

Post-weaning Multisystemic Wasting Syndrome (PMWS) in pigs: an attempt to bring together the pieces of the puzzle.

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I- Introduction

PMWS was first described in Canada (Harding 1996, Clark 1997) and soon after, the condition was recognized in several other countries: the USA (Daft et al 1996, Sorden et al 2000) and the EU where reports came from Spain (Segalès et al 1997), France (Le Cann et al 1997) and the UK-Northern-Ireland (Kennedy et al 1998). At the initial stage, a limited number of PMWS-affected herds were detected in each country but whilst their number increased, the disease was recognized in several other countries throughout the world like in 1998 in Korea and Japan (Lyoo et al 1999, Sato et al 2001), in 1999 in Taiwan (Chen Shihping et al 2001), in 2000 in Switzerland, Poland and Denmark (Borel et al 2001, Pejzak et al 2001, Vigre et al 2005). Later on, in 2003 it was diagnosed in other countries like New-Zealand, Sweden and Norway (Stone 2004, Wallgren et al 2004, Brunborg et al 2004). During 2005 and 2006 numerous severe cases were reported in Canada (Ellis et al 2006). Within a few years, PMWS has become a worldwide animal health main concern to the pig industry and a real challenge to the veterinary science community. A small single stranded DNA virus (Porcine Type 2 Circovirus, PCV2) was rapidly found in the damaged tissues of affected pigs and suggested to play a pivotal role in disease onset through its impact on the immune system (Krakowka et al 2001). However as soon as the laboratory tools adequately tailored to PCV2 detection on large scale were available, it became evident that the virus was widespread and found as well in PMWS-affected as in non affected farms ; Additionally, retrospective studies consistently showed that it was so since decades far before PMWS was recognized and reported (Mesu et al 2000, Magar et al 2000). Despite differences were recently found in RFLP patterns of PCV2 isolates in Canada, to date there is no clear evidence of major genomic differences in PCV2 viruses recovered from pigs with and without PMWS that could explain expression or not of the disease (Larochelle et al 2003, Griesen et al 2004, De Boisseson et al 2004, Ellis et al 2006). Recently the role of retroviruses was assessed. Retroviraemia was found associated to pigs sampled in PMWS-affected farms (Tucker et al 2006). However to date PCV2 still remains considered as the principal infectious cause of PMWS. In the meantime epidemiological studies were carried out trying to get more knowledge about the on-farm conditions leading-predisposing to clinical PMWS, whereas an important laboratory research effort was directed at a better understanding of the pathological mechanism incurred in PMWS with an emphasis placed on the immune system. The present paper is an attempt to bring together the main aspects of current available knowledge that could help the farm managers to avoid the most detrimental consequences of PMWS. Therefore it is restricted to those points assumed to have a practical interest to herd health maintenance regarding PMWS, in relation to management and husbandry.

II- Disease, Diagnosis

When PMWS typically strikes, the postweaned-growing pig (7-15 weeks of age) is the favourite if not exclusive target. The pigs show unthriftiness and low feed intake ; in more advanced stages they become pale and exhibit laboured breathing. Fever is a common clinical sign (up to 41°C) as well as diarrhoea. In individual pigs, the situation evolves rapidly and, within 3-7 days, weigh loss can be considerable so as the concerned pigs soon look miserable. Wasting is often fatal whereas poor-doing pigs require euthanasia. Total mortality can easily reach 20-30 % at the batch level. The severity and type of disease expression is very different among pigs within a group. In a given compartment of contemporary pigs or a pen, whilst pigs are strongly depressed, the majority do not display any obvious sign of sickness through out weaning and fattening phases. In addition to wasting, in PMWS-affected farms, a number of pigs (much less than 1% on average but up to 5-8 % in the batches of some farms) show dermatitis. Irregular red-to-purple macules appear mainly on the hind legs and the perineal and rump area but also the ears and belly. They tend to coalesce and can cover an important part of the body. Due to simultaneous severe kidney lesions, the condition was named PDNS (Porcine Dermatitis and Nephropathy Syndrome). Case fatality is rather high with PDNS even in grow-finishing pigs. A point that can be surprising, in farrow-to-finish operations: no obvious consequences of PMWS are seen in the sow herd: sow productivity is maintained. The severity of PMWS varies depending on the farm. A litter (sow) effect was also found. The duration of clinical disease can vary to a large extent in a given farm. When adequate hygiene measures were strictly applied, severe disease was stopped within 3 to 6 months whereas in farms reluctant to changes the disease could hit for more than 2 years (Madec et al 2000).

