The crystalline sodium salt[2] used in these studies was reconstituted in water from the dried state. The aluminum salts[3] were received as unbuffered tablets with and without sodium benzoate. The alum-precipitated, penicillin-sodium benzoate tablet is identical with that reported on by Bohls and co-workers (*2*). The crystalline potassium penicillin was contained in gelatin capsules[2] and, when indicated, was taken at the same time as, but separately from, the sodium benzoate tablets.

TABLE 1

AVERAGE SERUM CONCENTRATION IN UNITS/ML.

Penicillin salt	Hours following administration (100,000 units)					
	½	1	1½	3	6	Average
Sodium	0.038	0.018	0.012	0.003	*	0.014
Aluminum	.009	.015	.015	.006	*	.009
Aluminum + sodium benzoate	.078	.101	.090	.027	.003	.060
Alum-ppt. + sodium benzoate	.054	.094	.094	.027	.003	.054
Potassium	.050	.040	.021	.009	*	.024
Potassium + sodium benzoate	.100	.136	.062	.024	.012	.067

* No assayable level with any of the 10 subjects.

The average serum concentrations for the 10 subjects appear in Table 1. To facilitate comparisons, the over-all averages for each preparation are also presented. In the absence of sodium benzoate none of the penicillin salts produced an average level above 0.05 unit/ml. or an assayable level at 6 hours. In contrast, the simultaneous administration of sodium benzoate resulted in maximum averages approximating or exceeding 0.1 unit/ml. and, in some instances, assayable levels at 6 hours.

The striking variation in individual response deserves emphasis. When averages were computed from the levels produced by each subject for all six preparations, it was found that the figures ranged from .009 to .073, an 8-fold difference. One subject did not show a single assayable level when the benzoate salt was omitted. In contrast, another subject accounted for all of the 6-hour levels recorded in Table 1. In passing, it should be mentioned that a subject who produced relatively high levels with one preparation also did so with the remaining preparations. Similarly, the "poor absorbers" remained relatively low, regardless of the preparation being employed. Because individuals vary markedly in their ability to absorb orally administered penicillin, the indiscriminate use of any one such preparation is not justified until it can be demonstrated that none of a large number of test subjects fails to develop therapeutically effective serum levels.

The inaccuracy of serum penicillin determinations has been repeatedly emphasized by the authors cited earlier. Although the alum-precipitated, penicillin-benzoate tablet included in the present study is apparently identical with that employed by Bohls and co-workers (*2*), the high and prolonged levels reported by those authors were not seen. As an explanation for the discrepancy it should be pointed out that their subjects were infected persons who might be expected to show higher levels than normal individuals and who are reputed to produce larger amounts of antisubtilis factor (*5*). Certain of the prolonged levels reported by Bohls could have been due to antisubtilis factor which was apparently not taken into consideration. With respect to the present study, however, no instance of complete inhibition was observed in the clarase controls.

The present authors were impressed by the need of close inspection of the tests for evidence of growth. The test organism (*Bacillus subtilis*, N.R.R.L. # 558) usually developed in broth (2 per cent tryptose extract) as a sediment with some diffuse turbidity rather than as a pellicle. Careful observation often revealed a small amount of sedimented growth or a faint turbidity. Final readings were made after 21–24 hours incubation, and the levels were frequently lower than those recorded 5 hours earlier. Therefore, a standardized incubation time is desirable.

The ability of sodium benzoate to increase and prolong serum levels appears to be established. The choice of a dose of 1.2 gram/100,000 units, as employed in the present study, was purely arbitrary. In view of the relatively innocuous nature of this compound (*7*), the value of using larger amounts in combination with oral penicillin should be determined.

One subject in the present study developed a reaction which was attributed to penicillin sensitization. Fifteen minutes after the administration of the third compound urticaria appeared, followed later by edema. No other untoward effects were noted.

[2] Kindly supplied by Dr. L. W. Smith, of Commercial Solvents Corporation.

[3] Kindly supplied by Dr. Roger Reid, of Hynson, Wescott and Dunning.

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Action of Thiamine Applied Directly to the Cerebral Cortex

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It is generally claimed that vitamin B_1 (thiamine) exerts influence on the nervous functions. This assumption is based more on data obtained from deficiency states than on an effective action of thiamine on the specific functions of the nervous system. Indeed, it has been verified that this vitamin presents no typical or characteristic pharmacological effect on normal animals. Large doses by the intravenous route are tolerated, showing only discrete reactions in the blood pressure or urinary excretion (*7*, *12*). Death occurs by respiratory failure (*12*).

