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Relation of Sex and Age to Resistance of Mice to Experimental Histoplasma Infections.* (22046)

SAMUEL SASLAW AND JOHN SCHAEFER.
Department of Medicine, College of Medicine, Ohio State University, Columbus.

Preliminary studies from this laboratory indicated that age affected the resistance of white Swiss male mice to experimental histoplasmosis(1). Campbell and Saslaw(2) using 14- to 17-g white mice noted a greater mortality in males. Salvin(3) reported no sex differences in mortality of 35-day-old mice. The purpose of this report is to elucidate further the sex and maturity factors relative to histoplasma infections in mice.

Materials and methods. Five-week-old white Swiss mice of both sexes were obtained at one- or 2-week intervals and kept until there were groups representing these age intervals from 5 through 23 weeks. The numbers of mice used in each group varied according to availability. The mice were inoculated intraperitoneally with 23 or 35 million yeast phase *H. capsulatum* organisms in 0.5 ml of 5% hog gastric mucin. All mice were weighed on the day of inoculation, and at weekly intervals. The mice were observed for a 30-day period and necropsy performed on those dying during this interval.

Results. Table I summarizes the results of these studies. Column A in Table I demonstrates that 10- to 15-week-old male mice receiving 23 million organisms showed increased resistance to fatal infection as compared to those 5 and 9 weeks old. A further increase in resistance was noted in those 16 weeks or older. With the 35 million dose (column C) the increased resistance was first noted at 17 weeks of age. The parallel studies in female mice with the lower dosage (column B) showed a similar increase in resistance at 8 weeks as compared to 10 weeks in males and a further increase in survival rate after 15 to 16 weeks of age. With the 35 million dose (column D) the 2 periods of comparative increased resistance were noted at 9 and 17 weeks in females and males, respectively. In comparing the death rates in both sexes receiving 23 million organisms the 8-week-old male mice showed 19 of 22 deaths (86.5%) as compared to 14 of 25 female deaths (56%); in the 9-week-old group, 9 of 10 males (90%), and 7 of 11 females (63.3%) died. Thereafter the incidence was similar except at 15 weeks when 8 of 12 males, as compared to 4 of 10 females, died. In those mice receiving 35 million organisms the differences in resistance of sexes became apparent in the 9-week-old mice where 15 of 16 males (93.7%) as compared to only 9 of 15 females (60%) died. This difference became less apparent by the 13th week and no appreciable variation was noted thereafter. Combining the total mortalities under both sex groups the 8- to 14-week period represented the time interval when apparent sex differences in susceptibility occurred (Table II). As can be seen in Table II, when all of the age groups were combined no significant difference between sexes was noted following inoculation with 23 million organisms, since 174 of 337 females (51.6%) died as compared to 183 of 331 males (55.3%). However, with the 35 million dose, the males were significantly more susceptible in that 105 of 145 males (72.5%)

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TABLE I. Effect of Age on Resistance of White Swiss Mice to Histoplasmosis.

Challenge dose, 23 million					Challenge dose, 35 million				
	Deaths					Deaths			
	A ♂		B ♀			C ♂		D ♀	
Age (wk)	No.	%	No.	%	Age (wk)	No.	%	No.	%
5	10/10*	100.0	10/10	100.0	5	15/15	100.0	15/15	100.0
6	31/32	96.8	32/33	96.9					
7	10/10	100.0	10/10	100.0	7	15/15	100.0	14/15	93.3
8	19/22	86.4	14/25	56.0					
9	9/10	90.0	7/11	63.3	9	15/16	93.7	9/15	60.0
10	13/25	52.0	13/26	50.0					
11	6/10	60.0	6/10	60.0	11	13/15	86.6	10/15	66.7
12	13/24	54.2	13/27	48.1					
13	8/11	72.7	6/10	60.0	13	10/12	80.0	11/16	68.7
14	16/26	61.5	14/23	60.8					
15	8/12	66.7	4/10	40.0	15	12/15	80.0	11/15	73.3
16	8/23	34.8	8/25	32.0					
17	3/9	33.3	4/10	40.0	17	7/15	46.7	6/15	40.0
18	6/27	22.2	8/26	30.7					
19	3/10	30.0	4/9	44.0	19	5/14	35.7	4/14	28.0
20	5/24	20.8	7/25	28.0					
21	3/10	30.0	3/10	30.0	21	7/15	46.7	5/14	35.7
22	8/26	30.7	7/27	25.9					
23	4/10	40.0	4/10	40.0	23	6/14	42.8	7/15	46.7

* Numerator = No. of deaths. Denominator = Total No. inoculated.

died as compared to 92 of 149 females (61.7%). As can be seen in Table III, the increase in resistance was not merely a difference of weight. For instance, while the weight of male animals from 5-9 weeks of age increased 4.4 g (12.9 to 17.3 g) there was no significant increase in resistance, but between the 9th and 10th week the fatality dropped from 94.4 to 59.2% while the weight increased only 0.2 g.