In individual pigs, at necropsy, the most frequent anomalies are enlarged lymph nodes and a number of other lesions widely reported in literature. Similarly, numerous histological lesions have been recorded like lymphocyte depletion and histiocytic and multinucleate giant cell infiltration in the lymphoid tissues (Rosell et al 1999). Establishing the diagnosis of PMWS at the herd level is still debated despite interesting inputs (Sorden 2000). According to an EU multidisciplinary consortium (Allan, 2006) a general definition is proposed: “The occurrence of PMWS is characterised by an excessive increase in mortality and wasting post weaning compared with the historical level in the herd”. The most recommended option is thus to refer to periods of time. The current time period is one or two months whereas the histological reference period should be at least three months. The diagnosis of PMWS is highly suspected when current losses (associated to wasting) significantly exceed the historical levels (χ^2 test). The authors insist on the necessity to have good on-farm records and to submit several typical wasting pigs to the laboratory to properly establish the diagnosis.

III- Epidemiology

- The close contact between infected/seeder animals and non infected/susceptible ones (ie: horizontal transmission), is believed to be the main way of PCV2 transmission. More precisely, the oral-nasal and oral-fecal routes are probably the most efficient for a pig to get infected. Experimental trials could demonstrate horizontal transmission. Sentinel (non inoculated) growing pigs raised in contact with inoculated ones, rapidly got infected. Beyond infection, clinical disease could be observed in the sentinel pigs (Albina et al 2001). Recent experiments with newborn piglets being cross-fostered, also showed the rapid spread of the PCV2 from infected to naïve piglets (Rose et al 2006). PCV2 shedding through colostrum was suggested (Shibata et al 2006). In relation to commercial

implications in PMWS as in other infectious diseases, movements of live pigs are thought to be by far the major way of disease spreading from farm to farm. PCV2 was also found in semen of infected boars (Laroche et al 2000, McIntosh et al 2006) suggesting the potential risk of dissemination of the virus on a large scale through artificial insemination. However descriptive epidemiological studies carried out in countries like Sweden failed to find any obvious physical link between PMWS-affected herds (Wallgren et al 2004) whereas in Denmark, spatiotemporal clusters were identified (Vigre et al 2005). In Great-Britain, a spatial, local distribution was also observed with a slow movement (Woodbine 2005). It can occur that the link with the health status of the farms supplying pigs (Weaners, gilts ...) fails to give consistent explanations. But it is rather risky to introduce pigs from PMWS-affected farms into healthy PMWS-negative farms since horizontal transmission of the disease is demonstrated. In New-Zealand the affected farms could be linked to one another (Lawton et al 2004) and farm assessment revealed that most of the affected farms gave little consideration to biosecurity. However, in the pig producing countries where it strikes, PMWS has never shown a clear spatial spreading pattern with clear epidemiological links as it could be expected for an infectious disease having such an impact. European wild boars were found to be PCV2 positive (Vicente et al 2004) but no relationship could be established between the contamination of in-door raised commercial pigs and the wildlife.

- There are converging findings especially from experiments that corroborate the main role of PCV2 in the disease causation. However the fact that the PCV2, without any obvious currently recognized major difference in virulence, can be isolated from both diseased and healthy pigs, from diseased and healthy herds, raises comments. The main one is the very probable need for additional associated causes or specific circumstances that trigger PCV2 replication up to an overwhelmed immune system. The field of analytic epidemiology is the search for such circumstances due to increase the probability of disease onset (or to increase its severity) and called "risk factors". Surveys of different design were performed around the world about PMWS. A cross-sectional study with a limited number of farms (n = 25) targeted on PCV2 detection in poor-doing pigs, was carried out in Canada (Cottrell et al 1999). The general health status of the piglets in nursery and poor biosecurity were suggested as risk factors. In the USA a case-control study was performed at the individual pig level about the strength of the association between infectious agents and PMWS (Pogranichniy et al 2002). PCV2 was strongly related to PMWS but occurrence of PMWS was higher when the pigs were concurrently infected by PRRSV (Porcine Reproductive and Respiratory Syndrome Virus). Similar conclusions came out of a Dutch study (Wellenberg et al 2004). The results of a cohort study in the UK (Woodbine 2005) suggested that purchasing breeding stock was a risk factor. In France it was found that piglets born to certain sows were much more prone to develop PMWS (Madec et al 2000). Additionally, in severely affected farms, whereas sow productivity (prolificacy, fertility rate, piglet survival around birth and during lactation ...) was maintained, management and husbandry showed shortcomings when compared to PMWS-free farms. It was hypothesized that these could act as challenges to the immune system. An emergency plan made of 20 points was set-up and proposed on voluntary base. It appeared that as far as the farmers could comply to most of the recommendations, a significant reduction of the losses could be obtained (Madec et al 2000). Later on, a case-control survey involving 149 farrow-to-finish farms was launched (Rose et al 2003). The risk factors obtained were for most in line with the 20 point plan. In a further step, a follow-up observation was designed at the individual pig level, starting at insemination of the dams. The study once again confirmed elements of the previous surveys but it also pointed out more refined factors. Hence it was found that the offspring of sows showing high levels of PCV2 antibodies in

