VI CONGRESSO INTERNAZIONALE DI MICROBIOLOGIA

ROMA 6-12 SETTEMBRE 1953

Segretario Gen.: E. BIOCCA *Presidente: V. PUNTONI*

ATTI
DEL VI CONGRESSO INTERNAZIONALE DI MICROBIOLOGIA

VOLUME IV

SEZIONI XI-XII

N. 1-110

SEZIONE XI - Rickettsiae

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ATTI

DEL

VI CONGRESSO INTERNAZIONALE DI MICROBIOLOGIA

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SEZIONE XI

RICKETTSIAE

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1.

ANTIBIOTIC THERAPY OF RICKETTSIAL DISEASES

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Treatment of the rickettsial diseases of man with broad-spectrum antibiotics is a relatively recent development in therapeutics, since chloramphenicol, aureomycin and terramycin were first described in the interval from 1947 to 1950 (1, 2, 3). Nevertheless, the few years that have elapsed since 1947 have provided the medical practitioner with detailed, reliable information regarding the usefulness of these three antibiotics in a variety of diseases. It is a privilege to be invited here today to summarize the experiences of ourselves and of a large number of our colleagues who have utilized the broad-spectrum antibiotics, both in the laboratory and in the clinic, in the never-ending and age-old battle against the rickettsial diseases of man.

When initially examined in the laboratory, all three antibiotics were shown to inhibit the growth of all rickettsiae with which they were tested, although none of the antibiotics was found to be rickettsiocidal (4, 5, 6, 7). The first of these characteristics was manifested by prolongation of life of infected laboratory animals or embryonated eggs, or by the actual reduction of mortality in such hosts. The failure to sterilize the tissues of treated infected animals was demonstrated by the successful isolation of the infecting rickettsial agents from animals during chemotherapy or immediately following recovery from disease.

As soon as the first of the broad-spectrum antibiotics had been shown in the laboratory to have potential therapeutic value against the rickettsial agents, animal and human pharmacologic studies were initiated to investigate the acute and chronic toxicity of this drug. Subsequent studies on the other two showed that all three were well tolerated orally in normal individuals in dosages large enough to produce blood levels of antibiotic sufficient to inhibit growth of rickettsiae.

General remarks on clinical use of the broad-spectrum antibiotics. The first antibiotic to be employed clinically in therapy of rickettsial diseases of man was chloramphenicol, used in treatment of epidemic and murine typhus by Payne and colleagues in La Paz, Bolivia, (8) and Smadel and co-workers in Mexico City (9) late in 1947 and early in 1948. Dramatic therapeutic responses were reported by both groups even though the dosages employed are today considered minimal. These

early studies are probably to be remembered mainly because of their stimulus to further investigation and their demostration that the antibiotic was safe for administration to severly ill patients.

Clinical experience with chloramphenicol accumulated rapidly and was quickly supplemented by similar experience with aureomycin and terramycin. On the basis of this clinical material, the following dosage schedule is considered optimal for all three antibiotics: an initial loading dose of 50 to 60 mg./kg. body weight, followed by daily maintenance doses of 50 to 60 mg./kg. in 3 or 4 divided doses given until the patient becomes afebrile. This schedule has been used extensively in treatment of a number of rickettsial diseases and may be assumed to hold with each specific disease mentioned in this report.

Although the antibiotics under discussion are considered to be non-toxic in the dosages just outlined, certain undesiderable side effects have been noted with some frequency, namely, nausea, vomiting or diarrhea. Where these are a problem, the antibiotic may be administered more frequently in proportionally smaller doses, or temporarily discontinued.

Blood dyscrasias have been reported in rare instances in which chloramphenicol therapy has been employed, especially over lengthy periods (10, 11, 12, 13, 14). However there is no conclusive evidence that aplastic anemia results more frequently from administration of chloramphenicol than it does from use of other broad-spectrum antibiotics (15). Regardless of which antibiotic is used, the incidence of this complication is so low that it should not influence the decision to use these agents in therapy of the rickettsioses. This group of diseases is characterized by mortality rates which overwhelmingly exceed the risk of a serious blood dyscrasia which might result from specific therapy.

Clinical use of the broad-spectrum antibiotics. Scrub typhus fever will be used as a model for discussing the clinical use of antibiotics in rickettsial diseases because of our own greater experience with this disease. The immediate effect of chloramphenicol on the clinical course of a scrub typhus patient is well illustrated in Figure 1.

