damaged portions, thus separating the Kupffer cells and decreasing their number per unit weight of tissue.

The character of the injury in portal cirrhosis of the liver is quite different from that which has been described above, and it is possible that accompanying injury to the Kupffer cells results in the very low Vitamin A stores in this disease. However, the cause may be an insufficient supply of the vitamin, either because of impaired conversion of carotin in injured liver cells or inadequate intake of Vitamin A in patients with this disease.

Summary. In 3 cases of healed massive necrosis of the liver Vitamin A was more abundant in the parts of the liver from which hepatic cells had disappeared than in those where these cells had not been destroyed. Presumably it was stored in the Kupffer cells, which had been spared by the agent which produced the necrosis.

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Trypanocidal Action of 3-Nitrobenzoic Acid and Some Derivatives.

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Various sulfonamide derivatives prepared in this laboratory have been tested against *Trypanosome equiperdum* with negative results. 4-Nitrobenzoic acid which has a slight antibacterial action[1, 2] was found to have a trace of trypanocidal activity. Investigation of the isomers revealed that the meta derivative showed increased activity against trypanosomes, although without effect upon bacteria; 2-nitrobenzoic was inactive against both types of infection. A review of the literature revealed that Morgenroth found 3-hydroxybenzoic acid to possess some trypanocidal action.[3]

A more detailed study of 3-nitrobenzoic acid and some derivatives was undertaken. Mice were inoculated intraperitoneally with a quantity of trypanosomes that would cause death in 3 to 5 days. Therapy was usually begun on the second day after inoculation. The dosage

1 Mayer, R. L., and Oechslin, C., *Compt. rend. Soc. Biol.*, 1939, **130**, 211.

2 Rosenthal, S. M., and Bauer, H., *U. S. Pub. Health Rep.*, 1939, **54**, 1317.

3 Morgenroth, J., and Rosenthal, F., *Berlin. Klin. Wschnschr.*, 1912, **49**, 134.

used was in most cases one-half of the maximum tolerated single dose; this was repeated daily for 3 to 6 days to surviving animals. A few of the compounds were synthesized by one of us (H.B.). The others were obtained from Eastman Kodak Company.

The average survival time was calculated from the day of inoculation, using a maximum of 30 days.

Compounds with some activity are shown in Table I. The following derivatives also showed traces of activity; dosages in grams per kilo, administered subcutaneously, are shown in parenthesis. The soluble sodium salts of the acids were employed. Insoluble compounds were injected in olive oil. Dosages represent approximately one-half the single M.T.D.

3-Nitrobenzyl chloride (0.5), 3-nitrohippuric acid (2.0), 5-nitrosalicylic acid (0.5), and 3,5-dinitrosalicylic acid (0.1).

The following compounds were inactive:

2-Nitrobenzoic acid (0.5), 3-nitrophenol (0.25), 3-nitrochlorobenzene (0.25), 3-nitrobenzene sulfonamide (0.25), 3-nitrobenzene sulfonic acid (1.0), 3-nitrobenzoyl-2-amino-pyridine (0.4), 3-nitroanisole (0.5), 3-nitrophenetole (0.5), 3-nitroacetophenone (0.5), 3-aminobenzoic acid (2.0), 3-aminobenzene sulfonamide (1.5), nicotinamide (1.0), isophthalic acid (1.5), 3-nitrophthalic acid (2.0), 4-nitrophthalic acid (2.0), 3-nitrophthalimide (1.0), 3-nitrosalicylic acid (0.5), 3,5-dinitro-benzoic acid (0.25), 2,4-dinitrobenzoic acid (0.5), 3-nitro-4-hydroxy-toluene (0.5), 3-nitro-2-

TABLE I.

Trypanocidal Action of 3-Nitrobenzoic Acid and Some Related Compounds. Doses in most cases represent one-half the maximum tolerated single dose.

Compound	Route	g/kilo x days	No. of mice	Avg survival (days)
3-Nitrobenzoate sodium	s.c.	.5 x 6	60	13.3*
" " "	oral	.5 x 6	10	5.1
3-Nitrobenzoic acid (in oil)	s.c.	.5 x 4	30	6.8*
3-Nitrobenzyl alcohol " "	s.c.	.5 x 6	10	5.8
3-Nitrobenzal chloride " "	s.c.	.5 x 2	10	3.9
" " " " "	s.c.	1.0 x 5	9	5.7
3-Nitrotoluene " "	s.c.	.25 x 3	10	3.6
3-Nitrobenzoate methyl " "	s.c.	.5 x 4	10	8.2
3-Nitrobenzoate ethyl " "	s.c.	.5 x 4	10	6.2
3-Nitrobenzaldehyde " "	s.c.	.5 x 3	10	3.5
3-Hydroxybenzoate sodium	s.c.	.5 x 3	10	3.0
" " "	s.c.	1.5 x 4	10	5.5
3-Brombenzoate "	s.c.	.25 x 3	10	5.1
Nicotinic acid "	s.c.	1.0 x 3	10	4.0
4-Nitrobenzoate "	s.c.	.5 x 6	10	4.9
Controls			125	3.1*

*Average of several experiments.

aminotoluene (0.25), 3-nitro-4-aminotoluene (0.5), 3-nitro-2-iodotoluene (0.4), 3-nitro-4-amino-anisole (0.5), 3-nitro-4-aminophenetole (0.75), 3-nitro-4-acetylaminophenyl acetate (0.5), 3-nitrodiphenylene oxide (0.5).

The blood of most animals was cleared of parasites at the termination of therapy with subcutaneous injections of 3-nitrobenzoate, but the incidence of relapses was high and only 16% of the series remained parasite free. None of the derivatives reported herein proved of greater activity.

That the nitro group is not essential is shown in that some activity was retained by 3-hydroxy- and 3-brom-benzoic acid and by nicotinic acid.

The importance of the carboxy group is shown in that only those derivatives were active which contained this group or a closely related radical which could be converted into it. Replacement by OH or substituted OH groups, by Cl, SO_3H or SO_2NH_2 abolished activity.

3-Nitrobenzoate shows some action against *trypanosome equiperdum in vitro*. Concentrations up to 0.1% bring about marked swelling of the organisms with decrease in motility after exposure of one hour at room temperature. The ortho isomer was without effect.

Certain differences between bacterial and trypanosome chemotherapy were noted. While sulfanilamide and 4-nitrobenzoate are more active against streptococci by mouth than by subcutaneous injection, this relationship was reversed with 3-nitrobenzoate upon trypanosomes. While 4-aminobenzoic acid antagonizes the antibacterial action of the former compounds, 3-aminobenzoic acid and nicotinamide did not antagonize 3-nitrobenzoic acid.

In view of the relationship of 4-nitrobenzoic acid to sulfanilamide in bacterial chemotherapy, the possibility of obtaining more active trypanocidal agents related to 3-nitrobenzoic acid deserves further study.