mum curative intraperitoneal dose of penicillin. However, all 27 rats which received less than 40,000 units/kg. intraperitoneally either relapsed microscopically or were brain-blood-passage positive regardless of whether or not they received intracranial therapy. If we can accept the growing evidence that 1,000 units of penicillin is adequate to sterilize the brain of an infected rat, the relapses and positive brain passages in the 13 animals in this group, which received intracranial penicillin, were the consequences of inadequate intraperitoneal therapy to cure the blood stream and/or visceral tissues.

Fifteen rats received intraperitoneal penicillin totaling from 41,000 to 52,500 units/kg. body weight. Ten of these rats each received an additional 1,000 units intracranially. These 10 rats were subdivided into a group of 6 which received more than 40,000 units/kg. in 4 intraperitoneal injections and a group of 4 which received equivalent total amounts of penicillin in 10 to 14 intraperitoneal injections. The 5 remaining rats in this group, which received no intracranial penicillin, received from 47,600 to 52,500 units/kg. in 10 to 16 intraperitoneal injections.

The 6 rats which received only 4 intraperitoneal injections were not examined microscopically for relapses. Brains were passed from these animals within 6 days after treatment, and 3 were found to be positive. Since each brain passage includes varying amounts of adhering blood, we are inclined to interpret these 3 positive passages as instances of blood passage resulting from the short duration of the intraperitoneal therapy.

The 4 rats which received combined therapy and the more than 40,000 units/kg. intraperitoneally in 10 to 14 injections were examined microscopically for 31 days, during which time none relapsed. Brain passages from these 4 animals were all negative. Thus, it is again demonstrated that adequate combined intracranial and intraperitoneal penicillin therapy will cure both brain and blood-stream involvement in experimental relapsing fever.

The 5 rats which received no intracranial penicillin but received 47,600 to 52,500 units/kg. intraperitoneally in 10 to 16 injections were examined microscopically each day until they relapsed, or for 31 days. Three of these rats relapsed in 11 to 16 days. The two which did not relapse in 31 days were found to be brain passage positive and can be assumed to have been potentially capable of relapsing had the examination period been extended. This irregular relapse tendency undoubtedly has been the cause of much confusion in chemotherapeutic studies in experimental relapsing fever. We believe that the use of intracranial or intracisternal penicillin will serve as a distinct aid in future testing for the blood-visceral efficacy of other spirocheticidal agents in rats.

The results of these experiments prove that relapse after intraperitoneal treatment in experimental relapsing fever can result from spirochetes re-entering the blood after persistence in the central nervous system during the course of treatment. Undoubtedly some of the numerous instances of relapse after intravenous arsenic therapy in human relapsing fever can be explained similarly.

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The Ambiguity of International Antitoxic Units[1]

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The labels on the bottles of commercial polyvalent antitoxin now being used in the prophylaxis and treatment of gaseous gangrene are very misleading. For example, "one therapeutic dose" of a certain brand of such antitoxin is stated to contain:

10,000 units *B. perfringens* antitoxin
10,000 units Vibrion septique antitoxin
3,000 units *B. histolyticus* antitoxin
1,500 units *B. oedematiens* antitoxin
1,500 units *B. Sordellii* antitoxin

One would naturally suppose the units of these five antitoxins to be of equal protective power; such a serum would seem to be very strong in protective action against *B. perfringens* and "Vibrion septique" (*B. septicus*), less than a third as strong against *B. histolyticus*, and only about one-seventh as strong against *"B. oedematiens"* (*B. Novyi*) and *B. Sordellii*.

As a matter of fact, no two of the international units for these antitoxins have the same protective power in terms of minimal lethal doses of their respective toxins in mice. The papers of Bengston, Stewart, and Ipsen (*2, 3, 4*), who established the international standards for these antitoxins under the auspices of the Permanent Committee of Standardization of the Health Organization of the League of Nations, show the approximate values indicated in Table 1.

