int Arch Allergy Appl Immunol 1977;54:165–70.

32 Watanabe Y, Shimizu S, Yamaguchi N. Effect of maternal antigenic stimulation on the active immune response of their offspring. Relationship between the immune reactivity of mother mice and the induction of suppression in their young. Scand J Immunol 1984;20:327–32.

33 Izuchi K, Taniguchi K, Gondo H *et al.* Effects of immunization of mothers on the immune reaction of their offspring: inhibition of immune responses of offspring caused by antibody imported through the milk. Am J Reprod Immunol 1984;5:66–71.

34 Bangham CR. Passively acquired antibodies to respiratory syncytial virus impair the secondary cytotoxic T-cell response in the neonatal mouse. Immunology 1986;59:37–41.

35 Xiang ZQ, Ertl HC. Transfer of maternal antibodies results in inhibition of specific immune responses in the offspring. Virus Res 1992;24:297–314.

36 Siegrist CA, Barrios C, Martinez X *et al.* Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allows successful early prime-boost strategies in mice. Eur J Immunol 1998;28:4138–48.

37 Dresser DW. The influence of maternal humoral responsiveness on the specific immunocompetence of the progeny in mice. J Reprod Immunol 1990;18:293–9.

38 Izuchi K, Gondo H, Kawauchi H *et al.* Effects of immunization of mothers on the immune reaction of their offspring. II. Significance of enhanced antigen elimination by maternal antibodies on the suppression of the offspring. J Clin Lab Immunol 1985;16:41–6.

39 Harte PG, Rogers N, Targett GA, Playfair JH. Maternal inhibition of malaria vaccination in mice can be overcome by giving a second dose of vaccine. Immunology 1984;53:401–9.

40 Murphy BR, Prince GA, Collins PL, Hildreth SW, Paradiso PR. Effect of passive antibody on the immune response of cotton rats to purified F and G glycoproteins of respiratory syncytial virus (RSV). Vaccine 1991;9:185–9.

41 Lee CJ, Takaoka Y, Saito T. Maternal immunization and the immune response of neonates to pneumococcal polysaccharides. Rev Infect Dis 1987;9:494–510.

42 Desowitz RS. *Plasmodium berghei*: Enhanced protective immunity after vaccination of white rats of immune mothers. Science 1971;172:1151–2.

43 Ono Y, Sasaki T, Ishida N. Regulation of clonal development of immune responding cells by antibody of maternal origin. Nature 1974;250:593–4.

44 Sasaki T, Ono Y, Ishida N. Modification of fetal immune system by maternal anti-DNA antibody. I. Enhanced immune response to DNA in the mice exposed to anti-DNA antibody early in life. J Immunol 1977;119:26–30.