It may be seen that the patient's temperature dropped precipitously to normal within 30 hours after the initiation of a 24 hour course of chloramphenicol therapy on the fifth day of disease as indicated by vertical arrows and the black bar. The clinical diagnosis of scrub typhus was adequately confirmed by the laboratory isolation of *Rickettsia tsutsugamushi* from the patient's blood on the fourth and fifth days of disease. A diagnostic rise in Weil-Felix OX-K agglutination titer was not observed in this patient.

This clinical record was selected in order to provide an opportunity to discuss the relative efficacies of the laboratory procedures utilized to confirm the diagnosis of scrub typhus in the patient. Diercks has shown that isolation of the rickettsial

agent is the most accurate diagnostic aid, since it was positive in 93 percent of 127 patients with proved scrub typhus (16). Of the serologic procedures, the OX-K agglutination reaction gave a total of 75 percent positive reactors, and the complement fixation technique gave positive results in only 50 percent of the proved cases.

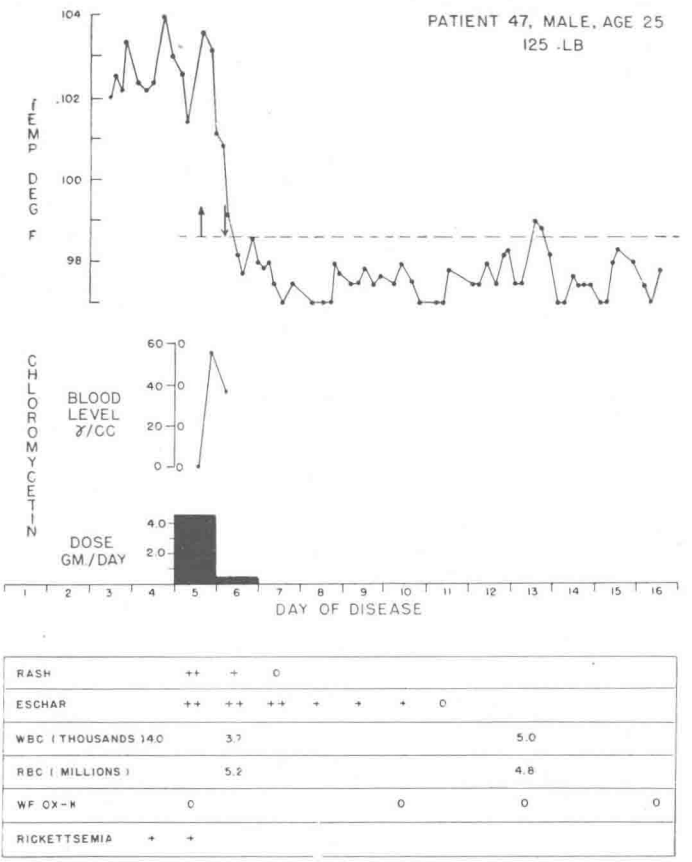

Fig. 1 - Clinical Chart of scrub typhus patient treated with chloramphenicol on fifth day of disease.

Therapeutic results with aureomycin and terramycin have paralleled those with chloramphenicol, and a summary of our experience with the use of these antibiotics in treatment of scrub typhus during the last 5 years is presented in Table 1 (17).

Ninety-four Malayan patients with scrub typhus have been treated with chloramphenicol which has produced defervescence in an average period of 31 hours. Similar information is presented for 30 patients treated with aureomycin and 46 treated with

terramycin. Although the speed with which the fever abated after start of antibiotic therapy varied from 25 hours with aureomycin to 37 hours with terramycin, all 3 antibiotics produced highly satisfactory clinical results — the patient would change from an extremely sick, toxic individual to an alert, afebrile, active person in 24 to 36 hours. Little more can be desired in a disease that generally produced 17 days of fever and caused death in 1 person of 15 in Malaya before the advent of the antibiotics.

TABLE 1

SCRUB TYPHUS PATIENTS TREATED WITH CHLORAMPHENICOL, AUREOMYCIN, TERRAMYCIN OR PARA-AMINOBENZOIC ACID.

