Stimson, Columbia Presbyterian Medical Center, New York; Owen H. Wangensteen, University of Minnesota; Capt. W. F. James (MC), U. S. Navy; Maj. Edward H. Vogel, Jr. (MC), U. S. Army; Brian B. Blades, Veterans Administration.

XIX. *Syphilis Study Section*

J. E. Moore, Medical Arts Building, Baltimore, *Chairman*; David E. Price, National Institute of Health, *Executive Secretary*; Harry Eagle, U. S. Public Health Service; J. R. Heller, Jr., U. S. Public Health Service; John F. Mahoney, V. D. Research Laboratory, U. S. Public Health Service; Lowell J. Reed, Johns Hopkins School of Hygiene and Public Health; John H. Stokes, 4228 Spruce Street, Philadelphia; Harry C. Solomon, Boston Psychopathic Hospital; Thomas B. Turner, Johns Hopkins School of Hygiene and Public Health; Maj. L. N. Altshuler, U. S. Army; Cdr. George W. Mast, U. S. Navy; Bascom Johnson, Veterans Administration.

XX. *Tropical Diseases Study Section*

Andrew J. Warren, Rockefeller Foundation, *Chairman*; Willard H. Wright, National Institute of Health, *Executive Secretary*; Ernest Carroll Faust, Tulane University School of Medicine; William W. Frye, Vanderbilt University School of Medicine; John F. Kessel, University of Southern California; Henry E. Meleney, New York University College of Medicine; Gilbert F. Otto, Johns Hopkins University; Cornelius B. Philip, Rocky Mountain Laboratory, Hamilton, Montana; Albert B. Sabin, Children's Hospital Research Foundation, Cincinnati; Wilson G. Smillie, Cornell University Medical College; Col. Karl R. Lundeberg (MC), U. S. Army; Capt. J. J. Sapero (MC), U. S. Navy; Brig. Gen. James S. Simmons, Veterans Administration.

XXI. *Virus and Rickettsial Study Section*

John R. Paul, Yale University, *Chairman*; Norman H. Topping, National Institute of Health, *Executive Secretary*; Charles Armstrong, National Institute of Health; P. F. Clark, University of Wisconsin; John F. Enders, Harvard Medical School; Ernest Goodpasture, Vanderbilt University School of Medicine; Robert G. Green, University of Minnesota Medical School; Wm. McDowell Hammon, University of California; Geoffrey W. Rake, Squibb Institute for Medical Research; T. F. Sellers, Georgia State Department of Public Health; J. C. Snyder, Harvard School of Public Health; Max Theiler, Rockefeller Institute for Medical Research; Joseph E. Smadel, U. S. Army; Capt. James J. Sapero (MC), U. S. Navy.

Technical Papers

A Toxicity Study of Thiamine Hydrochloride

THOMAS J. HALEY and ANNA MAE FLESHER
Research Division, E. S. Miller Laboratories, Inc.
Los Angeles, California

Reingold and Webb (*5*) have recently reported that death occurred after four intravenous injections of thiamine hydrochloride (100 mg./cc.) into a human. These injections were given over a period of about one month, and it was concluded that death was due to anaphylaxis. However, the symptoms described were similar to those seen in this laboratory when a similar solution was injected intravenously into rabbits. In our work a 200- to 300-mg. total dose of thiamine usually resulted in collapse and/or death in most of the animals. If the injection was stopped before respiration ceased, the animal usually recovered within five minutes and apparently suffered no ill effects. These results were obtained over a period of eight months using 20 animals of about 3 kg. body weight. Hecht and Weese (*2*), in 1937, reported that the intravenous injection of 80 mg./kg. of thiamine hydrochloride caused no ill effects but that 160 mg./kg. caused death by paralysis of the central nervous system. Stern (*7*), in 1938, reported that death occurred in a cat given 20,000 I.U. of thiamine hydrochloride by cisternal puncture. Evidence has been presented that anaphylaxis and sensitivity both play a part in human thiamine hydrochloride toxicity (*1, 3, 4, 6, 8*).

Anaphylaxis in the rabbit is entirely different from that seen in the guinea pig or in humans. The lungs are not directly involved. The pulmonary artery is constricted, and the right auricle is engorged with blood. Respiration continues after cardiac arrest (*9*).

