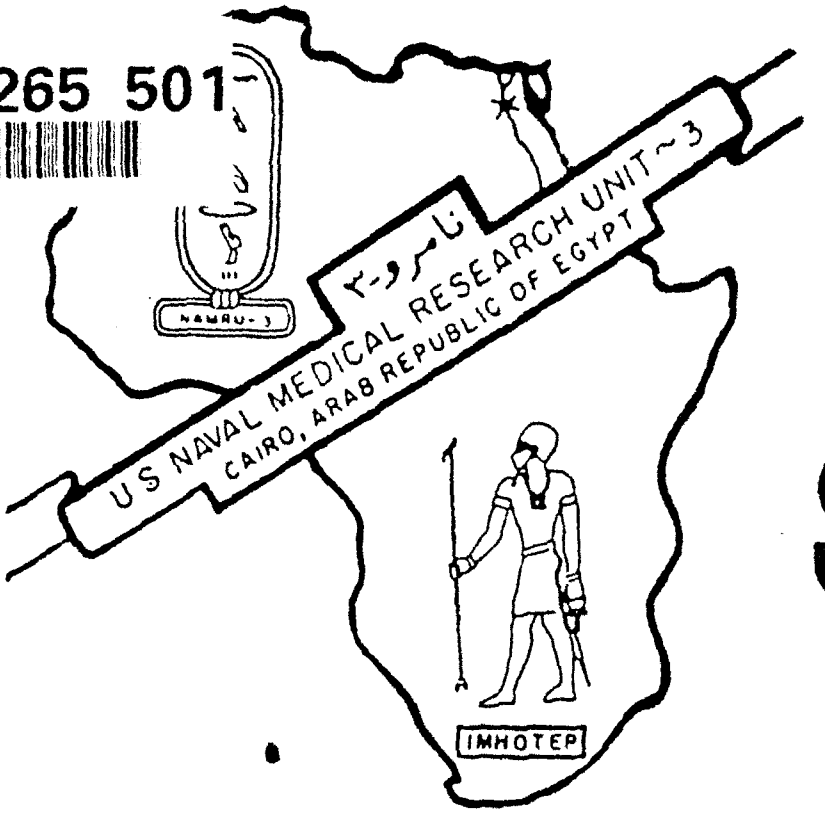

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COMBINED MICROAUTORADIOGRAPHIC AND HISTOPATHOLOGIC ANALYSIS OF THE FATE OF CHALLENGE SCHISTOSOMA MANSONI SCHISTOSOMULA IN MICE IMMUNIZED WITH IRRADIATED CERCARIAE

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COMBINED MICROAUTORADIOGRAPHIC AND HISTOPATHOLOGIC ANALYSIS OF THE FATE OF CHALLENGE *SCHISTOSOMA MANSONI* SCHISTOSOMULA IN MICE IMMUNIZED WITH IRRADIATED CERCARIAE

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Abstract. Combined microautoradiographic and histopathologic methods were used to locate and examine schistosomula of *Schistosoma mansoni* in the lungs of irradiated cercaria–immunized mice 21 days after percutaneous challenge infection with ^{75}Se-labeled cercariae. Of 75 schistosomula examined in serial sections, 53% were located in the pulmonary microvasculature, 23% in alveolar spaces, 3% with one end in a vessel and the other in an alveolar space, and the locations of 21% were not identified. Inflammatory reactions of variable intensity were observed around schistosomula in both vascular and alveolar sites, although the most intense category of reactions was associated almost entirely with alveolar larvae. All autoradiographic foci contained recognizable schistosomula. Although the concentration of reduced silver grains precluded cytostructural analysis, observations on schistosomular contour and shape provided no evidence of larval damage. Our findings suggest that immune elimination of schistosomula in mice immunized with irradiated cercariae is partly or largely effected by a process of alveolar extrusion of viable parasites during their lung migration.

Evidence from histologic and autoradiographic studies has indicated that the lungs represent a major site of *Schistosoma mansoni* elimination in both naive and immunized hosts.[1–11] The mechanisms responsible for this elimination and for the delay in migration to and from the lungs seen in most immune models have not been clearly defined. During the period when larvae disappear from the body, intense inflammatory foci, possibly representing sites previously occupied by larvae, have been observed in the lungs by light microscopy.[6] These foci were significantly more numerous in mice immunized with irradiated cercariae than in controls.