THERAPY	NUMBER OF PATIENTS	AV. DURATION OF FEVER AFTER TREATMENT (hrs)	FATALITIES
CHLOR-AMPHENICOL	94	31	0
AUREOMYCIN	30	25	0
TERRAMYCIN	46	37	0
PABA	15	89	0
DURATION OF DISEASE			
NONE	19	17 DAYS	1

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Results in scrub typhus. Reproduced from Annals of the New York Academy of Science, 1952, Bailey and Ley (17).

It is our thesis that this dramatic clinical response of the scrub typhus patient to therapy is a result of the rickettsiostatic properties of the antibiotics which essentially call a truce between the invading agent of disease and the patient for a period of 5 to 7 days. The eventual « cure » of the patient rests with the development of his immune defense against the disease. Assuming that the patient requires about 2 weeks time before the antigenic stimulus of infection produces an immune state, we may expect that some patients given the short course of therapy before the seventh day of disease may experience a relapse or recurrence of infection before their immune defense is fully developed. Such actually proves to be the case, as shown in Figure 2 in which the incidence of relapses is plotted against the time after onset at which a 24 hour course of therapy was started.

Over three-fourths of 13 patients treated within 24 hours of onset of illness experienced a recurrence of infection within 7 days after the short course of antibiotic therapy was discontinued. The proportion of relapses was 7 of 10 when treatment was delayed until the third day of disease, and dropped to 2 of 15, when delayed until the fifth day of disease. No relapses have been observed in persons

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treated on the seventh day of disease, or later, either in the 2 patients mentioned in Figure 2 or in the 49 other patients presented in Figure 3.

Further information in support of the idea of the interaction of waning chemotherapeutic control and waxing immunologic response being concerned with relapses is presented in Figure 3. The normal development of OX-K antibodies in 19 patients who received no antibiotic therapy is shown at the top, where it may be seen that the geometric mean of OX-K antibody titers reached a peak titer of 1 : 1280 on the 20th day of disease, and fell to a titer of 1 : 640 by the 28th day. It is of interest that on the 12th day of disease, at the time the antibody titer was rising, the temperature began to fall and reached normal levels by the 17th day.

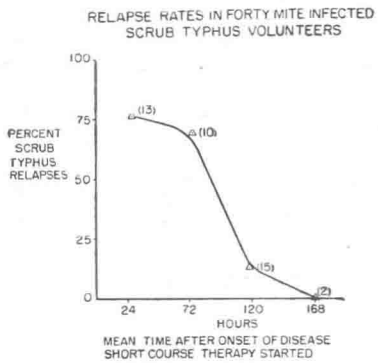

Fig. 2

The course of events in 49 patients who received antibiotic therapy late in the first week of disease (seventh day on the average) is shown in the next section of the figure. In this instance the antibody titer rose to a maximum of 1 : 320 on the 16th and 20th days of disease and fell to 1 : 160 by the 28th day. This group of patients responded well to treatment and experienced no relapses. It is interesting to note that at the time the patients might have been expected to relapse, a week after cessation of therapy, the mean antibody titer was beween 1 : 160 and 1 : 320.

On the other hand, the next group of 34 patients treated early in the first week of disease (third day, on the average) responded well to therapy, but 62% of this group experienced a relapse. It may be seen that by the seventh day after antibiotic therapy was discontinued, at the time relapses were occurring, the mean OX-K antibody titer was only 1 : 40, the same as it had been on the fourth day of disease. The maximum antibody titer of 1 : 320 was attained on the 20th day of disease, and persisted at a titer of 1 : 160 on the 28th day.

It is pertinent to note that in all 3 groups thus far described peak antibody titers were observed on the 20th day of disease, irrespective of whether antibiotic

therapy had been given or not, and that although the maximum titers in the treated groups were somewhat lower than that of the group given no antibiotic, these differences are not statistically significant, *i.e.*, they could be expected to occur more than once in 20 such groups of patients on the basis of chance variation alone.

