TABLE II.
Resistance of Rabbit Families to Inoculation of Standard Doses of Bovine Tubercle Bacilli.

.2 mg Ravenel intracultaneously		.001 mg Ravenel per kilo intravenously	
Rabbit No. generation and family	Survival in days	Rabbit No. generation and family	Survival in days
A 3-9	291		
A 3-11	296		
A 3-12	241*		
Avg	276 ± 25		
B 3-5	176	B 3-12	125*
B 3-6	123*	B 3-13	196
B 3-7	196	B 3-16	170
		B 3-15	159
Avg	165 ± 30	Avg	162 ± 25
H 2-19	123	H 2-29	79
H 2-22	108	H 2-31	73
H 2-23	133	H 2-26	78
H 2-24	134	H 2-32	82
Avg	124 ± 21	Avg	78 ± 4

*Tuberculosis complicated by an intercurrent infection.

of these families to tuberculosis has been tested by the inoculation of standard quantities of tubercle bacilli by various routes. Two such titrations of the families A, B, and H are presented in Table II.

It is clear from this table that the A family is most resistant. The B family is of intermediate resistance and the H family of lowest resistance of the 3 families considered. This is the same order of resistance that these families exhibited when they acquired tuberculosis by contagion.

In the succeeding paper further corroborative evidence is presented of the relative resistance of these families to standard doses of tubercle bacilli.

10139 P

Nature of Inherited Natural Resistance to Tuberculosis.

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In an endeavor to elucidate the physiological bases of the inherited constitutional resistance to tuberculosis in the families discussed in the preceding report the following experiment was performed. About 4 litter mates of each of the third or fourth gen-

erations of the families A, B, C, D, F, and H were treated with standard quantities of heat-killed bovine tubercle bacilli. The volume of inflammation that resulted from the primary intracutaneous injection of 1.0 mg of the killed tubercle bacilli served as a measure of the primary inflammatory response of the tissues of the different rabbit families to the injected bacilli. The treatment with dead tubercle bacilli was then continued until a maximum sensitivity developed to a standard quantity of tuberculin injected intracutaneously. The volume of inflammation due to the tuberculin was regarded as a measure of the innate capacity of the tissues to acquire inflammatory responsiveness as a result of sensitization; for under these conditions the antigen responsible for the sensitization was constant, as it could not multiply. After a certain period all these rabbits were then infected uniformly with 0.2 mg of living virulent bovine Ravenel tubercle bacilli intracutaneously. The development of the local lesion and its course were carefully observed, together with the progress of the disease in the draining lymph nodes and internal organs. The volume of inflammation that resulted after intracutaneous injection of a standard quantity of tuberculin at the height of sensitivity during the course of the disease was regarded as a measure of the sensitization of infection or allergy. On the seventy-second day following the virulent infection all the rabbits were given an intracutaneous injection of 0.5 cc of a 1:5 dilution of India ink. On the next day the area of spread of the ink was determined. This area was regarded as a measure of the permeability of the tissues to particulate matter. The rabbits were then permitted to die from their disease. It may be stated here that preliminary treatment with heat-killed tubercle bacilli did not as a rule materially affect the survival of these animals as determined by previous experience, though it must be admitted that an element of acquired resistance was probably introduced by this treatment. It must be emphasized, however, that sensitization did not alter the relative resistance of these families. The resistance to tuberculosis of each individual rabbit as measured by its survival was correlated with the spread of India ink in its own skin, the primary inflammatory response of its skin to heat-killed tubercle bacilli, the degree of responsiveness of its tissues to sensitization with heat-killed tubercle bacilli, the degree of its sensitization from the virulent infection, the rate of development and healing of its lesion at the portal of entry.

Table I presents the arithmetical average of each of the above observations for each of the 6 families studied. The families are arranged in the order of decreasing resistance. It will be noted in the

TABLE I.

Relation in Rabbit Families between Resistance to Tuberculosis and
(a) Permeability of Skin to India Ink.
(b) Primary Inflammatory Response of Tissues to Tubercle Bacilli.
(c) Acquired Inflammatory Responsiveness of Tissues.
(d) Sensitization of Infection (Allergy).
(e) Rate of Reaction at Portal of Entry.
(f) Rate of Healing at Portal of Entry.

