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# EXPERIMENTAL ANIMAL MODELS IN VACCINATION AGAINST SCHISTOSOMIASIS.

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It has long been assumed that the newly penetrated schistosomulum is the likely target of both innate and acquired resistance to schistosomiasis; this notion gained popularity principally because schistosomula rather than older worms are readily killed by a variety of humoral and cellular effector mechanisms in vitro, but also from in vivo experiments in which larvae were quantified after being recovered from various organs by tissue mincing and incubation. More sophisticated experiments using animal models of the disease have recently indicated however, that the assumption is invalid; there seems instead to be a much broader window of schistosome susceptibility than was previously appreciated. Once accepted, this concept has the added attraction of resolving discordant results published by different groups of workers on the sites and mechanisms of parasite elimination, despite use of apparently identical experimental techniques.

## INNATE RESISTANCE

With the advent of the squashed organ autoradiographic tracking technique it became clear that very few if any primary infection schistosomes were lost in the skins of rodent hosts. Instead, there seems to be a uniform consensus amongst workers in the field that the major phase of parasite loss in naive animals occurs during and/or immediately after the lung phase of worm migration; this is true of mice, rats and guinea pigs (reviewed in Dean, 1983; McLaren & Smithers, 1987). The discord between data obtained from autoradiography and those obtained from tissue mincing and worm recovery techniques have been ascribed to the improved efficiency of the tracking protocol (Mangold & Dean, 1983).

The 129 strain of mouse is of particular interest in the context of innate resistance to schistosomiasis, since around 70% of any given population of WEHI/129J mice or 129/Ola mice is non-permissive to a primary infection with S. mansoni (reviewed by Mitchell, 1989; Elsaghier, Knopf, Mitchell & McLaren, 1989); the remaining 30% of 129 individuals exhibit identical susceptibility to other permissive mouse strains. It has been suggested that elucidation of the basis of this phenomenon might indicate new strategies for the design of anti-schistosome vaccines (Mitchell, 1989). We have now demonstrated that segregation of 129/Ola cohorts into permissive and non-permissive individuals can first be detected on day 21 post infection and becomes more obvious thereafter (Elsaghier et al., 1989). Non-permissive mice harbour adult

parasites in their lungs and these worms eventually succumb to the action of locally recruited inflammatory cells, particularly eosinophils. Parasite damage is characterised by intestinal herniation, which leads to rupture of the gut through the tegument; eosinophils ultimately invade worm lesions (Elsaghier et al., 1989). It has been shown elsewhere, that non-permissive WEHI/129 individuals are high responders to an adult worm antigen, identified as glutanthione S transferase, which is thought to function in detoxifying insoluble haematin pigment that accumulates in the parasite gut; antibodies directed against this antigen are presumed to inhibit enzyme function and result in gut obstruction. The morphological evidence of gut trauma in lung located schistosomes would be consistent with this notion. By using the technique of vasculature casting we have shown that there is a marked reduction in the number and extent of peripheral blood vessels in both the liver and the lungs of non-permissive 129/Ola mice (Elsaghier & McLaren, 1989a). Further, we have demonstrated, by surgically implanting lung stage schistosomes into the liver vasculature, that these changes facilitate worm relocation from the liver back to the lungs in the non-permissive sub set of individuals (Elsaghier et al., 1989).

There is thus persuasive evidence that the lungs constitute a major barrier to primary infection worms in both permissive and non-permissive strains of mice and a possibility that the parasite gut and its associated enzymes might represent potential targets of future control strategies.

## ACQUIRED RESISTANCE

Experiments designed to investigate acquired resistance to schistosomiasis centre upon rodents immunised by exposure to normal cercariae (the infection model), radiation-attenuated cercariae (the irradiated vaccine model), or defined antigens. The present article discusses current views on the basis of vaccine immunity and attempts to reconcile apparently conflicting data.