The last group of 18 patients presented in Figure 3 requires additional comment. They were immunized against the Karp strain of *R. tsutsugamushi* by the viable vaccine-chemoprophylatic method (18). This procedure has so far been applied to

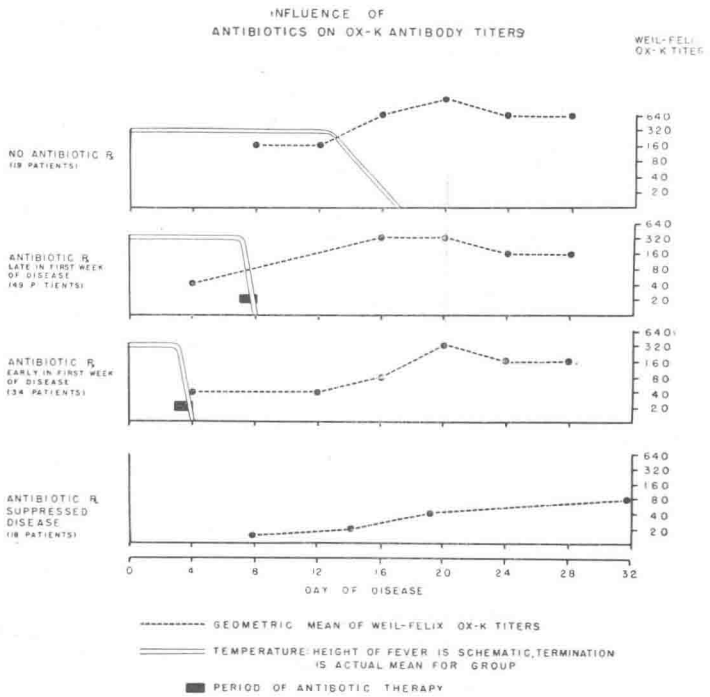

Fig. 3

human immunization only with the scrub typhus agent, but was independently developed by Weiss and his South African co-workers for the immunization of sheep against the rickettsial disease, heart water (19). The 18 men in the suppressed disease group received an infective dose of *R. tsutsugamushi* and subsequent oral doses of chloramphenicol carefully spaced so that clinical manifestations of disease did not appear but immunity developed. None of these individuals developed clinical signs of disease after chemoprophylaxis was stopped, yet all were resistant to subsequent reinfection with the Karp strain of the agent. Although they were immune, this group developed a mean OX-K antibody titer of only 1 : 40

by the 20th day after the time at which they would have developed disease, had prophylaxis not been given. The maximum mean OX-K antibody titer of 1 : 80 was reached only after 32 days.

These serologic observations, like those of other investigators, indicate that the development of OX-K antibodies is correlated generally with the development of the immune state in the naturally infected patient. However, the correlation is not absolute even under these circumstances and it breaks down almost completely under the conditions of immunization by the viable vaccine-chemoprophylactic procedure.

The subject of relapses deserves some additional comment. They have been observed primarily in scrub typhus patients treated with any of the three antibiotics, although they have been reported for murine typhus patients treated with chloramphenicol (20). All such recurrences of infection have responded well to a second course of therapy with no indication that the rickettsial agent has developed resistance toward the therapeutic agent.

The therapeutic results obtained with the 3 antibiotics in treatment of the rickettsial diseases of man are presented in summary form in the Table 2.

This information has been culled from available case reports in the literature. For each disease, the response to the antibiotic is measured by the average length of the febrile period between initiation of therapy and defervescence.

A total of 26 epidemic, or louse-borne, typhus patients have been treated with chloramphenicol by Payne (8) and by Smadel (9); 4, with aureomycin by Fu (21); and 32, with terramycin, by Knight and Ruiz-Sanchez (22), by Killough (23), and by Zapff-Gross (24). The response times for the 3 antibiotics are 2, 3 and 4 days respectively. Only 2 antibiotics have been reported to have been used in the treatment of recurrent epidemic typhus, or Brill's disease. Chloramphenicol produced defervescence in about 4 days in each of 2 patients reported separately by Murray and colleagues (25) and by Knight and Ruiz-Sanchez (22). Aureomycin caused disappearance of fever in 2 days in 2 patients reported by Blumberg and co-workers (26) and in 1 patient treated by Schoenbach (27).

In murine, or flea-borne, typhus fever, aureomycin has eliminated pyrexia in 2 days, as reported in a total of 64 patients by Knight and colleagues (28), by Ruiz-Sanchez (20), by Giroud and his French colleagues (29), and by Knight and Ruiz-Sanchez (22). The 17 patients treated with chloramphenicol by Ley and colleagues (30) and by Ruiz-Sanchez (20), and the 5 patients who received terramycin in the hands of Bauer and co-workers (31) and Knight and Ruiz-Sanchez (22) all became afebrile approximately 3 days after beginning therapy.

Although the subject of antibiotic therapy of scrub typhus has already been adequately covered, the essential data are included in this chart for comparison. It may be seen that all 3 antibiotics produce defervescence in about 2 days.

