

STUDIES UPON EXPERIMENTAL PNEUMONIA IN RABBITS.

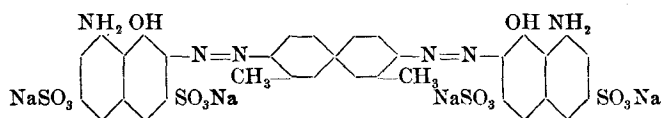
IV. IS THERE A PARALLELISM BETWEEN THE TRYPANOCIDAL AND PNEUMOCOCCIDAL ACTION OF DRUGS?*

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Morgenroth and his collaborators have shown that derivatives of quinin and cuprein, and especially of hydroquinin and hydrocuprein, possess therapeutic powers against both trypanosomes and pneumococci. In order to determine whether a general parallelism exists between the trypanocidal and pneumococcidal action, experiments were carried out to investigate the effect of the various other groups of drugs that possess chemotherapeutic properties for trypanosomiasis.

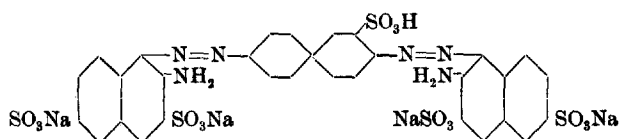
Our investigations upon the vital staining of the pneumonic exudate have shown that the benzidin dye, trypan-blue,



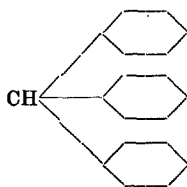
which Nicolle and Mesnil had shown to be a specific for experimental trypanosomiasis, has the power of selectively staining the pneumonic exudate. Since the drug is thus concentrated in the diseased area, we were led to the hope that if this parallelism existed it might be particularly well shown by this substance. Unfortunately such was not the case, and no marked difference could be distinguished between the vitally stained animals and the controls. Indeed, doses which had no deleterious effects upon normal animals seemed to hasten death in those with pneumonia. Equally

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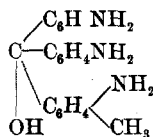
negative were the results obtained by using the iodine derivative of trypan-blue prepared by one of us which probably contained five atoms of iodine in its molecule. Equally negative also were the results obtained with trypan-red,



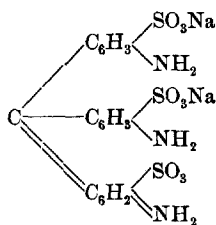
with a series of dyes of the triphenyl methane series,



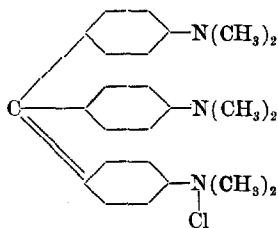
basic fuchsin,



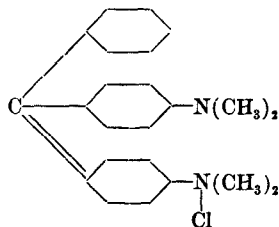
acid fuchsin,



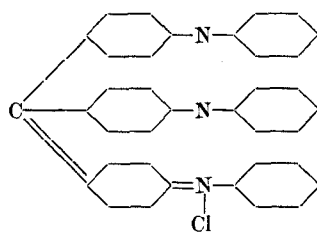
crystal violet,



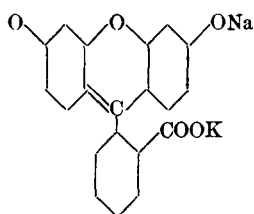
malachite green,



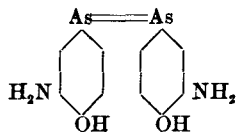
gentian violet,



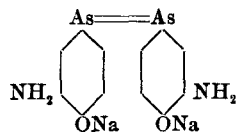
and also with erythrosin,



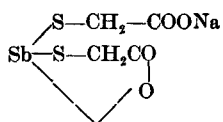
acid salvarsan,



and alkaline salvarsan,

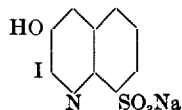


and with sodium antimony thioglycollate,

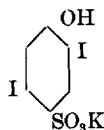


which Abel and Rowntree have shown exerted particularly marked trypanocidal powers.