their sera at farrowing were less at risk to develop PMWS at the growing stage than those whose dam had a low titre. On the other hand when the sow had a high titre against PPV at farrowing (Porcine Parvo Virus, HI titre ≥ 10240) attesting a PPV infection during pregnancy, the offspring were more at risk. They were also more at-risk when they had been mixed (several commingled litters at weaning, and again mixing of pens in the grow-finish compartment) and when the sow showed injuries (ie: abscesses) at her neck at the location of injections. All the pigs seroconverted at the end of finishing phase (around 6 months of age). But those which seroconverted early (8-12 weeks of age) following an early PCV2-antibodies depletion, were more at-risk to develop the disease. We could not detect any difference in PMWS expression in relation to genetics and the use of pure-bred pietrain boar as sire (Rose et al 2005). With the exception of the breed effect, similar results were obtained in Spain (Lopez-Soria et al 2005). In Denmark, a case-control study was carried out in 2003-2004 (Enoe et al 2006, Botner et al 2006); 74 herds fulfilling the criteria for PMWS were selected as cases. Each of them was matched with a control herd from the veterinary surgeon's practice. A strong association between the occurrence of PMWS and the infection with PRRSV-US strain was found. The other risk factors mainly related to biosecurity failures and therefore support the hypothesis of an unknown infectious aspect of PMWS, although none has been identified yet. Good hygiene including, freedom from parasites (ascarid infestation) and proper flooring was also put forward in the USA in a study conducted in 101 farms (Engle and Bush 2006).

IV- Control

Efforts to treat PMWS and PDNS through the use of drugs have failed so far. Medication were prescribed with the aim of reducing the infection pressure of secondary pathogens (ie: bacteria) that could find proper conditions to massively proliferate as soon as the immune system was highly depressed. In case of heavy losses, some vets took the option of serum therapy (Waddilove and Marco 2002). The principle is to collect sera from market-age pigs that survived the problem and thereby assumed to have high antibody titres in their blood. This "hyperimmune" sera is injected to young piglets in order to give them protection, before the critical period for wasting. Inconsistent results were obtained and the large scale use of serum therapy is to be discouraged because of the biosecurity risks incurred, (ie: "recycling" into piglets of pathogens from slaughter pigs ...).

PCV2 can be viewed as an associated cause to PMWS. The disease although in a mild form could be obtained after PCV2 inoculation to naïve pigs (Albina et al 2001, Kennedy et al 2000). As a consequence, it could easily be expected important research means being directed at the preparation of vaccines. Experimental results showed that vaccination against PCV2 had a good potential to prevent PMWS (Blanchard et al 2003). Commercial vaccines are now becoming available. One is an inactivated adjuvanted vaccine used for sows and gilts. The goal is to protect the piglet through passive transfer of PCV2 antibodies by the dam's colostrum. Other inactivated vaccines are scheduled for use in young pigs. Fighting a disease through the neutralisation of the infectious cause by vaccines is a common rule in veterinary and human medicine. As far as the commercial products are available, safe and officially approved by the *ad hoc* authorities, decision-making (ie: vaccinate or not against a non-notifiable disease) should be backed to a proper cost-benefit analysis. Obviously a most delicate aspect of the exercise relates to the evaluation of the benefit of vaccination. The question is especially difficult to address with PMWS and PCV diseases since through adequate management and hygiene at large, the impact of PCV2 infection can be negligible. In other words it is daily evidenced that despite being infected by the PCV2, a herd can perform normally. The point relies on the demonstration that the PCV2 is present in the vast