Over the last 70 years, there have been numerous observations of schistosomula in pulmonary air spaces.[7, 12–19] Most recently, Crabtree and Wilson used an ingenious method to identify ultrathin sections of lung tissue containing radioactivity associated with ^{75}Se-labeled larvae.[7] Examination of these sections by electron microscopy revealed that in both normal mice and mice immunized with irradiated cercariae, schistosomula shifted from vascular to alveolar sites with increased time spent in the lungs. Dead or damaged schistosomula were not detected in either site.

In the present study, we have combined microautoradiographic and histopathologic techniques to examine by light microscopy the autoradiographic foci produced in the lungs by ^{75}Se-labeled schistosomula. This approach complements those previously used to search for and examine schistosomula undergoing elimination. Conventional light microscopic images obtained with thin sections[6] and free of autoradiographic grains[4, 6] provide a more detailed picture of schistosomular morphology, but the addition of autoradiography provides a means of searching for sites occupied by larvae that have disintegrated beyond the point of recognition. The autoradiographic-electron microscopic method[7] provides a better means of assessing the condition of individual schistosomula, particularly those showing early or subtle damage, while light microscopy makes it possible to examine more larvae and to examine them in complete sets of serial sections.

The results of this microscopic study, coupled with macroautoradiographic tracking data for the

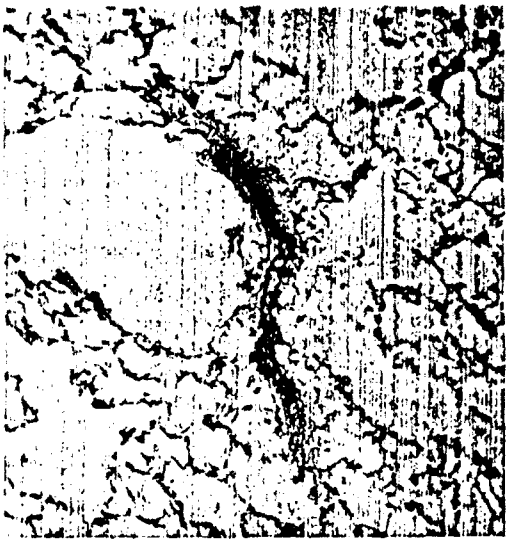

FIGURE 1. Schistosomulum of *Schistosoma mansoni* migrating along an interalveolar capillary, cut at its full length. Note the absence of an inflammatory reaction (hematoxylin and eosin stained, original magnification × 360).

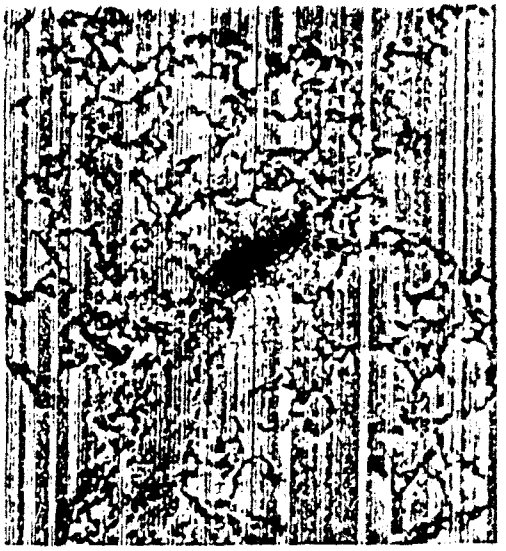

FIGURE 2. A somewhat contracted schistosomulum of *Schistosoma mansoni* occupying a dilated pulmonary venule. Note the absence of an inflammatory reaction (hematoxylin and eosin stained, original magnification × 360).

same batch of immunized mice,[11] our previous macroautoradiographic studies,[1-3] and other light and electron microscopic observation,[4-6,7] indicate that new hypotheses are needed to explain the process of schistosome elimination from the lungs.