Thirty-one Rocky Mountain spotted fever patients have been treated with chloramphenicol by Pincoffs (32) and by Parker (33); 13 have been treated with

aureomycin by Ross and colleagues (34); and 9, with terramycin by Bauer (31) and by Powel (35). The response times were 4, 3, and 4 days respectively for the 3 antibiotics.

TABLE 2

ANTIBIOTIC THERAPY OF RICKETTSIOSES, I.

DISEASE	TREATMENT AND RESPONSE		
	ANTIBIOTIC USED*	NUMBER PATIENTS	DAYS FEBRILE AFTER START Rx
EPIDEMIC TYPHUS (LOUSE-BORNE)	C	26	2
	A	4	3
	T	32	4
BRILL'S DISEASE	C	2	4
	A	3	2
MURINE TYPHUS (FLEA-BORNE)	C	17	3
	A	64	2
	T	5	3
SCRUB TYPHUS (MITE-BORNE)	C	94	2
	A	30	2
	T	46	2

* C=CHLORAMPHENICOL, A=AUREOMYCIN; T=TERRAMYCIN.

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ANTIBIOTIC THERAPY OF RICKETTSIOSES, II.

DISEASE	TREATMENT AND RESPONSE		
	ANTIBIOTIC USED*	NUMBER PATIENTS	DAYS FEBRILE AFTER START Rx
ROCKY MOUNTAIN SPOTTED FEVER	C	31	4
	A	13	3
	T	9	4
RICKETTSIALPOX	C	8	2
	A	9	
	T	8	
AFRICAN TICK-BORNE TYPHUS	C	5	3
	A	40	3
	T	59	2
Q FEVER	C	24	3
	A	52	5
	T	7	3

* C=CHLORAMPHENICOL; A=AUREOMYCIN, T=TERRAMYCIN.

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A total of only 25 patients with the mild rickettsial disease, rickettsialpox, have received antibiotic therapy. Rose (36) reports that defervescence occurred in about 2 days regardless of which antibiotic was used.

The African tick-borne fever entity includes patients with boutonneuse fever as well as those with South African tick bite fever in accordance with the recommendations of the World Health Organization Technical Report No. 23 (37). Chloramphenicol has been employed in the treatment of 4 patients by Janbon and colleagues

(38) and 1 patient by Fouquet and Morin (39) with a response time of 3 days. Aureomycin has been used with 2 patients by Le Gac and Rouby (40), 8 patients by Henderson and co-workers (41), and 30 patients by Gear (42) and has produced defervescence in about 3 days. Fifty-nine such patients have received terramycin, and in these the response times reported by Nina (43) and by Baussay (44) have been 2 days.

In recent years Q fever has attracted increasing attention both here in Europe and in the United States, and the therapeutic reports in the literature have been increasing rapidly. Chloramphenicol has been used in a total of 24 patients and has terminated fever in 3 days as reported by Zarafonetis and Bates (45), by Clark and Lennette (46), by Fellers (47), and by Scuro (48). Fifty-two patients have received aureomycin with an average response time of 5 days as reported by Clark and Lennette (46) and by Fellers (47). Giunchi (49) and Anderson (50) have reported treatment of 7 patients with terramycin which produced defervescence in an average period of 3 days.

DISCUSSION AND SUMMARY

It is apparent that all 3 broad-spectrum antibiotics currently available are effective in treatment of rickettsial diseases of man in daily oral doses of 50 to 60 mg./kg. body weight, supplemented by an initial loading dose. With certain diseases, particularly scrub typhus, the institution of specific therapy early in the course of disease has resulted in recrudescence of illness after the rickettsiostatic effect of the drug has been dissipated and before the patient has had sufficient time to develop his own immunologic defense. In such instances an additional short, 24 hour course of antibiotic is indicated about 6 days after the end of the first course to buy time until the patient's immunity mechanisms can control the infection.