majority of commercial farms around the world, if not all, and it is so since decades. Only a low proportion of these farms experienced clear PMWS. It means that most of the farms can currently live in peace with the PCV2 as probably all the farms did before the mid 90's. Analytic epidemiology already provided clues in this respect. Even if further laboratory findings tell us that there are PCV2 strains that vary in virulence or that PCV2 is acting in conjunction with other pathogens (eg: agent x, parvovirus etc ...), there is no doubt that PMWS is multifactorial. PCV2 plays a causative role but upstream in the fallacious pathogenic process, it needs additional triggers/enhancers. Moreover, besides those conditions able to launch the process, the severity of disease expression depends on the husbandry conditions the pigs are offered during nursery and growing phase. The current knowledge obtained by the authors is summarized in Table 1. Figure 1 tries to locate the potential factors assumed to interfere with PMWS expression along with the time scale. It shows that in relation to PMWS expression in growing pigs, an important part of the game seems to be played early in life (in utero and within 2 days of birth, after colostrum intake). Most of those factors can be viewed as challenges to the immune system ; hence it can be hypothesized that they may have the potential to induce the release of an immune response and thereby a humoral and cellular environment suitable to PCV2 massive replication as far as the piglet is infected. A PCV2 load in the tissues overwhelming the resistance capacity of the pig is to be avoided. It should be remembered that PCV2 is a small and simple-designed virus, when compared to other viruses. It needs specific help from the host cell machinery to massively replicate and become highly detrimental to the pig. The detailed sequence of events is not yet known. To date from disease prevention standpoint, complying to a set of coherent technical measures has to be encouraged. Instead of testing each factor separately, the factors are combined and scheduled together for improvement in a time-scaled plan. Those plans have to be tailored to each farm situation.

As regard the spreading pattern of the disease, no real wave was observed in the different countries comparable to previous typical epidemics of infectious diseases affecting pigs in densely populated pig areas⁽¹⁾. The geographic clusters which are observed on some occasions can be partially explained by failure in biosecurity. But in the particular case of PMWS, not only PCV2 (ie: the currently presumed infectious cause) has to be targeted. The associated factors (triggers, enhancers ...) also need full consideration. They might be infectious or not and they may easily spread through normal local and/or international trade in the pig industry. In this respect, despite farms are told "totally closed operations", there are inevitably a number of goods entering, eg: feed (ie: tons of various ingredients, coming from all sides ... their related microflora ...), vaccines, semen and/or replacement stock ... ; and able to disrupt the balance that maintained PCV2 silent, up to a certain point. Those PCV2 triggering factors are not yet fully identified. However to date, several pieces of puzzle are on the table. Figure 1 is an attempt to build scenarios whereas Table 1 enumerates the conditions which are believed, by the time being, to be involved in the prevention of the most detrimental consequences of PMWS.

V- Conclusions

There are 10 years since PMWS was first described and the problem in its essence remains puzzling. Questions are still pending and they feed debates in the veterinary community on key issues like aetiology and pathogenic process. Even the nomenclature to be used in Porcine Circovirus-associated diseases is discussed (Allan 2006). The outbreaks of PMWS in the

⁽¹⁾ An example could be initial attack of PRRS (Porcine Reproductive and Respiratory Syndrome) in the Netherlands where it floored 400 000 piglets in hundreds of farms within 2 months. With PMWS nothing comparable could be seen.

major pig producing countries worldwide should be an occasion to learn, especially to revise our methods of addressing complex, multifactorial diseases. The vet microcosm tends to confine to its conventional field of infectious agents whilst in other branches of animal science (nutrition, genetics ...) each discipline also tends to work separately. A broader multidisciplinary and more integrated approach of animal health is needed. The nasty PMWS in our pig herds might simply result from a change in our farm practices. In other words, unintentionally, we might have been doing something wrong, creating the conditions, a cascade of events, predisposing to an adverse influence of the PCV2 which remained silent up to the first clear descriptions. Except if finally a presently unknown pathogen is involved with the PCV2 (or if the cause is a specific virulent strain of PCV2) and that has been spreading across the borders, the above mentioned hypothesis is plausible. In this respect we should worry about the future. Other “man-made diseases” will come along. Our permanent quest for better income and performance from our farm animals leads to take risks. Negative side-effects of well-identified technical improvements might occur. The latter are largely unexpected and hardly predictable especially when the scientists and professionals keep going in their sharp but rather narrow field. In that, PMWS sounds like a call for a better integration of knowledge. It also reminds us all that animal housing, management and husbandry are too often overlooked to the benefit of pharmacological solutions. Over-reliance on the latter is to be discouraged. Rather, animal hygiene in its broad acceptance should be the corner stone of herd health maintenance.