### Skin phase immunity

There is clear evidence from a variety of techniques that in some irradiated vaccine mouse models, challenge attrition occurs predominantly in the skin, with only a minor phase of worm loss being accomplished in the lungs (reviewed in McLaren & Smithers, 1987). Skin phase immunity is characterised by subdermal focal inflammatory reactions comprising roughly equal numbers of eosinophils and macrophages, that trap and eliminate challenge larvae amongst the adipose cells (Ward & McLaren, 1988). Vaccine resistance in this mouse model can be ablated significantly by an anti-leucocyte monoclonal antibody (McLaren, Strath & Smithers, 1987), as well as by sub lethal doses of whole body irradiation (Delgado & McLaren, 1989a), protocols which both significantly ablate eosinophils from the skin reactions; radio-sensitive cells, perhaps eosinophils, are thus implicated as crucial effectors of cutaneous attrition in the murine host. It may also be pertinent in this context that specific depletion of CD4+ cells during the skin phase of challenge migration has been reported by others to ablate vaccine immunity (Kelly & Colley, 1988). Although serum from once vaccinated mice fails to confer protection upon naive

recipients, serum harvested from polyvaccinated donors does confer protection passively (McLaren & Smithers 1988); recipients exhibit about 70% of donor immunity and develop identical subdermal focal reactions to those seen in vaccinated/challenged individuals (McLaren & Smithers, 1988). Serum transferred immunity is also abolished by prior exposure of the recipients to whole body irradiation (Delgado & McLaren, 1989b). Polyvaccine serum thus seems to act through the recruitment of radio-sensitive effector cells. Interestingly, IgG1 antibodies are stimulated preferentially in the serum donor mice by multiple exposure to radiation-attenuated cercariae and the protective capacity of whole serum resides in this isotype (Delgado & McLaren, 1989b). Silica, an agent which is known to subvert macrophage activity to phagocytosis and is ultimately lethal for these cells, has no effect on the expression of vaccine resistance in this mouse model (Delgado & McLaren, 1989a); such data accord with those obtained from whole body irradiation experiments, thereby confirming that radio-resistant cells probably have no important role. An interesting and unexpected feature of skin phase immunity is that those challenge parasites which become trapped within subdermal focal reactions of either vaccinated or serum protected mice exhibit the morphology of lung stage rather than skin stage larvae (Ward & McLaren, 1988; McLaren & Smithers, 1988). This leads us to believe that vaccine immunity involves immobilisation and trapping of the challenge parasites, such that they are unable to complete normal migration from the skin to the lungs, yet are able to transform from the skin stage to the lung stage of development (Ward & McLaren, 1988). Parasite damage is associated with the subtegumental musculature (Ward, 1988), a feature noted elsewhere from *in vitro* studies and ascribed either to the action of eosinophil cationic protein (McLaren, Peterson & Venge, 1984), or to activated macrophages (McLaren & James, 1985). It is presently unclear whether the trapped parasites are killed as consequence of cellular cytotoxicity, or if they die through failure of some vital metabolic process (Ward & McLaren, 1988). The concept of parasite immobilisation and trapping has the added attraction of perhaps resolving the discrepancy between *in vitro* and *in vivo* data with respect to the identity of the target of immunity; it may be that a two step process of this kind, particularly the trapping of larvae confined within blood vessels, is impossible to mimic in the test tube.

Lung phase immunity

Other mouse models of vaccine resistance to *S. mansoni* show only a minor phase of immune dependent challenge elimination in the skin, the major loss of parasites being effected in the lungs (Dean, Mangold, Georgi & Jacobson, 1984; Wilson, Coulson & Dixon, 1986). In this case, resistance is not ablated by whole body irradiation (Aitken, Coulson, Dixon & Wilson, 1987; Vignali, Bickle & Taylor, 1988) and the inflammatory reactions that develop around challenge parasites in the lungs are dominated by mononuclear cells (Vignali et al., 1988). The finding that P strain mice, which have a defect in the processes leading to macrophage activation, do not develop vaccine immunity (reviewed by Sher & James, 1989) may be especially pertinent in this regard. Trapping of challenge larvae has also been proposed to occur in mouse models

characterised by pulmonary attrition (Wilson, 1987). Lung phase immunity can again be transferred by polyvaccine but not once vaccine mouse serum, and the protective activity of whole serum resides in the IgG fraction (Mangold & Dean, 1986).