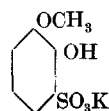
The fact that both trypan-blue and trypan-red, which are salts of sulphonic acids, are taken up selectively by the exudate led us to investigate a series of other sulphonates. Sodium iodo-o-oxy-quinolin sulphonate,



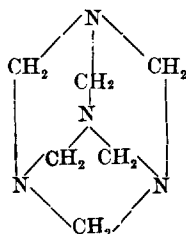
(formerly sold under the trade name of loretin or griserin) possesses this group in common with the vital stains on the one hand, and on the other hand the oxyquinolin radical in common with the quinin and cuprein derivatives used by Morgenroth, and, moreover, has been shown by Claus and his co-workers to be a strong antiseptic *in vitro* and quite harmless when injected into animals. No effect could, however, be noted from the administration of this drug, nor from potassium diiodophenolsulphonate (potassium soziodol),



nor potassium guaiacolsulphonate (thiocol),

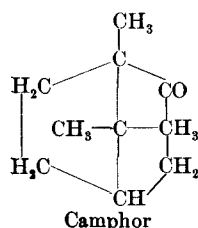


for both of which beneficial effects had been claimed in clinical therapy of the respiratory tract. Hexamethylenamin,



which Crowe and subsequent workers have shown to possess marked prophylactic and therapeutic action in various infections, was also without effect, although the milk sulphuric acid and ferric chloride test showed it to be present in large quantities in the diseased area of lung.

Seibert claims to be able to prevent death from pneumococcus septicemia in rabbits by treating them with subcutaneous injections of three to five cubic centimeters of 30 per cent. camphorated oil.



We have tried this treatment in four rabbits, but they all died as early as the controls.

Further investigations upon the chemotherapy of experimental pneumonia are in progress.

We desire to express our thanks to Dr. Carl Glaser for advice and assistance in the preparation of iodotrypan-blue and iodoxy-quinolin sulphonic acid.

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TABLE I.
Drugs and Vital Staining.

	No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Pericarditis.	Mediastinitis.	Remarks.
					Fibrinous.	Effusion.			
Control	P 1	1,550	121 (killed)	Right upper, left upper	+		Fibrinous		Culture positive.
Control	P 8		72	None					6 mg. phenolsulphonephthalein 1 hr. before death.
Control	P 14		20 (killed)	Entire left					Culture positive.
Sodium antimony thioglycollate	P 4		24	Right lower					10 mg. antimony thioglycollate intramuscularly (1 c.c. 1 per cent. solution).
Sodium antimony thioglycollate	P 4	1,070	24	Left					10 mg. sodium antimony thioglycollate 1 hr. before inoculation.
Sodium antimony thioglycollate	P 6	1,250	15	Left lung	Left	Left		+	12 mg. sodium antimony thioglycollate 1 hr. before inoculation. Blood cultures positive.
Sodium antimony thioglycollate	P 7	1,140	18						3 mg. sodium antimony thioglycollate 1 hr. before inoculation. Blood cultures positive.
Sodium antimony thioglycollate	P 10	850	14	Left lower					4 mg. sodium antimony thioglycollate 1 hr. before inoculation. Blood cultures positive.
	P 12	1,720	36	Entire left	Left		Fibrinous	+	Blood cultures positive.
Trypan-blue	P 13	1,550	14	Lower and parts of right upper					20 c.c. trypan-blue 1 per cent. solution (200 mg.) 1 hr. before inoculation. Deep blue staining of most tissues and of consolidated portions of lungs.

TABLE I.—Continued.

	No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Pericarditis.	Mediastinitis.	Remarks.
					Fibrinous.	Effusion.			
Trypan-blue	P 5 See also B 24 and B 22	1,300	14	Entire left tip of right upper		Left (blue)			20 c.c. 1 per cent. solution trypan-blue (200 mg.) before injection. Staining as in P 13.
Iodotrypan-blue	1	Died 1 hr. after inoculation		injection of iodotrypan-blue, 3 hrs. after inoculation					Died 1 hr. after injection of 5 c.c. 0.6 per cent. solution pentaïodo trypan-blue, 3 hrs. after inoculation. No vital staining of tissues or kidneys.
Iodotrypan-blue	2		18	Entire left		Bi-lateral	Fibrinous	+	5 c.c. 0.6 per cent. pentaïodo trypan-blue injected intravenously 3 hrs. after inoculation. No vital staining.
Trypan-red	1		36	Middle					5 c.c. 1 per cent. trypan-red intravenously 3 hrs. and 22 hrs. after inoculation. Vital staining especially of fibrin and diseased lung.
Trypan-red	2		54	Middle		Right			5 c.c. 1 per cent. trypan-red intravenously 3 hrs. and 22 hrs. after inoculation. Vital staining especially of fibrin and diseased lung.
Basic fuchsin (Casella)	1	Died at once							10 c.c. 0.33 per cent. fuchsin (Casella) intravenously.
Basic fuchsin (Casella)	2		18	Right lower					10 c.c. 0.33 per cent. fuchsin (Casella) subcutaneously. Slight staining of diseased area of lung. No other organs stained except subcutaneous tissue.