A group of five virgin female rabbits weighing between 1.5 and 1.9 kg. was given intravenous injections of a solution containing 100 mg./cc. of thiamine at the rate of 1 cc. every two minutes. Another group of five animals was given similar injections of a 0.35-per cent chlorobutanol solution. The solutions were given in this manner to determine which chemical was the cause of toxic manifestations seen when a solution containing 100 mg./cc. of thiamine hydrochloride and 0.35 per cent chlorobutanol (the usual commercial strength) was injected intravenously. The results of the thiamine injections are shown in Table 1. Each of the rabbits in the second group received 35 mg. of chlorobutanol (10 cc. of solution) and, when observed

over a period of one week, showed no pathological reaction to the injection.

As it had been reported that anaphylaxis plays a part in thiamine toxicity, those animals surviving were given a sensitizing dose of 100 mg. of thiamine, and one week later injected intravenously with 100 mg./cc. of thiamine solution until death occurred. The reaction of the animals was the same as previously described, but the toxic dose was almost doubled (from 375 to 500 mg./rabbit). There was no evidence of anaphylaxis, but auricular extrasystoles were seen in five of six animals injected. The usual rate was 3:1.

TABLE 1

RESULTS OF INTRAVENOUS INJECTION OF 100 MG./CC. THIAMINE HYDROCHLORIDE

Animal	Weight (kg.)	Total dose (mg.)	Results
21	1.591	220	Extreme vasodilatation at 220 mg., convulsions, cyanosis, inability to stand; animal recovered.
22	1.704	180	Vasodilatation at 120 mg., convulsions at 140 mg., death by respiratory paralysis at 180 mg. Autopsy showed lungs collapsed but normal; other organs normal; auricular extrasystoles, rate of 3:1.
23	1.818	220	Vasodilatation at 200 mg., convulsions at 220 mg., at which point respiration stopped but started again, with ensuing death by respiratory paralysis. Blood was definitely venous and the animal cyanotic. Autopsy revealed the same conditions as in #22.
24	1.591	200	Vasodilatation at 120 mg., death by respiratory paralysis at 200 mg. No convulsions; otherwise the same as #22.
25	1.704	240	Vasodilatation followed by collapse at 240 mg. No convulsions. Respiration very slow and animal cyanotic; recovered in five minutes.

Electrical stimulation of the muscles of the diaphragm showed that the muscles were still able to contract. Further, electrical stimulation of the phrenic nerve caused the diaphragm to contract, thus showing that the observed respiratory paralysis was central in origin. This could only mean that the respiratory center of the medulla was paralyzed.

CONCLUSIONS

(1) The above results are the same in every way as those observed when a solution containing 100 mg./cc. of thiamine hydrochloride and 0.35 per cent chlorobutanol was injected intravenously.

(2) The toxicity encountered upon injection of 100 mg./cc. of thiamine hydrochloride solutions is due to the thiamine content and not to the preservative.

(3) Symptoms of thiamine hydrochloride toxicity may be summarized as follows: (a) peripheral vasodilatation; (b) decreased respiration due to direct action on the respiratory center in the medulla; (c) asphyxial convulsions due to anoxia resulting from decreased oxygenation of the blood; (d) death by paralysis of the respiratory center; and (e) cardiac arrhythmias, probably due to anoxia and not a direct action of thiamine hydrochloride on the cardiac muscle or the conducting system.

(4) Anaphylaxis plays no part in thiamine hydrochloride toxicity as seen in rabbits. However, injection of a sensitizing dose apparently increases the resistance of the animal to toxic injections of thiamine hydrochloride.

(5) The lethal dose of thiamine hydrochloride by intravenous injection into rabbits is approximately 126 mg./kg.

(6) After a sensitizing dose of 100 mg. of thiamine hydrochloride the lethal dose is approximately 238 mg./kg.

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Effects of Whole-Wheat and White Bread Diets on Susceptibility of Mice to Pneumococcal Infection

GEORGE H. HITCHINGS and ELVIRA A. FALCO
The Wellcome Research Laboratories
Tuckahoe, New York

It was reported recently (*1*) that when mice are maintained on a "synthetic" diet they are much more resistant to the intraperitoneal injection of Type I, SV-1 strain pneumococcus than mice maintained on the usual laboratory diet. The explanation was advanced that the cruder diet supplies some factor (or factors) which is necessary for the rapid multiplication of the pneumococcus *in vivo*, and maintains a higher level of this factor in the tissues and fluids of the mouse than prevails during its absence from the diet. Belief in the validity of this explanation has been strengthened by the outcome of later experiments. When certain crude foodstuffs are added to the "synthetic" diets, the susceptibility of the mice to pneumococcal infection is increased. Moreover, extracts of these foods are capable of stimulating the *rate of growth* of the pneumococcus *in vitro*.[1]

[1] Unpublished experiments with Marion B. Sherwood.