MATERIALS AND METHODS

Host and parasite

The female C57Bl/6J mice used in this study were obtained from the Jackson Laboratories (Bar Harbor, ME). A Puerto Rican strain of *S. mansoni* maintained in *Biomphalaria glabrata* was used.[20] The cercariae used for immunization were exposed to 50 kilorads of gamma radiation from a cesium-137 source at a rate of 1,300 rads/min. Mice were immunized by three percutaneous (tail immersion) exposures to 539–572 irradiated cercariae at 0, 101, and 129 days. Twenty-six days after the third immunization, two mice were challenged by tail immersion exposure to 1,243 cercariae (mean of 1,228 penetrants) labeled with ^{75}Se-L-selenomethionine as previously described.[3] Both mice were killed 21 days after challenge. (Immunity of this batch of immunized mice to challenge infection was demonstrated in the accompanying report,[11] using the same pools of immunizing and challenge cercariae.)

Lung-stage schistosomula were obtained by exposure of mice to 3,000–4,000 radiolabeled cercariae and recovery of schistosomula seven days later by mincing and incubation of lungs.[21] The schistosomula were killed by suspending them in 1.0 ml of Earle's lactalbumin hydrolyzate medium (Gibco, Grand Island, NY) containing 5% normal mouse serum in a 12-ml glass conical tube and immersing the tube in a swirling 50°C bath for 5 min. They were then diluted with the same medium and approximately 2,100 schistosomula in 0.4 ml were introduced into each of two immunized mouse by tail vein injection.

Histologic and microautoradiographic analysis

Twenty-one days after percutaneous challenge or two days after intravenous injection of killed lung schistosomula, mice were killed by inhalation of CO_2. The lungs were slowly inflated by tracheal injection with neutral 10% formalin, stored in the same formalin, and embedded in paraffin. A portion of the lungs of each mouse was serially cut into 10-μ sections. All sections were dipped in Eastman Kodak (Rochester, NY)

FIGURE 3. Comma-shaped schistosomulum of *Schistosoma mansoni* in an alveolar space, outside the border of an adjacent, dense inflammatory focus (hematoxylin and eosin stained, original magnification × 360).

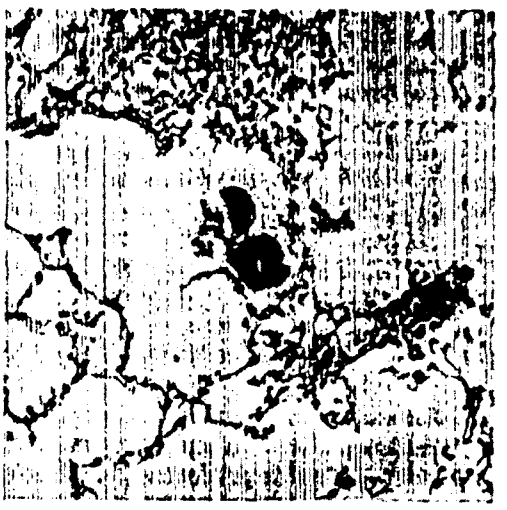

FIGURE 4. Shortened, broadened schistosomulum of *Schistosoma mansoni* in an atrial pulmonary air sac adjacent to an inflammatory focus (above) and to a distended pulmonary capillary (below) (hematoxylin and eosin stained, original magnification × 360).

NTB emulsion, air-dried, and stored in light-excluding black boxes at 4°C for 12–14 weeks. The slides were then developed in D-19 developer (Eastman Kodak) for 3 min, washed twice in distilled water, fixed for 2 min in acetic acid, washed for 10 min in distilled water, and lightly stained with hematoxylin and eosin.

Cellular reactions to schistosomula were classified as negative, with no focal accumulation of inflammatory cells above background levels; + (mild), with leukocyte density in the vicinity of schistosomula somewhat above background levels; ++ (moderate), with dense focal leukocytic reactions 2–5-cells thick or more diffuse reactions intermediate between + and +++; +++ (intense), with large, dense reactions more than five cells thick, which were usually highly focal and completely enveloping larvae and/or surrounding alveoli.

RESULTS

Percutaneous challenge

Immunized mice in this experiment were resistant to a challenge infection with 155 of the same batch of cercariae used for microautoradiography; adult worm burdens were reduced 75.3% relative to challenge controls.[1]

Autoradiographic foci were examined in 10-μ sections of the lungs of two immunized mice 21 days after challenge with ^{75}Se-labeled cercariae. Every autoradiographic focus found contained a schistosomulum. No schistosomula free of autoradiographic foci were found. Eighty-one serial sections (39 continuous sections from one mouse and 42 from the second) were examined. Seventy-five schistosomula and associated autoradiographic foci were examined in complete sets of serial sections (35 from one mouse and 40 from the other).