It is, of course, impossible to establish and maintain an exact relationship between the number of

[1] The work in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University. Dr. Frank L. Meleney, of the Subcommittee on Surgical Infections, was the responsible investigator.

minimal lethal doses of different lots of toxin and a "unit" of antitoxin, owing to the varying ratios of active toxin and inactive toxoid occurring in different toxic filtrates. It is well known that both toxins and toxoids combine with antitoxins. The original standard units of diphtheria, tetanus, and botulinus antitoxins were based upon test doses of more or less stabilized toxins measured in minimal lethal doses for guinea pigs of standard weights from which an initial

TABLE 1

Antitoxin	Approximate number of mouse M.L.D.'s neutralized by 1 unit	Units in "therapeutic dose"	Approximate number of mouse M.L.D.'s of toxin neutralized
B. perfringens	50 to 70	10,000	500,000 to 700,000
B. septicus (Vibrion septique)	40 to 64	10,000	400,000 to 640,000
B. histolyticus	45	3,000	135,000
B. Novyi (*B. oedematiens*)	5,000	1,500	7,500,000
B. Sordellii	1,900 to 3,800	1,500	2,850,000 to 5,700,000

provisional and reasonably stable unit of serum could be defined, but it was always necessary to titrate each lot of toxin against the standard antitoxic unit when ascertaining the titer of new lots of antitoxins. And the number of minimal lethal doses in the test doses from different lots of toxin was found to vary considerably. In fact, the same antitoxin tested against different toxins equated to the same standard unit sometimes gave different values. The same principle holds for the gas-gangrene antitoxins, yet there is, in all cases, an approximate relationship between unitage and protective power. It thus appears in the above "therapeutic dose" of polyvalent gas-gangrene antitoxin that while the number of units of *B. perfringens* and *B. septicus* antitoxin is large, their protective power is greatly exceeded by a much smaller number of units of *B. Novyi* and *B. Sordellii* antitoxin.

There has been considerable discussion as to the most desirable composition of polyvalent gas-gangrene serums. Some manufacturers, starting some years ago with a mixture similar to the above, in some cases including 1,500 units of tetanus antitoxin, subsequently eliminated all but the antitoxins for *B. perfringens* and *B. septicus* on the ground that these two were the most common causative agents in gaseous gangrene. Tetanus antitoxin was to be given prophylactically in a separate dose. But owing to the increased number of cases of infection with *B. Novyi* in the military campaign in the Middle East (*6*), recent practice has been to include *B. Novyi* antitoxin as well, omitting the antitoxins for *B. histolyticus* and *B. Sordellii* on the ground of relative infrequency. I favor the inclusion of all five in approximately equal protective ratios, because experience shows that all the above anaerobic bacilli give rise to serious wound infections, and it is impossible for a bacteriological examination to determine the significant species present in a given case in time to decide which monovalent serum should be used.

It is really unfortunate that the standardization of antitoxin serums was not developed so that an approximately equal protective power was always denoted by the term "antitoxin unit." Even the much older units of diphtheria, tetanus, and botulinus antitoxins differ from each other and from the above in relative protective power. The diphtheria unit was originally defined as that amount of serum which would protect a 250-gram guinea pig for 96 hours against a test dose (L_+) of diphtheria toxin of 100 minimal lethal doses (*5*), while the tetanus antitoxin unit was defined in the United States as 10 times that amount of serum which would protect a 350-gram guinea pig against a test dose of 100 minimal lethal doses (*7*), and botulinus antitoxin was standardized like tetanus antitoxin except that guinea pigs weighing 250 grams were used (*1*).

The gas-gangrene antitoxin units defined in terms of minimal lethal doses of toxin for mice are all different from those of diphtheria, tetanus, and botulism in terms of minimal lethal doses of these toxins for guinea pigs. Although the values overlap between *B. perfringens* and *B. septicus* antitoxins and between *B. tetani* and *B. botulinus* antitoxins, the discrepancies in the list as a whole and the over-all range are conspicuous.

Perhaps a new international committee on standardization might consider redefining antitoxic units in terms of approximately equal protective power in order to simplify as far as possible our now confused conceptions.

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