It is difficult to convey to you the significance and the extent of the changes in therapy of rickettsial diseases that have resulted from use of the broad-spectrum antibiotics. Of the 588 patients mentioned in this review, who have been treated by various groups of investigators in different parts of the world, not a single death has been reported in persons receiving adequate dosage of antibiotic before the terminal stages of disease. Furthermore, we know of no unpublished instances in which the broad-spectrum antibiotics, given a reasonable chance, may be said to have failed and to have permitted the rickettsioses to proceed to fatal conclusion. The present results seemed almost impossible only a few short years ago, and today one recalls with difficulty the prolonged febrile courses and the all too frequent deaths of patients with rickettsial diseases. The efficacy of these therapeutic agents and their rapidity of action have increased the need for early diagnosis of the rickettsioses and have modified the application of immunization and vector control under certain circumstances. Thus, it may be more practical to treat the few cases of rickettsial disease that develop annually in an endemic area than it is to apply

control measures to the entire population exposed to risk. We have in mind, for example, Rocky Mountain spotted fever in the central Atlantic states or boutonneuse fever in some Mediterranean areas.

The clinical experience with specific rickettsiostatic antibiotics summarized here is so satisfactory that there is no longer a strong urge to search for other rickettsiostatic agents. However, should an antibiotic be found which in the laboratory is both rickettsiocidal and non-toxic, it would be worthy of immediate clinical investigation.

ABSTRACT

The authors reviw some fiifty articles dealing with the use of chloramphenicol, aureomycin and terramycin in 588 patients suffering from one of the typhus or spotted fevers or from Q fever. Their own experience in the treatment of scrub typhus is employed to illustrate the salient features of the therapeutic and immunologic responses of such patients. With adequate doses of any of the three antibiotics, i.e., 50 mg./kilo per day, patients became afebrile within 2 to 4 days and no deaths were recorded in infected persons receiving adequate therapy before the terminal phase of this disease. The influence of this signal advance in the treatment of rickettsioses on the need control measures is discussed.

(1) Ehrlich, J., Bartz, Q.R., Smith, R.M., Joslyn, D.A. and Burkholder, P.R.: Chloromycetin, a new antibiotic from a soil actinomycete, Science, 1947, *106*, 417.

(2) Duggar, B.M.: Aureomycin, a product of the continuing search for new antibiotics, Ann. N.Y. Acad. Sci., 1948, *51*, 177-181.

(3) Finlay, A.C., Hobby, C.L., P'an, S.Y., Regna, P.P., Routien, J.B., Seeley, D.B., Shull, G.M., Sobin, B.A., Solomons, I.A., Vinson, J.W. and Kane, J.H.: Terramycin, a new antibiotic, Science, 1950, *111*, 85.

(4) Smadel, J.E., Jackson, E.B. and Cruise, A.B.: Chloromycetin in experimental rickettsial infections, Jour. Immunol., 1949, *62*, 49-65.

(5) Wong, S.C. and Cox, H.R.: Action of aureomycin against experimental rickettsial and viral infections. Ann. N.Y. Acad. Sci., 1948, *51*, 290-305.

(6) Anigstein, L., Whitney, D.M. and Beninson, J.: Aureomycin, a new antibiotic with antirickettsial properties: its effect on experimental spotted fever and epidemic typhus. Ann. N.Y. Acad. Sci., 1948, *51*, 306-317.

(7) Snyder, J.C., Fagan, R., Wells, E.B., Wick, H.C. and Miller, J.C.: Experimental studies on the antirickettsial properties of terramycin. Ann. N.Y. Acad. Sci., 1950, *53*, 362-374.

(8) Payne, E.H., Sharp, E.A. and Knaudt, J.A.: Treatment of epidemic typhus with chloromycetin, Trans Roy. Soc. Trop. Med. and Hyg., 1948, *42*, 163-170.

(9) Smadel, J.E., Léon, A.P., Ley, H.L., Jr. and Varela G.: Chloromycetin in the treatment of patients with typhus fever, Proc. Soc. Exper. Biol. and Med., 1948, *68*, 12-19.

(10) Rich, M.L., Ritterhoff, R.J. and Hoffmann, R.J.: A fatal case of aplastic anemia following chloramphenicol (chloromycetin) therapy, Ann. Int. Med., 1950, *33*, 1459-1467.

(11) Wilson, L.E., Harris, M.S., Henstell, N.H., Witherbee, O.O. and Kahn, J.: Aplastic anemia following prolonged administration of chloramphenicol; a report of two cases, one a fatality, Jour. Amer. Med. Ass'n, 1952, *149*, 231-234.

(12) Claudon, D.B. and Holbrook, A.A.: Fatal aplactic anemia associated with chloramphenicol (chloromycetin) therapy; report of two cases, Jour. Amer. Med. Ass'n, 1952, *149*, 912-914.

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