Table 1. The risk factors involved in PMWS (Rose et al., 2003 adapted)

1- At the herd level (farrow-to-finish farms)

- Porcine parvovirus (PPV) status of fattening pigs (At the end of finishing phase)
- PRRSV status of fattening pigs (end of finishing phase)
- Source of semen used
- Vaccination scheme/PPV + Erysipelas
- Cross-fostering

- Pen size at the nursery and growing stages
- Hygiene in weaning facilities
- Hygiene in farrowing facilities
- Type of housing for pregnant sows
- Hygiene vs. parasites (sow herd)

Less risky situation

seronegative

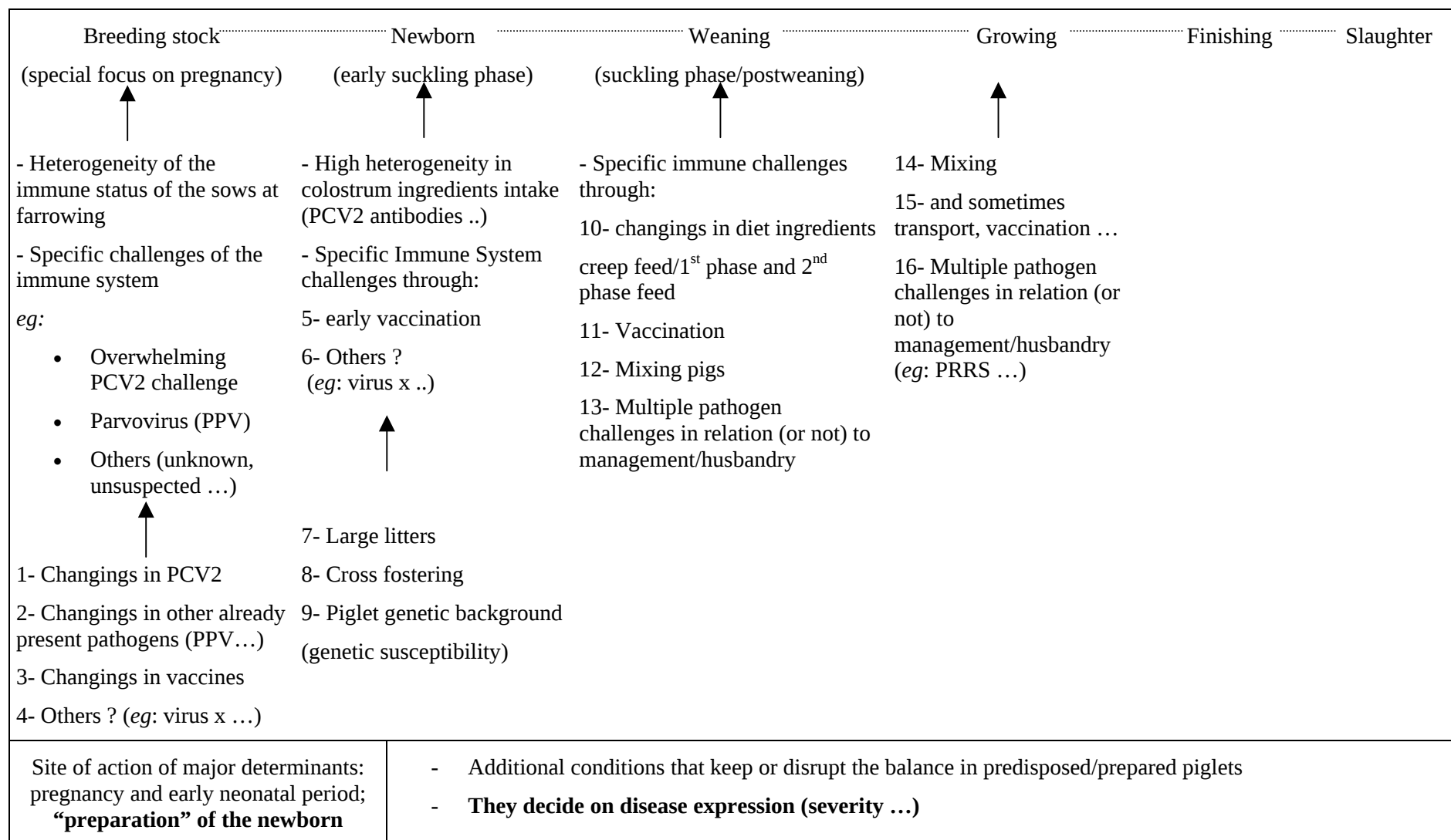
seronegative
PCV2 negative
Grouped and well performed
Limited and made very early (<15% piglets)
small pens, avoid mixing
perfect (all-in/all-out, per room)
perfect (all-in/all-out, per room)
group-housing
perfect

2- At the sow (litter) level

- PPV seroconversion during pregnancy
- Abscesses/injuries at the injection zone (neck)
- PCV2 serol. status at farrowing

no seroconversion
no abscess
highly positive

Figure 1. A tentative scenario resulting in PMWS emergence in the mid-late 90's



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