

Passive transfer of human atopic allergies into lemurs, lorises, pottos, and galagos: Possible primate-ordinal specificity of acceptance of passive sensitization by human atopic reagin

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Reaginic sera from patients with atopic allergy to various atopens were shown to confer passive sensitivity upon the skins of higher primates (Anthropoidea) and upon the lorisiforme and lemuriforme Prosimii. Of the Prosimii, Galago crassicaudatus was found to be most suitable for allergic serum transfer studies. Human allergic sera failed to sensitize the skin of the primate-like insectivore, Tupaia glis (tree shrew). Representative species of orders Carnivora, Ungulata, Lagomorpha, Rodentia, Marsupialia, and Microchiroptera failed to accept passive sensitization by human reaginic sera. Acceptance of passive skin sensitization by human atopic reagin may be an ordinally specific characteristic limited to the primates.

Atopic reagins are the serum antibodies responsible for the hypersensitivities of the mucous membranes observed in hay fever and some types of asthma.^{1, 2, 3} These abnormal antibodies may also mediate acute, immediate reactions observed in clinical skin tests, in status asthmaticus, and in systemic allergic shock.^{4, 5, 6} Atopic reagins of human allergic sera will passively sensitize skin and other tissues of normal nonallergic (nonatopic) human beings.^{1, 2} This passive transfer phenomenon is the basis of a useful diagnostic method by Prausnitz and Küstner² and is called in their honor the "Prausnitz-Küstner" (P-K) test for allergy.

The atopic reagins are nonprecipitating antibodies and are inactivated by heating at 56° C. for 1 to 4 hours.^{4, 7, 8} They appear to be gamma-1A (γ_{1A})-globulins.^{5, 7, 8}

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We have shown^{4, 9} that human allergic sera will confer passive atopic hypersensitivity (passive allergy) upon apes and upon monkeys of both the Old World and the New World. Human allergic sera also passively sensitized the slow loris (*Nycticebus coucang*) of Asia.¹⁰

We believe that it is of interest for primatologists and immunologists to know whether or not other genera of prosimians and the more common non-primates can be passively sensitized by allergic serum transfer. An important question to be answered in part is whether such acceptance of passive sensitization by human reagin is ordinaly specific for primates.^{9, 10, 11, 12, 13}

EXPERIMENTAL

The allergic serum transfer (AST) test in nonhuman primates has been described in detail by the author.^{4, 9} Briefly, it is as follows: Several skin sites in the experimental animals were injected intradermally with 0.05 ml. of undiluted sera from the blood of untreated allergy patients who had shown strongly positive skin scratch tests with the offending atopens. Twenty-four to 72 hours after passive sensitization, the animals were given intravenous injections of Evans-blue dye followed by intravenous challenge with an excess of the allergenic extract (atopen). The serum-injected sites were observed for visible reaginic reactions (erythema, whealing, piloerection, or extravasation of the blue dye). Ordinarily, the most reliable criterion of passive allergic reaction in the skin of monkeys is extravasation of dye; erythema and whealing, are usually absent even during strongly positive reaction accompanied by intense extravasation of dye.^{4, 9} The passively sensitized sites were photographed in color before challenge and again when allergic reactions were maximal.

ANIMALS

AST tests were conducted upon various macaques (rhesus, cynomolgus, speciosus), baboons, African cercopithecoid monkeys, and South American Aötus, capuchins, squirrel-monkeys, and marmosets, as well as on the prosimians, *Nycticebus coucang* (slow loris) of Asia, *Perodicticus potto* (potto) and *Galago crassicaudatus* (greater Bushbaby) of Africa, and *Lemur fulvus* (lemur) of Madagascar. We also tested five specimens of *Tupaia glis* (tree shrew) of Asia. The Aötus or "night monkey" of South America may be a prosimian.^{13, 14} The tree shrew is considered by some workers^{11, 12, 13} to be a lemuriforme prosimian. Other workers consider tree shrews to be Insectivora^{12, 13, 15} Nonprimate mammals tested were: Carnivora (dog, cat, kinkajou); Ungulata (swine, sheep); Lagomorpha (European hare); Rodentia (guinea pig, rat, mouse); Marsupialia (opossum); Microchiroptera (pallid bat).

Of the class Aves (birds) we tested only the White Leghorn chicken which belongs to the order Gallinaceae.

