



10 workshops on Immunology of preeclampsia

Chaouat Gerard

976 INSERM Hôpital Saint Louis, Pavillon Bazin, Avenue Claude Vellefaux 75010 Paris, France



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ABSTRACT

For the 10th issue of the « island workshops », now the Reunion Workshops, organised by Pierre Yves Robillard since the first one in Tahiti challenging the “vascular disease only” theory of pre eclampsia and introducing the primipaternity concept, we examined the reasons for considering an Immunological approach to the disease. This (brief) overview thus examines several important topics in an Immunological framework. I have chosen to present here the evolution of the main themes rather than a purely chronological vision.

1. Introduction

This is the 10th issue of the « island workshops », now the Reunion Workshops, organised by Pierre Yves Robillard since the first one in Tahiti in 1998 on the island of Moorea...

This workshop was motivated by discussions arising after the publication of the paper by Pierre Yves, Emile Papiernik and colleagues (Robillard et al., 1994) which was a real “pavé dans la mare” as we say in French...(incidentally, private jokes about pavés, the workshop ended may the 2nd, just for the 30th anniversary of May 68, and I was thus interviewed by French radio from there..).

Why was this paper important?

Because of the by then prevalence of the “vascular disease only” theory of pre eclampsia.

It should be recalled first here that the prevailing theory was that preeclampsia was ONLY a vascular disease and ONLY occurring in the first pregnancy.

It was even written that for any work speaking or even (mildly) invoking the existence (and even simply the possibility) of PE in a second pregnancy: “I would suggest that Editors reject any study of preeclampsia that includes multiparous unless they are analyzed separately” (Chesley, 2000). » (this “very scientific” approach, close to dictatorial censorship, IS unfortunately a quotation).

The workshop examined the reasons for considering an Immunological approach after the publication of this paper.

Afterwards, as we will see, it examined several important topics in an Immunological framework. I have chosen to present here the evolution of the main themes rather than a purely chronological vision.

Of course, not all the communications are discussed, but this does NOT mean that they were useless (nor bad!). In fact, they all contributed to the progress of our understanding of the disease.

2. Why Immunology from the 1994 Lancet paper?

The most salient point of the Lancet paper and, thus, the first workshop was the introduction of primipaternity, as a replacement of the primiparity concept.

The authors reported first that there were in French West Indies (Martinique and Guadeloupe) frequent occurrence of a 2nd preeclampsia in a multiparous woman. This was strongly correlated with the fact that the biological father had changed and that the affected pregnancy was in fact the first one with this specific individual. As Bob Marley would sing about West Indies behaviours, “shame and scandal in the family”, except the fact that multi partner is rather commonly accepted in French West Indies. Further explanation is needed: in what we may call the “slavery belt” (Brazil, Central America, the Caribbean’s, North America...), masters had strictly forbidden marriages between slaves during some 3 centuries. These people have then integrated in their specific reproductive culture a special scheme, and demographers had to invent the term of “women Family Structure” for these areas. Also what Jamaican health workers call “visiting sexuality”. Then, there, it is absolutely not reprehensible to have 4 children with 3 different fathers, everybody is aware (including the siblings, who have different family names), and, in Guadeloupe, all these families go every Sunday at the Catholic church together. This made the interviews, and thus the epidemiological investigations, much easier than in some Northern European countries where the search for a “non legal” father was much more difficult, if not almost impossible). Apart from that, a first occurrence of preeclampsia with that father was still protective in case of a 2nd pregnancy with the same individual.

Primipaternity if confirmed would imply.... This implied specificity, while, on the other hand, the protective effect per se was highly suggestive of a memory phenomenon.

E-mail addresses: gerard_chaouat@wanadoo.fr, gerardchaouat@aol.com.

URLS: [http://mailto:gerardchaouat@aol.com](mailto:gerardchaouat@aol.com), <http://mailto:gerardchaouat@aol.com>.

Specific memory is a feature shared only by the immune and nervous system.

The vascular theory, it was admitted, could explain the apparent protection (primigravidity), but had more difficulties in explaining the resurgence of the phenomenon in cases of a second occurrence linked to a change in biological father in multiparous women.

3. Setting some of the framework

3.1. First workshop

Wisely enough, since the “blood transfusion effect” was known since 1981 and was less suspicious amongst Immunologists than disquisitions on the now defunct “I-J sub-region”, Pierre Yves and Gus had invited Paul Terasaki, well known for the blood transfusion effect in kidney transplantation (Tokunaga and Terasaki, 1986) which lead us to discuss the role of “suppressor T cells”, and we recalled that since the work of Loblay, Pritchard Briscoe and Basten “multiple low dose tolerance” – in this seminal paper, to Human Gamma Globulin”, was associated with “suppressor T cell memory” – (Loblay et al., 1978).

This was of importance since the observation of the duration of sexual cohabitation enabled Gus Dekker to suggest the protective role of sperm exposure, and later on even question the protective effects of oral sex (Koelman et al., 2000), whereas Chris Redman was already there, and presented to us his views on inflammation as the cause of preeclampsia which he will develop all along the time course of the workshops till now, with adaptation to Immunology (see below).