Clearly then, a major phase of vaccine immunity can be expressed in either the skin **or** the lungs of mice and resistance is certainly not confined to only one of these sites. Parasite trapping within focal inflammatory reactions is apparently common to both organs, but the effector mechanisms which accomplish this process differ; radio-sensitive cells predominate in the skin and radio-resistant cells in the lungs. Once this concept is accepted, discordant results obtained by different groups of workers from essentially identical protocols are resolved. We have suggested four possible reasons to explain the anomaly of skin phase versus lung phase attrition in vaccinated mice (Elsaghier & McLaren, 1989b): a) variations in the final site of death of the vaccinating population of worms, b) variations in the skin sites chosen for presentation of the immunising or challenge parasites, c) variations in the immune responses of different mouse strains, and d) variations in behaviour of different parasite isolates. The first three of these suggestions have now been explored and eliminated (Elsaghier & McLaren, 1989b) and we have demonstrated, through exchange of schistosome infected snails with colleagues, that the parasite isolate is indeed responsible for determining where the major phase of immunity is expressed. We are presently investigating whether this phenomenon reflects genetic changes in the isolates, or the introduction of foreign schistosome material into the original culture.

There is clear evidence and indeed no debate, over the major site of challenge attrition in vaccinated rats; parasite loss occurs principally in the lungs (reviewed in McLaren & Smithers, 1987). There may be a minor phase of attrition in the skin, but vaccinated rats fail to kill challenge larvae implanted surgically into the liver vasculature (McLaren, Pearce & Smithers, 1985). Protection can be conferred upon naive recipients with vaccine serum (Ford, Bickle, Taylor & Andrews, 1984; McLaren & Smithers, 1985) and IgG2a is the important isotype (Ford, Dissous, Pierce, Taylor, Bickle & Capron, 1987). That macrophages rather than thymus derived effector cells are crucial to lung phase immunity in rats is demonstrated by the fact that vaccine serum is effective in Nu/Nu and Nu/+ recipients, as well as in individuals subjected to whole body irradiation (Ford et al., 1987). Challenge parasites have been identified within pulmonary focal reactions dominated by mononuclear cells, but also containing some eosinophils (Ward & McLaren, 1989; Vignali, Klaus, Bickle & Taylor, 1989); trapped parasites again exhibit traumatised subtegumental muscle cells (Ward & McLaren, 1989). The basic features of lung phase immunity thus seem common to vaccinated mice and rats.

Liver phase immunity

Vaccinated guinea pigs differ from both mice and rats in that vaccine immunity is expressed predominantly in the liver; a minor loss of challenge parasites can be detected in the lungs, but

not the skin (McLaren et al., 1985). Liver phase resistance is stage restricted however, being directed against parasites younger than three weeks of age; older worms are totally refractory (McLaren & Rogers, 1986). Whole body irradiation has no effect on the expression of liver phase immunity, but protection is significantly abrogated by agents such as silica that block macrophage function (Delgado & McLaren, 1989d); radio-resistant cells, perhaps macrophages, are thus implicated in this rodent model. Naive guinea pigs can be protected with serum harvested from polyvaccinated donors (McLaren, Delgado, Gordon & Rogers, 1989) and as with mice, IgG1 is the important isotype (Delgado & McLaren, 1989c).

## FACETS OF VACCINE IMMUNITY IN HETEROLOGOUS RODENT SYSTEMS

Although polyvaccine serum harvested from each of the rodent hosts discussed here is able to protect homologous naive recipients, comparable success has not been achieved in heterologous transfer systems (McLaren et al., 1989), even though the time of serum administration has been optimised for either the donor or the recipient species; this phenomenon seems likely to reflect incompatibility of the humoral and cellular arms of the immune response between heterologous rodent species.