Discussion. The data presented in these studies suggest that age, sex and dosage affect the susceptibility of white Swiss mice to experimental histoplasma infections. Increased resistance became apparent by the 8th and 10th weeks, respectively, in females and males when 23 million organisms were inoculated. With more severe challenge (35 million organisms) increased resistance was noted at 9 weeks of age in females; the males showed equal susceptibility through 15 weeks, but increased resistance at 17 weeks. These latter results differ slightly from those previously reported by us in which the period of increased resistance in males was noted at 14 weeks of age(1). This difference may be attributed to the fact that a more careful definition of age was made in this study in that all mice were originally obtained at 5 weeks of age, and then held until the desired age group was obtained. In the previous study the specified age groups were ordered from the animal farm which could have resulted in more variation in comparative ages. Thus, it appears that females become more resistant at a slightly earlier age (8 weeks, as compared to 10 in males) with 23 million organisms as inoculum, but this difference was more marked after the 35 million dose, in that females showed significantly greater survival as early as 9 weeks of age, as

TABLE II. Comparison of Resistance of Male and Female Mice of Same Age Groups.

Dose (million)	Sex	5-7-wk mice		8-14-wk mice		15-23-wk mice		Total	
		Deaths							
		No.	%	No.	%	No.	%	No.	%
23	♀	52/53*	98.1	73/132	55.3	49/152	32.2	174/337	51.6
23	♂	51/52	98.0	84/128	65.6	48/151	31.7	183/331	55.3
35	♀	29/30	96.7	30/ 46	65.2	33/ 73	45.2	92/149	61.7
35	♂	30/30	100	38/ 43	88.4	32/ 72	51.4	105/145	72.5

* No. of deaths/No. of mice infected.

TABLE III. Comparison of Weights with Age and Resistance of Mice.*

Age (wk)	Sex	Variations in avg wt (g) of age groups	Increase in avg wt (g) of age groups	Avg % fatalities of group
5- 9	♂	12.9-17.3	4.4	94.4
10		17.3-17.5	.2	52.0
11-15		17.5-21.3	3.8	59.2
16		21.3-21.4	.1	34.8
17-23		21.4-23.5	2.1	28.7
5- 7	♀	12.6-15.3	2.7	98.1
8		15.3-15.7	.4	56.0
9-14		15.7-19.0	3.3	55.3
15		19.0-19.3	.3	40.0
16-23		19.3-22.4	3.1	32.2

* Inoculated with 23 million yeast phase *H. capsulatum* in 0.5 ml mucin.

compared to 17 weeks in males. Between 8 to 14 weeks of age females appeared to be especially more resistant than males. This observation can probably be attributed to the fact that female mice mature more rapidly than males(4). Thus, before and after full development of sexual maturity the differences in susceptibility were not appreciable. These results are also comparable to those observed by Theiler(5) in which the morbidity and mortality rates in experimental encephalomyelitis of mice were lower in mice over 12 weeks of age. The recognition of such differences in susceptibility in different age and sex groups can assist in the evaluation of data in a variety of studies employing the mouse as the experimental animal.

Conclusions. Age, sex, and dose are important factors in comparative susceptibility of mice to fatal histoplasma infections. Both sexes may show lower mortality ratios with increasing age. Females develop resistance earlier than males. This difference is most apparent between 8 to 14 weeks.

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Laboratory and Clinical Observations on Mecamylamine as a Hypotensive Agent.* (22047)

JOHN H. MOYER, RALPH FORD, EDWARD DENNIS, AND CARROLL A. HANDLEY.
(With the technical assistance of Ann Hall and C. Polk Smith.)
Baylor University College of Medicine, Houston, Texas.

Currently available ganglionic blocking agents used for the treatment of hypertension produce an inconstant day to day reduction in blood pressure largely due to incomplete and variable absorption of the quaternary ammonium compounds (bisammonium) from the intestinal tract. Mecamylamine, a secondary amine† is the first known ganglionic blocking agent which is completely absorbed after oral administration. The hemodynamic effects have been studied both in the laboratory as well as in patients with hypertension.

Methods and materials. Laboratory observations: Observations on the blood pressure response and on ganglionic blockade were made on 29 dogs anesthetized with 30 mg/kg of pentobarbital. The dogs were divided into 2 groups. Group I consisted of 12 dogs on which observations were made relative to doses which effectively blocked the autonomic ganglia and consequently reduced the blood pressure. Group II consisted of 17 dogs on which observations on the effect on renal hemodynamics and the excretion rates of water and electrolytes were made. *Group I.* Arterial blood pressure was measured by direct intra-arterial manometry in these ani-

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† 3-Methylaminoisocamphane hydrochloride. Available as Inversine by Sharp & Dome, Division of Merck & Co., West Point, Pa.