Order of resistance to tuberculosis measured by survival in days after a standard infection	Order of permeability of the skin to India ink measured by spread of a standard quantity of India ink 24 hr after intracutaneous injection	Order of primary inflammatory response of tissues to tubercle bacilli measured by vol. of inflammation resulting 5 days after primary intracutaneous injection of standard quantity of heat-killed tubercle bacilli	Order of acquired inflammatory responsiveness of tissues to tuberculin measured by vol. of inflammation resulting from injection of a standard quantity of tuberculin after max. sensitization with heat-killed tubercle bacilli	Order of sensitization of infection—allergy measured by vol. of inflammation resulting from injection of standard quantity of tuberculin during height of allergy of infection	Order of rate of reaction at portal of entry measured by vol. of local lesion on fourteenth day after inoculation	Order of rate of healing at portal of entry measured by rapidity with which local lesion attained its max. and % of its healing during course of the disease	
Survival in days	Area in mm²	Volume in mm³	Volume in mm³	Volume in mm³	Volume in mm³	Rapidity in days	Healing in %
A 350	B 153	A 44	A 679	F 1941	B 262	A 28	100
B 164	A 208	B 70	D 634	A 1380	A 615	B 35	76
F 133	F 306	F 84	H 633	D 827	C 645	D 35	74
H 129	D 314	C 88	F 574	H 597	D 661	F 35	70
D 126	H 390	D 90	C 311	B 319	F 733	H 44	68
C 100	C 404	H 107	B 283	C 259	H 749	C 52	68

first column that the A rabbits are outstandingly resistant, the B family is of intermediate resistance, the F, D, and H rabbits are of approximately the same low resistance while the C rabbits are outstandingly susceptible.

The factors with which this resistance is correlated are arranged in increasing or decreasing order depending upon their relationship to resistance. In the second column it is seen that the permeability of the skin to particulate matter tends to be greatest with the most susceptible families and least with the most resistant, though the relationship is not an exact one. It is noteworthy that in normal litter mates of these same rabbit families the order of permeability of the skin to India ink was essentially relatively the same. Thus 3 normal B rabbits spread the India ink in the skin over an average area of 255 mm^2, 6 A rabbits over 355, 6 D rabbits over 379, 3 C rabbits over 575, and 4 F rabbits over an average area of 604 mm^2. It is clear that the presence of tuberculosis reduces the permeability of the skin to India ink as has been noted before[1] but it does not transform a permeable into an impermeable skin. Figures 1 and 2 illustrate the spread of India ink in a susceptible and a resistant rabbit.

In the third column it is seen that, in general, the primary inflammatory response is inversely related to resistance. The greater the primary inflammation produced by the tubercle bacillus in the skin of

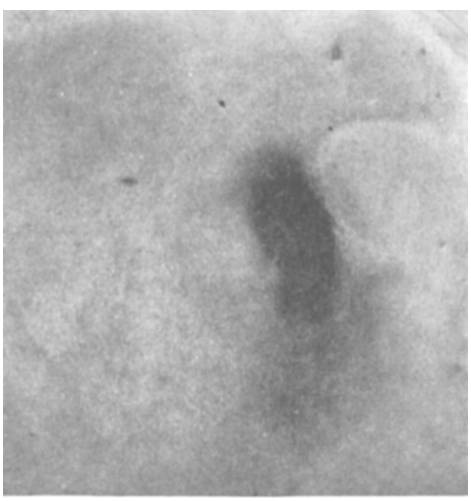

FIG. 1.
The spread of India ink in the skin of rabbit F 3-28 of the susceptible family F.

[1] Lurie, Max B., *J. Exp. Med.*, 1936, **63**, 923.

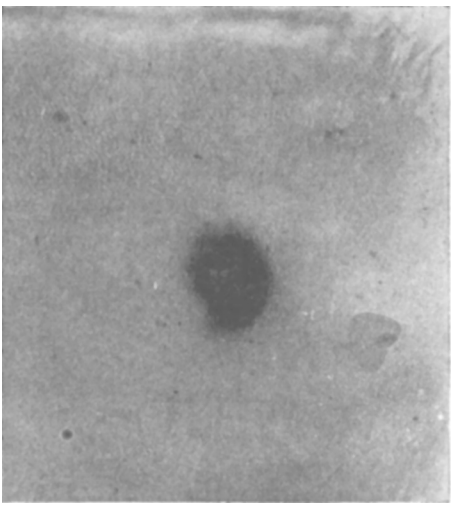

FIG. 2.
The spread of India ink in the skin of rabbit A 4-16 of the resistant family A.

a rabbit, the greater is the susceptibility to tuberculosis. It is clear that this inflammation is to a considerable extent related to the permeability of the skin and, as shown by Thomas and Duran-Reynals,[2] is influenced by the spread of tubercle bacilli in it. The acquired responsiveness of the tissues to tuberculin is not definitely related to resistance. The most resistant family developed the greatest degree of sensitivity to tuberculin on treatment with dead tubercle bacilli, while among the least responsive was found the most susceptible family. The allergy of infection was similarly intense in the most resistant family and least developed in the most susceptible. But in both these factors it is apparent that the relationship is not parallel to resistance as evidenced by families B and D and H in the former, and F and B in the latter relationship. No constant correlation could be found between the permeability of the skin and the degree of inflammatory response to tuberculin on sensitization with dead or living tubercle bacilli. However it must be noted that in 50 unsensitized litter mates of these families the inflammatory response of the skin 48 hours after the injection of concentrated tuberculin is definitely related to the permeability of the skin as shown by Thomas and Duran-Reynals,[2] being most marked in the B family with the least permeable skin and least in the C family with the most permeable skin, while the other families occupy an intermediate position closely related to the order of their respective permeabilities. It is seen in the sixth column that, to a certain extent, the rate of

