Final conclusions cannot be drawn. Further investigation of other diseases for the occurrence of tobacco hypersensitiveness must be carried out before its importance in thrombo-angiitis can be definitely established. It has been clearly demonstrated, however, that a large percentage of patients suffering from thrombo-angiitis obliterans belong to the category of allergic individuals and that this allergy is essentially characterized by a hypersensitiveness to tobacco.

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Oral Immunization of Rabbits Against Pneumococcus Pneumonia and Septicemia.*

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As shown by Ross[1] it is possible to actively immunize rats against Type I pneumococcus septicemia by the oral administration of tissues carrying this organism as well as by feeding acid-killed, bile dissolved and mechanically disrupted organisms and the specific polysaccharide. Kolmer and Amano[2] found that rabbits could be sometimes immunized against highly fatal pneumococcus meningitis and septicemia, especially that produced by Type I pneumococcus, by the oral administration of heat killed and living vaccines. We have thought it worth while to ascertain if rabbits could be vaccinated against the pneumococcus pneumonia and septicemia induced by the intratracheal injection of living cultures as employed by Cecil and Steffen[3] in the production of pneumococcus pneumonia of monkeys. Cecil[4] reported that 3 subcutaneous injections of Type I pneumococcus vaccine protected these animals against pneumonia when inoculated intratracheally 3 weeks later.

Since it may be that the oral administration of pneumococcus vaccines may engender an equal or even higher degree of immunity

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1 Ross, V., *J. Exp. Med.*, 1930, **51**, 585; *J. Immunol.*, 1926, **12**, 219, 237; *J. Lab. and Clin. Med.*, 1927, **12**, 566; PROC. SOC. EXP. BIOL. AND MED., 1926, **24**, 273.

2 Kolmer, J. A., and Amano, K. W., *Archiv. Otolaryngol.*, 1932, **15**, 547.

3 Cecil, R. L., and Steffen, G. I., *J. Exp. Med.*, 1921, **34**, 245; 1923, **38**, 149.

4 Cecil, R. L., *Arch. Int. Med.*, 1928, **41**, 295.

than subcutaneous injections we thought it advisable to start with the highly susceptible rabbit and to continue the experiments with monkeys in case encouraging results were obtained. Three kinds of vaccines were employed after the methods developed by Ross. That designated as "milk-heated" was prepared by cultivating the organisms in sterile milk for 24 hours and heating at 60°C. for an hour. That designated as "acid-killed" was prepared by cultivating the pneumococci in a broth medium for 24 hours and adding sufficient N/1 hydrochloric acid to give a N/15 concentration. After standing for 2 hours at room temperature the vaccines were subcultured for sterility. That designated as "bile-dissolved" was prepared as follows: Broth cultures were cultivated for 24 hours at 37°C. They were then thoroughly centrifuged and the cocci from each 50 cc. dissolved in 5 cc. of a 1% solution of sodium taurocholate. Medium sized rabbits were given 7 daily doses of each vaccine by stomach tube. The dose of the milk-heated and acid-killed vaccines was 10 cc. per animal or approximately 5 cc. per kilo of weight while the bile-dissolved vaccine was given in dose of 5 cc. per animal or approximately 2 cc. per kilo. One week after the last or seventh dose each animal was injected intratracheally† with sufficient amounts of living broth cultures to produce the pneumonia and septicemia characteristic of these animals. With our Type I pneumococcus the intratracheal injection of 0.5 cc. of a 1:30 dilution of 6 to 8 hour broth culture invariably produced a fatal pneumonia and septicemia (positive heart blood cultures) in 3 to 5 days. Our Type II strain, however, was much less virulent, as the injection of as much as 2 cc. of a 6 hour broth culture produced fatal pneumonia and septicemia in only about 50% of the unvaccinated controls. The same was true of the Type III strain, since the injection of 2.5 cc. of 6 hour broth culture produced fatal infections in about 40 to 50% of the controls.

We believe that the results definitely show that rabbits may be effectively immunized against virulent Types I, II and III pneumococci by the oral administration of these 3 kinds of pneumococcus vaccines. Particularly good results were observed with the Type I vaccines and especially the acid-killed and milk-heated ones. As shown in the results of an experiment summarized in Table I as an example of several, while all of 12 unvaccinated controls succumbed to the pneumonia and septicemia induced by intratracheal inoculation, from 33 to 75% of the immunized animals survived indefinitely.