SERA

Reaginic sera were obtained from clinical patients of Dr. Raphaël Panzani, Marseilles, France, and Dr. Frank Perlman, Portland, Oregon. Sera selected for passive transfer were obtained from the blood of atopic patients who had never



Fig. 1

Anthropoidea (Macaca mulatta [rhesus]). Passive allergic skin reactions with extravasation of dye after intravenous challenge with castor bean protein. Lesions are visible on eyelid, jaw, and abdomen.

been given hyposensitization treatments. The sera were known to contain thermolabile skin-sensitizing antibodies, and none contained thermostabile skin-sensitizing antibodies to the atopens involved.^{4, 9} Some of these sera had also been tested by PK tests in human volunteers.

ALLERGENS

The allergens (atopens) used in testing the animals were: a nontoxic allergenic protein from the seed of *Ricinus communis* (castor beans),¹⁶ aqueous extracts prepared from Santos and Robusta varieties of green coffee,¹⁷ penicillin V potassium, and commercial extracts of giant ragweed, household insects, and mixed pollens of spring grasses. The castor bean protein, extract of green coffee, and penicillin V were each dissolved in isotonic saline to give test solutions containing 50 mg. of atopen per milliliter of solution. The commercial allergenic extracts were used as supplied by the manufacturer.*

RESULTS AND DISCUSSION

Catarrhine and platyrrhine primates

All of the higher primates (ape and monkeys) challenged by the appropriate allergens exhibited intense extravasation of the Evans blue dye into the allergic

*Berkeley Biologicals Company, Berkeley, Calif.

lesions in the passively sensitized sites.⁴ The lesions were pure blue; whealing and erythema were minimal or entirely absent. None of the monkeys exhibited significant respiratory or systemic distress during or after the skin reactions. Intensities of skin reactions are shown in Table I. Passive allergic skin lesions rather typical of those observed in all of the Anthropoidea are shown on the rhesus monkey in Fig. 1.

PROSIMIANS

Nycticebus coucang (slow loris) exhibited strong passive allergic skin reactions to intravenously injected castor bean protein but only faint reactions to extract of green coffee, ragweed, and penicillin V. The first appearance of the violet-colored lesions could be detected within the time from 2 to 5 minutes after challenge in healthy specimens (Fig. 2).

Passive allergic reactions in *Perodicticus potto* (potto) were essentially identical to those observed in the slow loris. Lorises and pottos have thick tough skins, hence it was necessary to cut the skin in order to make intravascular injections.

Young galagos are gentle and easily handled. Their skin is white, soft, and easily injected. The saphenous veins are just beneath the skin for the entire length of the legs. Passive allergic skin reactions were slightly retarded, and

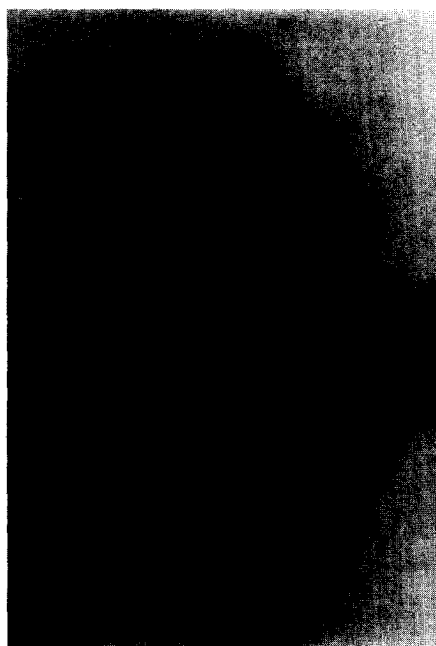


Fig. 2

Prosimian (*Nycticebus coucang* [slow loris]). Passive allergic skin reactions and extravasation of dye after challenge with castor bean protein. Lesions appeared as violet-blue rings surrounding relatively colorless injection site centers. Injection sites were marked with picric acid for ease of location.

were accompanied by whealing and intense extravasation of dye. Passive skin reactions to penicillin, house dust, and grass pollens (see Fig. 3) were much more intense than those observed in other prosimians, and were very similar to reactions observed in infant macaques and capuchins.

