October 31, 1929

Dr. Graham Edgar,
Ethyl Gasoline Laboratory,
320 Yonkers Street,
Yonkers, N. Y.

My dear Edgar:

Replying to your letter of October 16 in regard to the toxicity of anilin and substitution compounds. I have gone over all the material I have on the subject, including the article to which you refer in the Journal of Pharmacology and Experimental Therapeutics. The latter does not give data on the relative toxicity of these compounds, but is simply a pharmacologic study of the mechanism of intoxication shown by compounds of this sort. It points out that a considerable amount of the previous information on the subject is very faulty, and indicates that the intoxication is probably not due to the formation of methaemoglobin but is due rather to circulatory failure plus some blood destruction due to the presence of para-aminophenol.

The information which is contained in Henderson and Haggert's book is substantially that available on the subject in literature. Much of it is a direct quotation of Alice Hamilton's book on Industrial Poisoning in the United States. What is said about the relationship of toxicity to chemical structure is practically a duplication of the statements of Alice Hamilton in her book. This has been gleaned from scattered points of information contained in a number of studies by German investigators. It is probably substantially true, but I should not be too sanguine about the direct relationships of toxicity to structure in and of itself. The factors of solubility and stability in the tissues are very likely to be much more important. However, from the literature there is available, there is no doubt that toludine, methylanilin and dimethylanilin are somewhat less toxic than anilin alone. There is apparently no wide difference in the toxicity of these three. Whether there is sufficient difference to be of any practical importance in such a problem as we have to consider, is another matter. I should suspect that the differences are not great enough to be of much importance in practical use. All of them work in substantially the same fashion and none of them seem to produce very striking chronic effects. However, I have not been able to find enough information in the literature to be of much help to me in arriving at definite conclusions on this latter problem, that is that of chronic poisoning. Such information

as I have been able to obtain at the DuPont plant, which is the result of a number of years' experience, indicates that there are no important chronic effects. Their experience, however, verifies the data in Henderson's book, which I think is taken from Kobert's work, that nitro-benzene is many times as toxic as anilin. In general, it seems to be quite certain that a nitro group renders a compound much more toxic than an amino or amido group; also the toxicity increases, though not in direct proportion with the increase in the number of nitro groups. The toxicity of anilin as given by Henderson corresponds very satisfactorily with that given by Kobert, who quotes the experimental work of Lehman.

In regard to your vaccine, I have spoken to Dr. Dorst today. He tells me that you should be able to notice some difference if you have continued the use of the vaccine for about a month. He advises the continuance of the vaccine in the manner which he previously prescribed. I reminded him that he had not sent you a bill, and suggested that you would feel very much better about it if he would send you one. He is notoriously slow in tending to matters of this sort, so that I should not trouble about it if I were you. You will probably receive a bill eventually.

One thing this vaccine should do whether it accomplishes anything else or not, is to make you less susceptible to re-infections from organisms of the type that go to make up the vaccine. If it does no more than this, I believe it will give you considerable benefit, though it is of course difficult to prove the value of preventive measures. It is always possible to conclude that the thing which you are attempting to prevent might not have happened anyhow. There is very good experimental evidence, however, that vaccines are effective in this way.

With kindest personal regards.

Very truly yours,

RAK:EJ