2 Thomas, R. M., and Duran-Reynals, F., *J. Exp. Med.*, 1935, **62**, 39.

reaction to the inoculation of living tubercle bacilli at the portal of entry is somewhat related to resistance, in the sense that in the susceptible families the local lesion develops more rapidly than in the resistant animals. However, exceptions to this rule are evident in families C and A. It is clear from the last column that the most resistant, the A family, responded at the portal of entry of living tubercle bacilli with a lesion which reached its maximum development in 28 days and healed completely, whereas the most susceptible, the C family, responded with a lesion that attained its maximum development in 52 days and, at death, was far from healed. In families of intermediate resistance the rate of healing at the portal of entry was of intermediate speed. It is to be emphasized that similar though less pronounced differences in the rate of healing at the portal of entry were obtained in these same families which had not undergone preliminary sensitization with heat-killed tubercle bacilli. An analogy has thus been found between naturally highly resistant and artificially immunized rabbits. In both instances the reaction to the tubercle bacillus is abortive as compared with the response on first infection of rabbits of low inherited resistance.

Figures 3, 4, and 5 illustrate the rate of healing at the portal of entry in 3 rabbits belonging respectively to families of low, intermediate and high resistance to tuberculosis. They depict the skin lesion and drainage lymph nodes on the 60th day after an intracutaneous inoculation of 0.2 mg bovine type tubercle bacilli intracutaneously in 3 rabbits, *viz.*, C 3-16 of the C family which survived 88 days, B 4-22 of the B family, which survived 155 days, and A 4-17 of the A family, which survived 424 days.

FIG. 3.
Rabbit C 3-16 of the most susceptible C family.

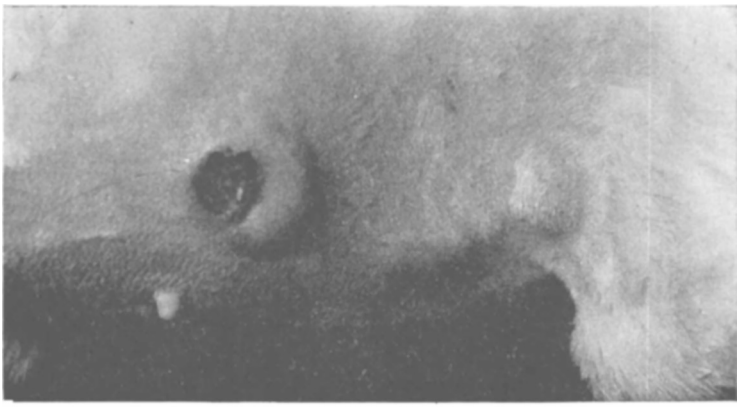

FIG. 4.
Rabbit B 4-22 of the B family of intermediate resistance.

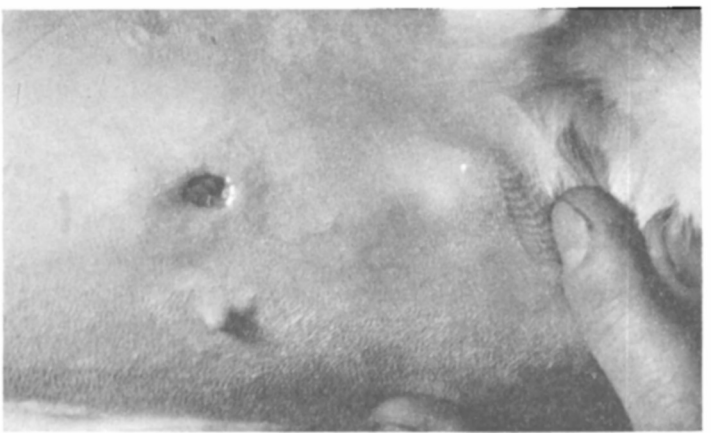

FIG. 5.
Rabbit A 4-17 of the most resistant A family.

The figures in this table help to show that the most resistant families possess more qualities which are associated with resistance, while the most susceptible families have more characteristics associated with susceptibility. It is evident that there is no one factor which by itself determines resistance; rather it is the interplay of these factors which determines resistance. This is particularly evident in the case of family B. While it possesses some of the characters associated with resistance, other factors, as yet not studied, would seem to lower its resistance.

No definite conclusions are drawn at present from these results. They serve as a foundation for further studies.