Fifty-three percent of the schistosomula observed were clearly within blood vessels (Figures 1 and 2), and 23% were clearly in air spaces (Figures 3 and 4). Three percent had one end in a vessel and the other end in an air space. The locations of the remaining 21% could not be determined (Table 1). A few alveolar larvae were associated with hemorrhages rather than with inflammatory foci.

Intense (+++) inflammatory responses were associated with 42.1% of the alveolar schistosomula, compared with only one (2.5%) intravascular schistosomulum (Table 2). Approximately twice as many vascular schistosomula were associated with mild (+) or moderate (++) reactions as were alveolar schistosomula, and 37.5% of vascular schistosomula and 26.3% of

TABLE 1

Distribution of Schistosoma mansoni *schistosomula in the lungs of irradiated cercaria-immunized mice 21 days after challenge with ^{75}Se-labeled cercariae**

Location of schistosomula	No. (%)
Blood vessels	40 (53)
Alveolar spaces	17 (23)
Both†	2 (3)
Undetermined location	16 (21)

* The mice examined were from experiment no. 4 reported in the accompanying paper.[11]

† These two schistosomula clearly had one end in a vessel and the other end in an alveolar space. Several in the undetermined location category were possibly of this type.

TABLE 2

Intensity of inflammatory cellular responses associated with Schistosoma mansoni *schistosomula in the lungs of irradiated cercaria-immunized mice 21 days after challenge infection with ^{75}Se-labeled cercariae*

Inflammatory response	% of schistosomula		
	Vascular	Alveolar	Undetermined
N (none)	37.5	26.3	18.8
+ (mild)	15.0	10.5*	6.2
++ (moderate)	45.0	21.1	18.8
+++ (intense)	2.5	42.1*	56.2

* Includes one schistosomulum with one end in a blood vessel.

alveolar schistosomula were completely free of focal inflammation. Most cellular reactions consisted of small and large mononuclear cells, together with some neutrophils and eosinophils. In some cases, granulocytes outnumbered mononuclear cells, while a few reactions were composed almost entirely of small mononuclear cells with granulocytes limited to their perimeters, resembling granulomas.

Brush-like inflammatory reactions,[6] either distal to or in the vicinity of schistosomula, were often seen in ++ reactions, especially those associated with vascular schistosomula. The +++ reactions associated with alveolar schistosomula were all dense and highly focal. In some cases, the cellular infiltrates filled the air spaces, obscuring their contours and surrounding the schistosomula. In others, the cells were limited to the adjacent tissue, revealing intact schistosomula free within the air spaces.

Both alveolar and vascular schistosomula appeared to be free of structural damage. Even when surrounded by intense inflammatory foci, no attachment of leukocytes to schistosomular surfaces could be detected. However, subtle parasite damage or cell attachment could not be conclusively ruled out by histologic analysis, since the thickness of the tissue sections and the density of autoradiographic foci often restricted detailed visualization.

Comparison of heat-killed with live challenge schistosomula

Two days after intravenous injection of heat-killed ^{75}Se-labeled lung schistosomula into the lung vasculature of immunized mice, all schistosomula had disintegrated beyond recognition. Nevertheless, numerous dense inflammatory foci were seen, and all of these foci contained schistosomular debris with overlying silver grains, identifiable as autoradiographic foci. Conversely, all autoradiographic foci observed were associated with dense inflammatory reactions. Although the autoradiographic foci produced by lung squashes were macroscopically found to be less numerous and less intense on day 2 than on the day of injection,[11] it is likely that the microautoradiographic method was sensitive enough to allow detection of injected larvae on day 2. Following a percutaneous challenge, numerous focal inflammatory reactions free of recognizable schistosomula were observed in the lungs, as had been reported previously.[6] None of these reactions was associated with concentrations of reduced silver grains that might represent the remains of a disintegrating schistosomulum.