Since mice and guinea pigs are at opposite ends of the spectrum in terms of the sites at which vaccine immunity is mediated (skin versus liver), we have recently devised experiments to ask whether liver stage mouse worms that are essentially refractory in vaccinated mice are susceptible to the liver phase immunity which characterises vaccinated guinea pigs. Surgical transfer experiments showed that this was indeed the case. Moreover, mouse-derived parasites, like age matched guinea pig worms, were susceptible only until 3 weeks of age (Delgado & McLaren, 1989d), thereby revealing a common end point to the window of susceptibility.

## THE SYNERGISTIC INTERACTION BETWEEN VACCINE IMMUNITY AND PRAZIQUANTEL

A number of workers have recently shown that the schistosomicidal compound Praziquantel seems to depend for its efficacy upon the immune status of the host. Such studies have centred upon chronically infected mice depleted of T or B cells and then treated with drug (Sabah, Fletcher, Webbe & Doenhoff, 1986; Brindley & Sher, 1988), or on naive mice treated concomitantly with Praziquantel and immune serum (Doenhoff, Sabah, Fletcher, Webbe & Bain, 1987). We have taken a different approach and looked for synergy between Praziquantel and vaccine resistance in mice (Flisser, Delgado & McLaren, 1989); the features of skin phase challenge attrition in our mouse model are now well documented (see above), so that drug induced changes in this pattern may be readily detected. In essence, only a marginally significant synergy is recorded when Praziquantel is administered to coincide with skin phase resistance, but a highly significant synergy is seen when drug treatment is tailored to coincide with worm migration through the lungs (Flisser et al., 1989). We have shown in addition that Praziquantel unmasks disguised parasite antigens on the surfaces of lung stage larvae(Flisser & McLaren, 1989) and that in consequence, the worms become trapped and eliminated within macrophage-rich focal

inflammatory reactions in the pulmonary vasculature (Piper & McLaren, unpublished data). Drug treatment therefore facilitates the expression of an additional phase of lung immunity in a mouse model normally characterised by a predominance of cutaneous attrition.

## SUMMARY AND CONCLUSIONS

Contrary to previous expectations, innate resistance to a primary schistosome infection is mediated predominantly in the lungs of many laboratory rodents. In addition, the phenomenon of non-permissiveness seen in a sub population of 129 strain mice, is associated with worm relocation from the liver to the lungs and is facilitated by dramatic alterations to the lung and liver vasculature; lung located adult worms exhibit gut damage and are ultimately destroyed within eosinophil-rich inflammatory focal reactions. It is now clear that the immunity induced by exposure to radiation-attenuated cercariae can be effected in the skin (mice), the lungs (mice and rats) or the liver (guinea pigs) of laboratory rodents. Moreover, the fact that skin phase resistance involves radio-sensitive cells, while lung and liver phase immunity centres on radio-resistant leucocytes, resolves current discord in the literature. Immobilisation and trapping of challenge larvae within focal inflammatory infiltrates is nevertheless common to both skin and lung phase attrition. Hyperimmunisation of rodents with irradiated cercariae is associated with a switch in immunoglobulin isotype and serum harvested from such donors is able to protect naive recipients passively; transferred serum recruits effector cells. Challenge parasites exhibit a broader window of sensitivity to vaccine immunity than was originally envisaged; stages ranging from the 3 to 4 day old skin/lung stage larva to the 3 week old juvenile liver worm constitute targets of protective resistance <u>in vivo</u>. This is at variance with the fact that newly transformed schistosomula constituting the primary targets of <u>in vitro</u> effector mechanisms, a feature perhaps related to our inability to mimic the process of intravascular parasite immobilisation and trapping in the test tube. Finally, schistosomicidal drugs such as Praziquantel can, by re-exposing disguised parasite antigens, facilitate the expression of vaccine immunity in sites additional to those at which resistance is normally mediated.

Animal models have thus yielded much new information over the last two years about mechanisms of vaccine immunity to schistosomiasis and although we do not know which of the available laboratory systems represents the best correlate of human immune responsiveness, it would appear that a putative vaccine for human use must bracket a broader range of parasite stages than was originally envisaged.

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