	No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Percarditis.	Mediastinitis.	Remarks.
					Fibrinous.	Effusion.			
Acid fuchsin (Weigert)	1		18	Right lower (not stained)		Right			10 c.c. 5 per cent. acid fuchsin intravenously. No vital staining except faint pink in tubules and pelvis of kidneys. About 10 per cent. of the fuchsin in the urine.
Acid fuchsin (Weigert)	2		70	Right middle and lower	Bilateral		Fibrinous		5 c.c. 5 per cent. acid fuchsin intravenously 3 hrs. after inoculation.
Crystal violet	2		40 min.	after injection					5 c.c. 0.33 per cent. crystal violet. No vital staining except capsule of adrenal and lungs.
Crystal violet	1			Died within an hour					
Malachite green	1			Died half an hour after injection					5 c.c. 0.33 per cent. malachite green.
Malachite green	2			Died in half an hour					No vital staining.
Gentian violet	1		24	Right lower					5 c.c. 0.33 per cent. gentian violet 3 hrs. after inoculation. No vital staining; no specific staining of consolidated areas.
Gentian violet	2		36	Right lower					5 c.c. 0.33 per cent. gentian violet 3 hrs. after inoculation. No vital staining; no specific staining of consolidated areas.
Erythrosin	1		44	Right lower	Right				5 c.c. 0.33 per cent. erythrosin intravenously 3 hrs. and 22 hrs. after inoculation. No <i>intra vitam</i> staining; repeated daily.

TABLE I.—Continued.

	No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Pericarditis.	Mediastinitis.	Remarks.
					Fibrinous.	Effusion.			
Potassium diiodo-phenolsulphonate (sozotodol)	2	1,590	36	Entire left	Left		Effusion		10 c.c. 1.8 per cent. solution subcutaneously 2 hrs. before and 20 hrs. after inoculation.
Potassium diiodo-phenolsulphonate (sozotodol)	1		100	Right lower					10 c.c. 1.8 per cent. solution subcutaneously 3 hrs. before and 19 hrs. after inoculation; 5 c.c. 67 hrs. after.
Sodium iodoxyquinolinsulphonate (sodium loretinate or griserin)	1		22	Right lower and middle					10 c.c. 8 per cent. sodium loretinate subcutaneously 3 hrs. after inoculation. On boiling diseased lung gives slight red color with ferric chloride.
Sodium iodoxyquinolinsulphonate (sodium loretinate or griserin)	2		24	Lower right	Bilateral		Fibrinous		10 c.c. 8 per cent. sodium loretinate subcutaneously 3 hrs. after inoculation. On boiling diseased lung gives slight red color with ferric chloride.
Acid salvarsan	1		60	Left upper	Left				5 mg. acid salvarsan intramuscularly 8 hrs. after inoculation.
Acid salvarsan			40	Middle					7.5 mg. acid salvarsan intramuscularly 8 hrs. after inoculation.
Alkaline salvarsan	1	1,800	20	Right lower and middle					25 c.c. alkaline salvarsan (25 mg.) intravenously 8 hrs. after inoculation.
Alkaline salvarsan	2		28	Lower left	Left				26.7 c.c. alkaline salvarsan (25 mg.) intravenously 8 hrs. after inoculation.

	No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Pericarditis.	Mediastinitis.	Remarks.
					Fibrinous.	Effusion.			
Camphor	1		36	Entire left					5 c.c. 30 per cent. camphorated oil 7 hrs. after inoculation; 5 c.c. 20 per cent. camphorated oil 36 hrs. after inoculation.
Camphor	2		24	Entire left					5 c.c. 30 per cent. camphorated oil.
Camphor	3		18	Entire left					5 c.c. 30 per cent. camphorated oil.
Camphor	4		18	Entire right					5 c.c. 30 per cent. camphorated oil.
Hexamethylenamin	1		18	Right lower	Right				5 c.c. 10 per cent. solution hexamethylenamin subcutaneously 7 hrs. later. Hexamethylenamin test in lung tissue positive and very marked.
Hexamethylenamin	2		18	Left lower					Injection as above.
Hexamethylenamin	3		12	Right and left upper	Right			+	5 c.c. 10 per cent. hexamethylenamin 2 hrs. before inoculation.
Potassium guaiacolsulphonate (thiocol)	1	1,800	36	Entire left	Left				5 c.c. 5 per cent. thiocol subcutaneously 7 hrs. after inoculation; 10 c.c. 20 hrs. and 25 hrs. after injection.
Potassium guaiacolsulphonate (thiocol)	2		18	Right upper and lower					10 c.c. 5 per cent. thiocol subcutaneously 7 hrs. after inoculation.
Benzol	B 2	3,030	24						Leucocytes at time of inoculation 640.
	B 6	1,960	22	Right multiple					Leucocytes 280.