45 Okamoto Y, Tsutsumi H, Kumar NS, Ogra PL. Effect of breast feeding on the development of anti-idiotype antibody response to F glycoprotein of respiratory syncytial virus in infant mice after post-partum maternal immunization. J Immunol 1989;142: 2507–12.
46 Stern CM. The materno-foetal transfer of carrier protein sensitivity in the mouse. Immunology 1976;30:443–8.
47 Kindred B, Roelants GE. Restricted clonal response to DNP in adult offspring of immunized mice: a maternal effect. J Immunol 1974;113:445–8.
48 Jarrett EE, Hall E. IgE suppression by maternal IgG. Immunology 1983;48:49–58.
49 Dastur FD, Shastry P, Iyer E *et al.* The foetal immune response to maternal tetanus toxoid immunization. J Assoc Physicians India 1993;41:94–6.
50 Jarrett E, Hall E. Selective suppression of IgE antibody responsiveness by maternal influence. Nature 1979;280:145–7.
51 Roberts SA, Turner MW. Specific suppression of rat IgE responses with milk from immunized females and with feeds of serum antibody. Immunology 1983;48:195–9.
52 Seeger M, Thierse HJ, Lange H, Shaw L, Hansen H, Lemke H. Antigen-independent suppression of the IgE immune response to bee venom phospholipase A2 by maternally derived monoclonal IgG antibodies. Eur J Immunol 1998;28:2124–30.
53 Cookson WO, Young RP, Sandford AJ *et al.* Maternal Inheritance Atopic Ige Responsiveness on Chromosome 11q [Published Erratum appears Lancet 1992 October 1992;31:1110] [see comments]. Lancet 1992;340:381–4.
54 Jerne NK. Idiotypic networks and other preconceived ideas. Immunol Rev 1984;79:5–24.
55 Rajewsky K, Takemori T. Genetics, expression, and function of idiotypes. Annu Rev Immunol 1983;1:569–607.
56 Strayer DS, Lee WM, Rowley DA, Kohler H. Anti-receptor antibody. II. Induction of long-term unresponsiveness in neonatal mice. J Immunol 1975;114:728–33.
57 Augustin A, Cosenza H. Expression of new idiotypes following neonatal idiotypic suppression of a dominant clone. Eur J Immunol 1976;6:497–501.
58 Hiernaux J, Bona C, Baker PJ. Neonatal treatment with low doses of anti-idiotypic antibody leads to the expression of a silent clone. J Exp Med 1981;153:1004–8.
59 Kearney JF, Pollok BA, Stohrer R. Analysis of idiotypic heterogeneity in the anti-alpha 1–3 dextran and anti-phosphorylcholine responses using monoclonal anti-idiotype antibodies. Ann N Y Acad Sci 1983;418:151–70.
60 Vakil M, Sauter H, Paige C, Kearney JF. *In vivo* suppression of perinatal multispecific B cells results in a distortion of the adult B cell repertoire. Eur J Immunol 1986;16:1159–65.
61 Weiler IJ, Weiler E, Sprenger R, Cosenza H. Idiotype suppression by maternal influence. Eur J Immunol 1977;7:591–7.
62 Victor C, Bona C, Pernis B. Idiotypes on B lymphocytes: association with immunoglobulins. J Immunol 1983;130:1819–25.
63 Bernabe RR, Coutinho A, Cazenave PA, Forni L. Suppression of a 'recurrent' idiotype results in profound alterations of the whole B-cell compartment. Proc Natl Acad Sci USA 1981;78:6416–20.
64 Rothstein TL, Vastola AP. Homologous monoclonal antibodies induce idiotope-specific suppression in neonates through maternal influence and in adults exposed during fetal and neonatal life. J Immunol 1984;133:1151–4.
65 Stein KE. Network regulation of the immune response to bacterial polysaccharide antigens. Curr Top Microbiol Immunol 1985;119: 57–74.
66 Wikler M, Demeur C, Dewasme G, Urbain J. Immunoregulatory role of maternal idiotypes. Ontogeny of immune networks. J Exp Med 1980;152: 1024–35.
67 Martinez C, Toribio ML, De la Hera A, Cazenave PA, Coutinho A. Maternal transmission of idiotypic network interactions selecting available T cell repertoires. Eur J Immunol 1986;16:1445–7.
68 Kearney JF, Vakil M. Idiotype-directed interactions during ontogeny play a major role in the establishment of the adult B cell repertoire. Immunol Rev 1986;94:39–50.
69 Andrade L, Martinez AC, Coutinho A. Mother-derived selection of immune repertoires: nongenetic transmission of developmental choices. In: Chaouat G, ed. The Immunology of the Fetus. Boca Raton: CRC Press, Inc., 1990:187–92.
70 Marshall E. Disputed results now just a footnote [news]. Science 1996;273:174–5.
71 Sacks DL, Esser KM, Sher A. Immunization of mice against African trypanosomiasis using anti- idiotypic antibodies. J Exp Med 1982;155:1108–19.
72 Stein KE, Soderstrom T. Neonatal administration of idiotype or antiidiotype primes for protection against Escherichia coli K13 infection in mice. J Exp Med 1984;160:1001–11.
73 Ruiz PJ, Wolkowicz R, Waisman A *et al.* Idiotypic immunization induces immunity to mutated p53 and tumor rejection. Nat Med 1998;4:710–2.
74 Magliani W, Polonelli L, Conti S *et al.* Neonatal mouse immunity against group B streptococcal infection by maternal vaccination with recombinant anti-idiotypes. Nat Med 1998;4:705–9.
75 Bona C. Idiotype vaccines: Forgotten but not gone. Nat Med 1998;4:668–9.
76 Lemke H, Lange H, Berek C. Maternal immunization modulates the primary immune response to 2-phenyl-oxazolone in BALB/c mice. Eur J Immunol 1994;24:3025–30.
77 Lange H, Kobarg J, Yazynin S *et al.* Genetic analysis of the maternally induced affinity enhancement in the non-Ox1 idiotypic antibody repertoire of the primary immune response to 2-phenyloxazolone. Scand J Immunol 1999;49:55–66.
78 Ismaili J, Brait M, Leo O, Urbain J. Assessment of a functional role of auto-anti-idiotypes in idiotype dominance. Eur J Immunol 1995;25:830–7.
79 Berek C, Milstein C. Mutation drift and repertoire shift in the maturation of the immune response. Immunol Rev 1987;96:23–41.
80 Pennisi E. A new look at maternal guidance. Science 1996;273: 1334–6.
81 Rook GAW, Stanford JL. Give us this day our daily germs. Immunol Today 1998;19:113–6.
82 Kandel ER, Schwartz JH, Jessell TM. Neurowissenschaften. Heidelberg: Spektrum Akademischer-Verlag, 1995:652–3.
83 Vakil M, Kearney JF. Regulatory influences of neonatal multispecific antibodies on the developing B cell repertoire. Int Rev Immunol 1988;3:117–31.
84 Elliott M, Kearney JF. Idiotypic regulation of development of the B-cell repertoire. Ann N Y Acad Sci 1992;651:336–45.
85 Martinez C, Bernabe RR, de la Hera A, Pereira P, Cazenave PA, Coutinho A. Establishment of idiotypic helper T-cell repertoires early in life. Nature 1985;317:721–3.
86 Haba S, Nisonoff A. Effects of syngeneic anti-IgE antibodies on the development of IgE memory and on the secondary IgE response. J Immunol 1994;152:51–7.

87 Haba S, Nisonoff A. Prolongation of the responsiveness of newborn mice to syngeneic IgE by inhibition of IgE synthesis. Immunol Lett 1995;47:205–8.

88 de Weck A, Derer M, Mayer P, Stumper B. Allergy starts in early life: clinical and experimental evidence. In: Sasaki S, Miyamoto T, Hopkin J, eds. Predictio and Prevention of Childhood Allergy. Osaka: Churchill-Livingstone, 1995:181–97.

89 Holt PG. Early acquisition of sensitization in childhood asthma. Pediatr Pulmonol Suppl 1995;11:44–6.

90 Lorenz K. Der Kumpan in der Umwelt des Vogels. J Ornithol 1935;83:137–213.

91 McFarland D. Biologie des Verhaltens. Evolution, Physiologie, Psychobiologie. Weinheim: VCH Verlagsgesellschaft 1989:334–42.