administered orally in a single dose to healthy subjects and to patients with myasthenia gravis was investigated. 2. Both healthy subjects and patients with myasthenia gravis excreted *p*-amino benzoic acid in essentially the same manner in respect to time of elimination and amounts of free and acetylated form. 3. It is inferred that there is no serious insufficiency of acetyl- radical in patients with myasthenia gravis.

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Action of Sulfonamides on Toxins of Agents of the Lymphogranuloma-Psittacosis Group.

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It has been shown elsewhere[1,2,3] that all four of the agents of the lymphogranuloma-psittacosis group[4] investigated so far produce a rapidly lethal toxin which in general resembles the bacterial endotoxins. These toxins are distinguishable one from the other by certain characteristics of the distribution curve of time of death and by differences, in certain instances, in the pathological picture produced, as well as by the sharp specificity of the toxin-antitoxin reaction. While intravenous inoculation of the agent of lymphogranuloma venereum results only in early deaths[1,2] that could hardly be due to anything other than toxin (since 83% of deaths occur within 24 hours and 95% within 36), the other 3 toxic materials produce diphasic distribution curves of time of death, the early curve of toxicity being followed by a later curve in which deaths are due to infection.[2,3]

Following the earliest report on the existence of these toxins the question has been raised as to how one could be sure that one was dealing with a toxin and not with an infection which was acting very rapidly. This point, while hardly valid in connection with the very early deaths, did seem to be pertinent in those cases where toxemia was followed, often without any distinct interval (*i.e.*, in the case of meningopneumonitis), by deaths certainly due to infection. Could one distinguish clearly between the two forms of death?

It has been possible to demonstrate that infection with 2 of these agents, namely, lymphogranuloma venereum and mouse pneumonitis, is controllable with sulfonamides[5,6] while the infection with feline pneumonitis (Baker[7,8]) and meningopneumonitis is not.[3,6] If the theories, which have been postulated elsewhere[1,2,3] and set out briefly above, concerning the cause of deaths following intravenous inoculation of mice with these toxins are correct it should be possible to demonstrate this fact by means of sulfonamide therapy. In the case of lymphogranuloma venereum only supposedly toxic deaths occurred and these should be unaffected by sulfonamides. In the case of mouse pneumonitis where there is a distinct interval between the early, supposedly toxic, deaths and the later infectious deaths the later deaths should be eliminated by sulfonamide therapy while the early deaths should not. Finally, meningopneumonitis and feline pneumonitis both give diphasic curves of death and the infectious deaths follow closely upon the toxic. Infections due to these agents are not affected

1 Rake, G., and Jones, H., PROC. SOC. EXP. BIOL. AND MED., 1943, **53**, 86.

2 Rake, G., and Jones, H., in press.

3 Hamre, D. M., and Rake, G., to be published.

4 Rake, G., Eaton, M. D., and Shaffer, M. F., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 528.

5 Bär, F., *Klin. Wschr.*, 1938, **17**, 588.

6 Rake, G., Jones, H., and Nigg, C., PROC. SOC. EXP. BIOL. AND MED., 1942, **49**, 449.

7 Baker, J. A., *Science*, 1942, **96**, 475.

8 Thomas, L., and Kolb, E. M., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 172.

TABLE I.
Effect of Sulfamerazine on Toxic and Infectious Deaths Following Intravenous Inoculation of L.V., M.P., and F.P.

Agent	Dilution	Control Sherman diet	Sulfamerazine 0.1% in diet
L.V. (Watson)	1/10	<17,* <17, <17, <17, <17, <17, <17, <17, <17, <17	<17, <17, <17, <17, <17, <17, <17
	1/40	<17, <41, <41, <41, S,* S, S, S, S, S	<17, <17, 25, <41, S, S, S, S, S, S
M.P. (Atherton)	1/5	<16, <16, <16, <16, **40, 43, <64, <88, <6d,** S	<16, <16, <16, S, S, S, S, S, S, S
,, ,,	1/5	1, 1½, <18, <18, <18, <18, <18, <18, <18, <18	1, 1½, 1½, 2, <18, <18, <18, <18, <18, <18
	1/7.5	23, **<46,* <46, <46, <46, <46, 47, 49, 50, 51, 51, 54, 56, 56, 56, <70, <70, <70, <70, <94**	S, S, S, S, S, S, S, S, S, S, S, S, S, S, S, S, S, S, S, S
F.P. (Baker)	1/40	<18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18	<18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, <18, 22, 22
,, ,,	1/320	**48, <62,** S, S, S, S, S, S, S, S, S, S, S, S, S, S, S	**54, <62, 70, <86, <6d,** S, S, S, S, S, S, S, S, S, S, S, S, S, S, S
,, ,,	1/240	**<65, <65, <89, <5d,** S, S, S, S, S, S, S, S, S, S, S, S, S, S	**<66, <66, <66, 73, 74, 76,** S, S, S, S, S, S, S, S, S, S, S, S

<17 = died in less than 17 hours.
S = survived for over 10 days.
<46 = died in less than 46 hours. Figures given in heavy type indicate deaths which in previous work and on the basis of other data[1,2,3] have been considered due to infection and not to toxemia.

by sulfonamide therapy and, therefore, one would expect the curves of death to be unaffected by such therapy.

Experiments were set up with 3 agents showing the 3 different types of response, namely, lymphogranuloma venereum (L.V.), mouse pneumonitis (M.P.), and feline pneumonitis (F.P.). The results are shown in Table I and completely confirm the theories postulated above. Thus sulfamerazine has no effect upon the early toxic deaths in the case of any agent even when only a border line dose is used. The late infectious deaths are eliminated in the case of mouse pneumonitis and are not affected in the case of feline pneumonitis even when border line doses are used.

Summary. Sulfamerazine has no effect on any of the endotoxins of the agents of the lymphogranuloma-psittacosis group and on the early deaths produced by such toxins, even when these are used in doses on the border line of lethality and are derived from lymphogranuloma venereum or mouse pneumonitis both of which infections are very susceptible to sulfonamide therapy. On the other hand, of the later deaths which occur following intravenous inoculation of the agents of mouse or feline pneumonitis, those occurring with mouse pneumonitis are entirely prevented with sulfamerazine while those with feline pneumonitis are not. These facts are in keeping with the previously postulated theory that these later deaths are due to infection while the earlier are due to toxemia.