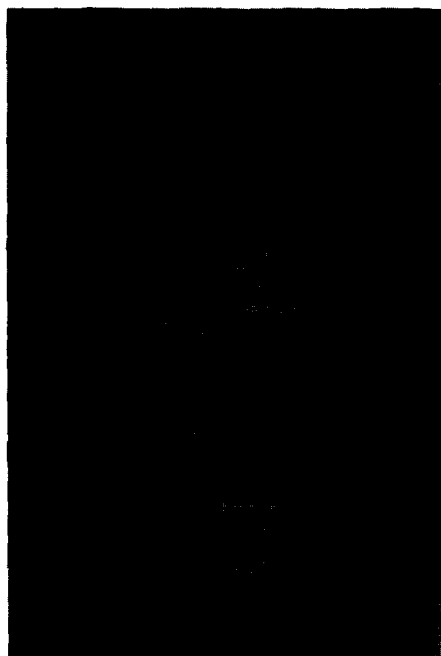
Our specimens of lemur had thin skin underlaid by a thick layer of fat over the whole abdomen and chest. Both the male and the female were injected with 6 of the castor bean reaginic sera that had been used in testing the monkeys, lorises, and pottos. Two nonreaginic sera were included as controls.

The male lemur was challenged via the femoral artery, first with green coffee administered together with the Evans blue dye. After 5 minutes and no visible reaction, we challenged via the femoral artery with 5 mg. of castor bean protein. In approximately 12 to 15 minutes extravasation became visible as purple lesions in the sensitized sites. There was no whealing at any time, nor was there erythema prior to extravasation of dye. This animal was photographed (Fig. 4) and returned to the cage to allow time for more intense color to develop. Next, the female lemur was challenged via the femoral artery with 5 mg. castor bean protein together with the Evans blue dye. By this time 22 minutes had elapsed since the male had been challenged. The male lemur became listless and appeared to be ill. Suddenly he coughed violently and expelled a large volume of mucus together with a small quantity of gastric contents. This



Fig. 3

Prosimian (*Galago crassicaudatus*) passive allergic skin reactions with whealing and extravasation of dye after challenge with penicillin G (left arm) and house dust (abdomen, right breast, and left hip).

**Fig. 4**

Prosimian (*Lemur fulvus*) Passive allergic skin reactions and extravasation of dye after intravenous challenge with castor bean protein.

animal was depressed and retched several times. He was immediately given epinephrine, cortisone acetate, and Benadryl, all intramuscularly. Three more times, the animal expelled volumes of mucus; the last mucus contained traces of the blue dye. The female had not yet shown any sign of reaction, but because of the value of the animal, we decided to administer prophylactic treatment. She was given 0.2 ml. of 1:1,000 epinephrine by the intramuscular route. This was followed by 12 mg. cortisone acetate and 4 mg. of Benadryl. These drugs apparently arrested (or prevented) allergic skin reactions. About 20 minutes after challenge with allergen, the female began to show respiratory distress and finally coughed up a volume of mucus. Her severe reactions subsided within a few minutes, but she continued to be listless. In the male, nausea and respiratory syndromes subsided slowly over a period of about two hours. No change in the violet skin lesions occurred after administration of the drugs. It appears that our specimens of *Lemur fulvus* had relatively low skin reactivity, similar to that of the loris. It also was evident that physiologically significant amounts of human allergic antibody were transferred from the injection sites in the lemurs' skin to the tissues of the respiratory and gastrointestinal systems, rendering these tissues exquisitely sensitive to the atopen. Similar passive allergic shock reactions (some fatal) have been produced in monkeys passively systemically sensitized by intravenous injection of human allergic sera.⁶

The Aötus is considered to be the most primitive platyrrhine monkey. Hanson and Montagna have suggested¹⁴ that this species might qualify as a New

World prosimian. Passive allergic skin reactions in the three healthy specimens that we tested were more similar to those observed in a debilitated slow loris than to the reactions exhibited by Capuchins, marmosets, and macaques.

Five specimens of *Tupaia glis* (4 males and 1 female) were tested. Only one of these, a male, showed slight extravasation in several sites when he was challenged 18 hours after serum injection; none of the *Tupaia* showed passive skin reactions when challenged 48 hours after serum injection. We were also unable to elicit systemic allergic shock or skin reactions in the one specimen that had been injected intravenously with 2 ml. of highly reaginic pooled sera⁶ from castor bean allergic patients. This same pooled serum sample had been tested and shown to sensitize monkeys for fatal passive allergic shock.⁶ We were forced to conclude that this species does not accept passive sensitization by ("recognize") human atopic reagin. The slight extravasation of dye observed in one probably was due to local nonspecific irritation by the human sera. We have

Table I. Results of allergic serum transfer (AST) tests for passive sensitization by human atopic reagents in the skin of primate and nonprimate species