† All intratracheal inoculations were conducted under ether anesthesia.

TABLE I.
Oral Immunization of Rabbits Against Type I Pneumococcus Pneumonia and Septicemia. Intratracheal Inoculation.

Vaccines	No. Immunized	Survived	Died	% Survivals
Acid-killed	12	9	3	75
Bile-dissolved	6	2	4	33
Milk-heated	6	4	2	66
Controls (12)	0	0	12	0

Furthermore this induced or active immunity has been found to endure for at least 4 months and possibly longer. At present all of a series of 12 rabbits immunized 4 months ago with 7 daily doses of "acid-killed" and "milk-heated" vaccines survived intratracheal injections while all of a control series of 4 animals succumbed in the usual period of 2 to 5 days.

With the Type II vaccines the results have been less definite and convincing, since about half of the unvaccinated controls survived intratracheal inoculation. In one experiment summarized in Table II as an example of several, the "acid-killed" and "milk-heated" vaccines protected all of the vaccinated animals while the "bile dissolved" vaccine produced much less protection. In some experiments, however, the latter gave results similar to those observed with the 2 former vaccines so that we have reason to believe that Type II pneumococcus vaccines by oral administration are capable of engendering some degree of active immunity.

TABLE II.
Oral Immunization of Rabbits Against Type II Pneumococcus Pneumonia and Septicemia. Intratracheal Inoculation.

Vaccines	No. Immunized	Survived	Died	% Survivals
Acid-killed	12	12	0	100
Bile-dissolved	6	4	2	66
Milk-heated	6	6	0	100
Controls (10)	0	5	5	50

Similar results were observed with Type III vaccines, the results of one experiment being summarized in Table III as an example of several conducted with Type III pneumococcus. While from 40 to 60% of unvaccinated controls survived indefinitely because of the low virulence of our strain, yet the percentage of survivals among the immunized animals was appreciably higher as indicated by the results of the experiment summarized in Table III.

No experiments were conducted with pneumococci belonging to Group IV. But at present we are investigating results of immunization with smaller doses of vaccine, the effects of fewer doses, and further experiments upon the duration of the active immunity.

In general it would appear that the "acid-killed" vaccine has pro-

TABLE III.
Oral Immunization of Rabbits Against Type III Pneumococcus Pneumonia and Septicemia. Intratracheal Inoculation.

Vaccines	No. Immunized	Survived	Died	% Survivals
Acid-killed	12	100	0	100
Bile-dissolved	6	100	0	100
Milk-heated	6	4	2	66
Controls (10)	0	6	4	60

duced the most encouraging and consistent results and our present experiments are being conducted only with this particular kind. Furthermore, we believe that the results require further study employing monkeys, in view of the fact that the induced pneumonia bears a closer resemblance to pneumococcus lobar pneumonia of human beings as shown by Cecil and his associates.

Summary. 1. It has been found possible to actively immunize rabbits against Type I pneumococcus pneumonia and septicemia produced by the intratracheal injection of virulent culture, by the oral administration of 7 doses of vaccines at daily intervals. 2. Of the 3 "acid-killed", "bile-dissolved" and "milk-heated" vaccines employed, the first mentioned appeared to engender the most immunity. 3. The induced immunity has been found to persist for at least 4 months and possibly longer. 4. Oral administration of similar vaccines of Types II and III pneumococci also produced active immunity but probably not of a degree equal to that engendered by Type I pneumococcus.

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Nuclear Phenomena Suggesting a Sexual Mechanism for the Tubercle Bacillus.

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This inquiry takes immediate origin in the suggestive rôle of the macrotetrads in the life cycle of the avian tubercle bacillus (Mellon, *et al.*[1]); more remotely, in the proven rôle of macrotetrads in diphtheroidal-streptococcus transformations.[2]

[1] Mellon, R. R., Richardson, R. D., and Fisher, L. W., PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 80.

[2] Mellon, R. R., *J. Med. Res.*, 1920, **42**, 61.