TABLE I.—Continued.

No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Pericarditis.	Mediastinitis.	Remarks
				Fibrinous.	Effusion.			
B 10	2,550	13	Entire right					Leucocytes 360.
B 9	1,500	17	Entire right					Leucocytes 3,600.
B 11	1,500	17	Entire left					Leucocytes 880.
B 15	1,890	41						Leucocytes 320; temperature 40.7° C.; 6 hrs. after inoculation, leucocytes 480, temperature 42° C.; 18 hrs. after, leucocytes 180, temperature 40.7° C.
B 18	1,790	20	Congestion and edema of left; no definite consolidation	Bilateral	Bilateral		Effusion	Leucocytes 850, temperature 39.2° C.; 7 hrs. after inoculation, leucocytes 430, temperature 38.8° C.
B 19	1,590	20	Left upper and lower					Leucocytes 500, temperature 40° C.; 6 hrs. after, leucocytes 640, temperature 40°.
Benzol control	B 21	1,800	Left upper and lower	Left		Fibrinous		
Benzol control, trypan-blue	B 22	1,875	Abscess in lungs; no consolidation					Leucocytes 6,400, temperature 40° C.; 6 hrs. after, leucocytes 4,600, temperature 41° C.; 19 hrs. after, leucocytes 7,100, temperature 40.7° C.; 43 hrs. after, leucocytes 7,300, temperature 40.5° C.; on 8th day leucocytes 10,600. Very sick; 65 hrs. after, 3 c.c. 1 per cent. trypan-blue injected. Crisis (?). Respiration tubular. On 7th day urine free from chloride; chloride low until 8th day when health seemed better.

	No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Pericarditis.	Mediastinitis.	Remarks.
					Fibrinous.	Effusion.			
Benzol control, trypan-blue	B 23	1,540	90	Left lower	Left		Fibrinous		Leucocytes 4,400, temperature 38.7° C.; 8 hrs. after, leucocytes 5,600, temperature 41° C.; 20 hours after, leucocytes 2,500, temperature 42° C.; 37 hrs. after, leucocytes 7,500, temperature 41.8° C.; 51 hrs. after, leucocytes 5,300, temperature 41° C.
Benzol control, trypan-blue	B 24	1,500	68 (killed)	Left lower (stained)	Left (stained)			Effusion	Leucocytes 7,500, temperature 39° C.; 7 hrs. after, leucocytes 2,100, temperature 41.2° C.; 3 c.c. 1 per cent. trypan-blue (30 mg.) intravenously. 19 hrs. after, leucocytes 3,800, temperature 41.5° C.; 43 hrs. after, leucocytes 3,000, temperature 41.5° C.; 67 hrs. after, temperature 40° C.
Benzol, 2d series	B 26	2,000	Died spontaneously in cage where rabbits had been kept	Middle and purulent bronchitis					Leucocytes 700.
	B 30	1,770	16	Entire left					Leucocytes 1,000; 6 hrs. after, leucocytes 410, temperature 40° C.
	B 31	1,500	26	Right; patchy consolidation of all lobes					Leucocytes 800. Urine shows curds with silver nitrate plus nitric acid.

TABLE I.—Continued.

No.	Weight in gm.	Survival (hours).	Lobes consolidated.	Pleurisy.		Pericarditis.	Mediastinitis.	Remarks.
				Fibrinous.	Effusion.			
B 32	2,770	27	Right upper and lower (partly), and caudate			Effusion		Leucocytes 300; 11 hrs. after inoculation, leucocytes 630, temperature 41° C.; 24 hrs. after, leucocytes 750. Urine cloudy; curds.
Benzol control		7	Entire left					Leucocytes 6,500; 11 hrs. after, leucocytes 3,000, temperature 40° C.; 26 hrs. after, leucocytes 5,000; 48 hrs. after, urine gives curds; 56 hrs. after, slight clouding with silver nitrate; 72 hrs. after, clouding with silver nitrate. No curds.
B 34		64	Entire right	Bilateral				Leucocytes 8,200; 23 hrs. after, leucocytes 10,000; temperature 39° C.; 24 hrs. after, leucocytes 4,600.
B 35		35	Entire left; tip of right	Left				Leucocytes 4,800; 11 hrs. after, leucocytes 1,700; 26 hrs. after, leucocytes 760.
B 36			Right lower				Effusion	Leucocytes 8,000; 11 hrs. after, leucocytes 2,600.
Tolhol	2,150	Recovered						Leucocytes 5,400; 4 hrs. after, leucocytes 8,000; 28 hrs. after, leucocytes 7,400; 100 hrs. after, leucocytes 5,600.
T 4	1,600	52						Leucocytes 5,400; 28 hrs. after, leucocytes 5,000.