Representative species receiving human sera	Sera from donors with clinical atopy to:	Relative intensities of extravasation during passive allergic skin reactions
Primates		
Anthropoidea:		
<i>Pan satyrus</i> (chimpanzee)	Castor bean (CB)	3+
<i>Papio cynocephalus</i> (baboon)	CB, insects, ragweed	4+
<i>Erythrocebus patas</i> (African red)	CB, celery, penicillin, grasses, ragweed	4+
<i>Macaca mulata</i> (rhesus)	CB, grasses, penicillin, green coffee	4+
<i>Macacus speciosus</i> (stump-tail)	CB, penicillin, pollens	4+
<i>Cebus capucinus</i> (capuchin)	CB, penicillin, pollens	4+
<i>Tamarinus nigrocollis</i> (tamarin)	CB, penicillin	4+
<i>Aotus trivirgatus</i> (night monkey)	CB, green coffee	2+
Prosimii:		
<i>Nycticebus coucang</i> (slow loris)	CB, ragweed, penicillin	3+
<i>Perodicticus potto</i> (potto)	CB, ragweed, penicillin	3+
<i>Galago crassicaudatus</i> (greater bush baby)	CB, penicillin, house dust, grass pollens	4+
<i>Lemur fulvus</i> (lemur)	CB, green coffee	3+
Nonprimates		
<i>Insectivora</i> (<i>Tupaia glis</i> [tree shrew])	CB, penicillin, green coffee	0 to $\pm$
<i>Carnivora</i> (dog, cat, kinkajou)	CB, penicillin, ragweed, green coffee	0
<i>Ungulata</i> (swine, sheep)	CB, ragweed, green coffee, penicillin	0
<i>Lagomorpha</i> (European hare)	CB, ragweed, green coffee	0
<i>Rodentia</i> (rat, mouse, guinea pig)	CB, ragweed, green coffee	0
<i>Microchiroptera</i> (pallid bat)	CB, penicillin, green coffee	0
<i>Marsupialia</i> (opossum)	CB, penicillin, green coffee, ragweed	0
Class Aves (birds):		
<i>Gallinaceae</i> (chicken)	CB, green coffee, ragweed	0

Scale: 5 mm. = +, 5-10 mm. = 2+, 10 to 15 mm. = 3+, 15-20 mm. = 4+. 0 = no reaction, $\pm$ = questionable.

observed similar nonspecific irritation and extravasation in monkeys injected with dye within 6 hours of the serum injections, and in guinea pigs injected within 4 to 6 hours after injection of undiluted rabbit serum. Ovary¹⁸ has described such traumatic (nonspecific) leakage of dye in guinea pigs. Stanworth¹⁹ has discussed reaginic reactions in man, and failure of nonprimates to fix human reagin.

None of the nonprimates that we examined showed any tendency to bind human reaginic antibodies in their skins. There were no passive, allergic skin reactions or systemic reactions when they were challenged intravenously with 25 mg. of the atopens. The kinkajou developed color in two sites injected with a serum from one French patient, but none of the other sites injected with 12 highly reaginic sera showed any reactions. The kinkajou died of injuries before we could repeat the tests. The Fish and Wildlife Service will not permit importation of this species for any purpose, hence we have been unable to re-examine the kinkajou. Results of allergic serum transfer tests upon several nonprimates are shown in Table I.

CONCLUSIONS

Major genera of primates of both suborder Anthropeidea and suborder Prosimii, excepting the tree shrew (*Tupaia glis*), accept passive sensitization by ("recognize") human atopic reagins. None of the nonprimates tested so far has accepted passive sensitization by human atopic reagin. The acceptance of passive sensitization by (recognition of) human atopic reagins may be an ordinarily specific phenomenon limited to the primates.

Frank C. Greene, M.Sc., assisted in testing slow lorises, pigs, and sheep. Dr. William Montagna, Director, Oregon Regional Primate Center, permitted us to utilize his lemurs and laboratory facilities. Dr. Arthur Malley arranged for assistants in tests run at the Primate Center: C. W. De Lannoy, D. V. M., treated the lemurs for allergic shock. Iris Turtle, M. Tech., assisted in testing the lemurs. Edward Duro, Jr., handled and attended to the lemurs. Human sera were provided by Raphaël Panzani, M.D., Marseilles, France, and Frank Perlman, M.D., Portland, Oregon. Photographic credit: William G. Murray, Western Regional Research Laboratory, and Ralph W. Prouty, B.A., Oregon Regional Primate Center.

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