

Arthritis, deformities, and runting in C5-deficient mice injected with human rheumatoid arthritis synovium

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SYNOPSIS The pathogenesis of rheumatoid arthritis might be more easily understood and the efficacy of therapeutic measures might be more accurately assessed if a convenient animal replica of this disease were available for laboratory study. Intraperitoneal injection of homogenates of inflamed synovium taken at operation from patients with rheumatoid arthritis produces inflammatory swelling and deformity in the tail and extremities of a proportion of injected mice from a complement (C5)-deficient inbred strain. Swelling of the paws leads to limping of the affected mice. The lesions are transmissible from generation to generation. The results support the theory of a transmissible agent in the inflamed synovium of rheumatoid arthritis patients.

It has been reported that intraperitoneal injection of synovium from affected joints of rheumatoid arthritis patients produced inflammation in the paws and tails of mice as well as in their non-injected progeny (Warren, Marmor, Liebes, and Hollins, 1969). Similar lesions were later also produced in chicks after inoculation of rheumatoid arthritis synovium homogenate into the air sacs of fertilized eggs and also in rats after ingestion of rheumatoid arthritis synovial tissue (Warren, Marmor, Boak, and Liebes, 1971; Warren, Marmor, Liebes, and Rosenblatt, 1972). We have injected homogenates of human rheumatoid arthritis synovial tissue into a C5-deficient strain of mice and have observed lesions similar to those described by Warren *et al.* We have also observed runting of growth in some of these mice.

Materials and Methods

Synovial tissues obtained during surgery from nine patients with active rheumatoid arthritis and five osteoarthritis patients were carefully freed of fat, washed in phosphate-buffered saline (0.01M, pH 7.1), homogenized, and stored at -70°C . C5-deficient SWR mice were originally obtained from the Jackson Memorial Laboratory (Bar Harbour, Maine). They were subsequently maintained in this labora-

tory by brother-sister mating. The complement deficiency of these mice was confirmed using the haemolytic test described by Cinader, Dubiski, and Wardlaw (1964). Aseptic techniques were followed during the collection, preparation, and injection of synovial tissue.

Pairs of adult male and female SWR mice of 20-22g were injected intraperitoneally with 13 mg wet weight of synovial tissue homogenate and then allowed to mate. The members of the resulting F_1 progeny were injected intraperitoneally within 24 hours of birth with 9 mg of synovial tissue homogenate (human). When 16 weeks old, members of this F_1 progeny were grouped in pairs of male and female and after intraperitoneal injection of 47.6 mg of synovial homogenate they were allowed to brother-sister mate. Each member of the newborn F_2 progeny received 4.76 mg of synovial homogenate intraperitoneally within 24 hours of birth. At maturity the members of the F_2 progeny were also grouped in male-female pairs, injected with 47.6 mg of synovial homogenate/mouse and then were allowed to mate. The newborn members of the F_3 generation similarly received intraperitoneal injection of synovial homogenate (4.76 mg/mouse) within 24 hours of birth, after which all injections of synovial homogenate were stopped. At maturity, the mice were separated in male-female pairs and were mated. Resulting offspring were not injected (see table).

Generation	Number	Abnormalities		
		Swollen Tail	Swollen Feet	Runts
F ₂	28	3	5	0
F ₃	72	1 ¹	7	6
F ₄	31	1	5	0

Table Results of injection of synovium from rheumatoid arthritis patients

¹Offspring which were not injected.

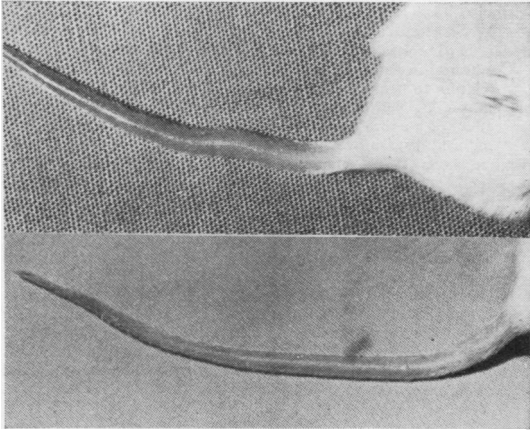


Fig 1 A rheumatoid synovium-injected F₂ SWR mouse with inflamed and swollen tail. The tail of an uninjected SWR mouse of approximately the same age is shown below for comparison.