DISCUSSION

Under most experimental conditions, the loss of *S. mansoni* from hosts immunized with irradiated cercariae following a challenge infection can be largely accounted for by the disappearance of schistosomula during the lung phase of migration.[4-10, 22] This was confirmed in the present study by macroautoradiographic observations in the accompanying report.[11] Exceptions that have been reported are elimination in the skin of monkeys,[23] elimination in the skin of CBA/Ca mice immunized with the Mill Hill strain of *S. mansoni*,[24-27] and additional larval elimination in the liver of guinea pigs.[25, 28]

von Lichtenberg and others observed that parasite-free inflammatory foci after challenge were significantly more numerous in the lungs of immunized mice than in control mice, and they

suggested that such residual inflammatory foci might represent sites of worm elimination.[6] At that time, testing of this hypothesis was precluded by the lack of markers for detecting schistosomular secretions or remnants in inflammatory foci. In the present study, ^{75}Se-L-selenomethionine provided such a marker. However, our examination failed to detect any parasite material in the lungs apart from that associated with structurally intact, apparently undamaged schistosomula. Clusters of reduced silver grains in the absence of larvae were seen only in sections adjacent to those containing larvae, and these sections were frequently completely free of silver grains. Similarly, Crabtree and Wilson did not find evidence of significant structural damage to lung-stage schistosomula of *S. mansoni* in their study.[7]

An important question is whether or not radioactive material left behind by disintegrating larvae would persist long enough in focal concentrations to allow detection of killing sites by autoradiography. In this study, heat-killed radiolabeled schistosomula injected into the lung vasculature continued to produce detectable autoradiographic foci for several days after the larvae had disintegrated beyond recognition. Similarly, larvae that died in the skin[29] and the lungs[4] from the effects of prior irradiation are associated with dense inflammatory foci prior to death, but can be identified morphologically (and therefore presumably by autoradiography) for some time after disintegration has begun. Therefore, it seems likely that any larvae that died in pulmonary inflammatory foci would leave behind radioactive evidence.

An alternative interpretation of parasite-free inflammatory lung foci is that they represent sites previously occupied by schistosomula, but subsequently vacated by them. This is an attractive hypothesis, but is difficult to test. As discussed above, radiolabeled larval products do not extend far beyond the schistosomular surface and therefore probably do not provide a reliable means of locating sites recently vacated by intact larvae.

The results of this study confirm the electron microscopic observations of Crabtree and Wilson,[7] which indicate that most *S. mansoni* schistosomula present in the lungs of irradiated cercaria–immunized mice after percutaneous challenge infection are intact and free of attached host leukocytes, in spite of the fact that they are often surrounded by large numbers of inflammatory cells. The finding that the most intense inflammatory reactions were associated almost exclusively with schistosomula located in alveoli (Table 2) could be due to the triggering of inflammatory responses by host tissue damage resulting from breaching of the capillary-alveolar barrier, the washing away of schistosomular exoantigens from schistosomula located in blood vessels, or both factors.

In conclusion, we believe there are three ways in which schistosomula could be eliminated from the lungs. First, schistosomula are destroyed in the lungs, but ^{75}Se-labeled parasite and host material is removed from the killing sites too quickly to be detectable as discrete autoradiographic foci. This seems unlikely in view of the present microscopic observations on migrating larvae, coupled with the data from previous studies on the numbers of parasites that disappear from the host lungs and body during the second and third weeks after challenge,[5, 11] and the fact that killed injected larvae and dying irradiated larvae[4, 29] are histologically detectable for several days. Second, the disappearing schistosomula may actively migrate out of the lungs by the vascular route and subsequently be destroyed in post-lung migration sites. Evidence against this proposal is provided by the failure of previous macroautoradiographic tracking studies to detect a post-lung site of larval accumulation other than the liver.[5, 11] Also, a great effort would presumably be required for schistosomula to return to blood vessels from alveolar spaces,[10] especially if surrounded by inflammatory cells. Third, intact live schistosomula may be eliminated from alveoli via the upper airways, and subsequently, via the gastrointestinal tract. This possibility was first suggested by Donato-Cioli and has been proposed by Crabtree and Wilson.[7] Evidence for such a mechanism has been provided by autoradiographic detection of schistosomula in the trachea and in the lumina of the esophagus, stomach, and intestines of nonimmune mice.[30] Additional evidence based on qualitative analysis of macroautoradiographic foci is presented in the accompanying report.[11]

Acknowledgment: The experiments reported herein were conducted according to the principles set forth in the current edition of the *Guide for the Care and Use of Laboratory Animals*, Institute or Laboratory Animal Resources, National Research Council.

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