Both myself and Pierre Yves had the feeling that he was more interested at the start of the workshop by vascular theories but inclined at the end to discuss Immunological ones.

3.2. The 2nd workshop

The 2nd workshop moved from the South Pacific to the Indian ocean, in that case Mauritius, due to the appointment of Pierre Yves in La Reunion, and thus his moving away from Tahiti/Moorea... Many of us who were there would of course remember the paradise like setting of the Moorea Lagoon...

Further clues were added: the role of sperm was tackled again by Satish Gupta, and the first mention of HLA-G was made by Debra Wohl (down regulation of HLA-G in the placenta of preeclamptic women) (Goldman-Wohl et al., 2000).

The first PE (artificially induced) animal model was introduced by Sasaki Hayakawa. It was a transfer of IL-12/IL-4 hyper-activated lymphocytes in pregnant mice and such abnormal activation of the innate immune system by selected cytokines did lead to a pre eclampsia like syndrome in mice (Hayakawa et al., 2000). Retrospectively, it is interesting to note that C3 deposits were observed in the kidneys of IL-4 treated animals, but this was not noticed enough at the time.

3.3. The continuation ...

From these two first workshops, the main discussion themes of the sessions to come were established.

These were:

- Evolutionary perspective
- Primiparity/primipaternity sperm exposure
- Diagnosis predictive (and indications for Therapy?): IPG VEGF
- IMMUNOLOGY and the vessels, itself divided into:
 - NK
- Complement
- Induction of « tolerance » to the foetal allograft
- Th1/Th2 cytokine unbalance
- Tregs
- The role of Inflammation, debris, small particles

All of the following workshops but one (held in Tioman) were held in Réunion island, (where we had the chance to have one during an eruption of the Volcano, and to fly above it by helicopter) and always in the same place...., hotel Iloha at Saint Leu, which made interactions easy.

4. Evolutionary perspective

Why preeclampsia in human? And great apes?

In the 1st Mauritius workshop, Jean Chaline suggested that preeclampsia might somehow be the price to pay by the human Homo Sapiens for a bigger brain...(Chaline, 2003).

He reminded us of the existence of preeclampsia in some big apes (albeit the experimental work is rather small for obvious reasons when dealing with protected/endangered species, some being moreover territorially aggressive: gorillas) and insisted on the fact that there is TWO waves of invasion in human placentation, preeclampsia being characterised in the 2nd one by a « shallow invasion » – data of Pijnenborg, see for example Naicker et al. (2003).

A part of the discussion later on, which is not fully settled yet, would be to establish if preeclampsia starts by then or, much earlier, around the implantation stage itself (see below).

At this 2nd workshop, Jean Chaline presented his views on the extinction of Neanderthal, and the possible relationship with failure to develop a large and complex enough brain.

The discussion went on about size of the brain and intelligence in such mammals as dolphins (an epitheliochorial placentation) and elephants, as well as on the preeclamptic (hemochorial placentation) great apes.

I must stress that this discussion occurred before the discoveries that Neanderthal was much more technically and culturally developed than what was thought in the 90s, and the realisation that there were close relations between Neanderthal and Sapiens communities, and even exchange of artefacts (commerce) and, even more, interbreeding, (Temme et al., 2014; and for a relatively recent general overview, Gibbons, 2014).

This has lead for example to a recent suggestion that disappearance of Neandertal would have resulted by “dilution” after a period of interbreeding...., but the ideas of genocides, acute competition, or inferior species as far as technology is concerned are no longer as dominant as they were by then.

Nevertheless, this evolutionary vision led us also to examine the very concept that allopregnancy had to be considered as a possible materno foetal immune conflict.

This lead to assess in depth Polly Matzinger remark “Reproduction cannot be a danger! it does not make evolutionary sense”. One must recall that it is precisely discussion about “non rejection of the foetal allograft” that lead Polly, during her discussions with Robert Schwab, of UCLA Davis, at a bar when she was then a cocktail waitress, to postulate that self/non self theory was wrong, and that the immune system was in fact reacting to the 4ds: danger, (“bad” cell) death (as opposite to “controlled cell death”, such as apoptosis), damage, and distress (Matzinger, 1994).

Thus we invited Elisabeth Bonney (Bonney, 2016) and Colin Anderson.

Though the danger model as such did not gain universal acceptance, their talk did cast further light on the importance of uncontrolled post implantation inflammation, as indeed seen in many cases of sterility and a subset of recurrent aborters.

The discussions on evolution lead also later to comparative analysis of viviparous mammals. Eutherian M. Elliott recently focused on the relationship between oxidative stress and the evolution of placentation in eutherian mammals (Elliott, 2016).

For him, epitheliochorial placentation, in which foetal tissues remain separated from maternal blood throughout gestation, has evolved as a protective mechanism against oxidative stress arising from

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