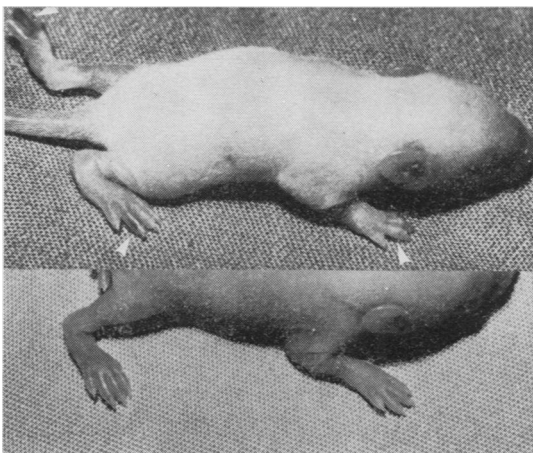


Fig 2 Red and swollen digits (marked with arrows) in the paws of a rheumatoid synovium-injected 2-week-old F₁ SWR mouse. The limbs of an uninjected SWR mouse of the same age are shown below for comparison.

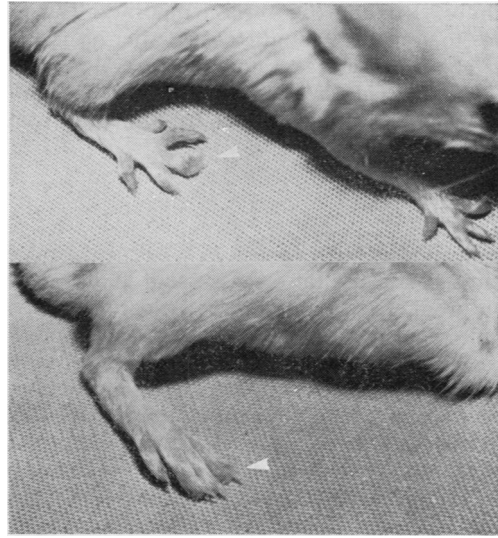


Fig 3 Crooked and terminally swollen digits after recurrent attacks of inflammation in a rheumatoid synovium/injected F₃, 9-month-old SWR mouse. The digits of the corresponding limb of an uninjected mouse of approximately the same age are shown below for comparison.



Fig 4 A 12-week-old rheumatoid synovium-injected F₃, SWR mouse showing 'runting'. Note the emaciation and ruffled fur.

Results

The type of abnormality and its observed incidence in the different generations of SWR mice is presented in the table. Swelling and inflammation of tails (fig 1) and paws (fig 2) were always transient. However, recurrent episodes of inflammation ultimately led to persistent deformities of the tails and limbs (fig 3). Usually the affected mice had lesions in all the

four limbs. Runting (fig 4) was temporary. 'Catch-up' growth took place about 16 weeks after birth. No similar abnormalities were noted in several generations of uninjected SWR mice or SWR mice similarly injected with homogenates of synovium from osteoarthritis patients.

Discussion

The indication of joint lesions in C5-deficient mice is interesting because this suggests that joint lesions can be produced without the participation of the classical complement cascade. This may be similar to those human conditions where arthritis similar to rheumatoid arthritis is found in agammaglobulin-aemic and complement-deficient patients (Christian, 1971; Lawrence, 1970).

Complement depletion by cobra venom in Freund's adjuvant arthritis in rats delays the onset of arthritis in these animals (Kourounakis, Nelson, and Kupusta, 1973). Whether the relatively low numbers of animals having arthritis in our work compared with the Warren model is due to the complement deficiency, we are unable to state at present. Though it confirms the observation of Warren *et al*, our study has not yet elucidated either the aetiology or the nature of arthritis in these

experimental models. Similarly the cause of runting and delayed skeletal development in these mice has yet to be explained.

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