On the other hand, there is some experimental evidence indicating a possible association of thiamine with acetylcholine in the processes of nervous excitation. Binet and Minz (*3*) have

obtained liberation of a particular substance from the vagus and other nervous trunks, *in vivo* and *in vitro*, by repetitive electrical excitation. This substance, which potentiates various effects of acetylcholine, was later identified by Minz (*9*) as thiamine. Recently, in a similar manner, Von Muralt (*16*) has described liberation of thiamine, in addition to acetylcholine, by electrical stimulation of cholinergic nerves. According to the latter, "aneurin (*i.e.* thiamine) is a reservoir substance closely connected with the formation and disappearance of acetylcholine."

In another field it has been shown that thiamine potentiates and increases the action of acetylcholine on the dorsal muscle of the leech (*11*, *13*, *15*), isolated intestinal loop (*1*, *2*, *5*), arterial pressure (*2*, *13*), blood vessels of the frog (*4*), and frog "rectus abdominis" muscle (*13*). Thiamine also intensifies the effects obtained by stimulation of certain nervous trunks (*10*). It was also independently found by various investigators that cholinesterase is inhibited by thiamine (*6*, *8*, *14*).

In order to study the action of thiamine on the central nervous system, we performed a series of experiments on 45 dogs, applying the referred substance directly and circumscribely to the cerebral "motor" cortex.

The animals were craniectomized, and a small region of the cortical "motor" area of one side was exposed. One of the "motor" points that elicited, by a minimum intensity of electrical stimulation, contractions of the contralateral eyelids (m. orbicularis oculi) and extension or flexion of the contralateral forelimb was determined by unipolar excitation.

We have used thiamine hydrochloride in solutions of 1, 2, 5, and 10 per cent, dissolved in physiological saline solution. A small, square filter paper, 3–3.5 mm. square, was soaked with the solution assayed and directly applied to one of the "motor" points previously located. The filter papers with the thiamine solution were substituted at regular intervals of 5–7 minutes, according to the requirements of the experiments. All observations were made on animals in an unanesthetized state.

We have observed that thiamine hydrochloride (2–10 per cent sol.) applied directly to the cerebral cortex, after 1–2 minutes, gives rise to motor reactions consisting of rhythmic contractions (clonus) of the muscle or muscular group corresponding to the cortical "motor" point submitted to the action of the substance. Initially, the rhythmic muscular reactions are weak and sometimes with irregular sequence, but generally, within 1–3 minutes after their appearance, the intensity is increased and the clonus well marked by rhythmic and regular contractions. With a second application of thiamine on the cortex, 6 minutes after the beginning of the experiment, the localized muscular clonus becomes stronger and better characterized, showing a definite increase in intensity and frequency of the contractions.

Usually, afferent, repetitive, mechanical stimulation of the cutaneous region connected with the muscle which is in rhythmic action, corresponding to the cortical "motor" point under the action of thiamine, increases the intensity or frequency of the motor reactions, or both.

Sometimes peripheral cutaneous stimulation determines a typical effect of facilitation on the muscular rhythmic contractions, which show a pronounced increase in intensity and frequency. Instead of being intermittent, the contractions become continuous, occurring one after another without interruption and with increasing frequency. On the other hand, the contractions may become vigorous, showing a progressive increase in intensity, with a marked tonic component on the clonic reactions. Then, the motor phenomena present the aspect of a localized convulsive reaction. With further peripheral cutaneous or simply spontaneous stimulations, it was possible to obtain gradual and progressive generalization of the motor convulsive reactions to other muscular groups of the animal, in a Jacksonian manner. When all skeletal musculature is involved, a typical and completely generalized epileptiform convulsion takes place, developing with the typical tonic-clonic sequence. After the convulsion stops, the former localized muscular clonus persists, presenting contractions with good intensity and frequency.

We were able to obtain epileptiform convulsions in 34 of the 45 dogs, using 2–10 per cent thiamine hydrochloride solution on the cerebral cortex. In some dogs, the convulsions were produced in 4–10 minutes after the beginning of the experiment, with only one or two applications of thiamine hydrochloride. In others, epileptiform fits occurred after a longer period (16–27 minutes), such a reaction depending on the convulsive predisposition of the animal as well as on the degree of concentration of the solution used. Employing 2 per cent thiamine hydrochloride solution, the time required to obtain a generalized epileptiform convulsion was greater than that observed with more concentrated solutions (5–10 per cent).

In some animals (11 dogs), only localized muscular clonic reactions could be obtained, even though 5–10 per cent solutions were used over a period of 30–35 minutes, with successive renovation of the substance each 6 minutes. These animals were considered as "not predisposed."

In the experiments performed with 1 per cent thiamine hydrochloride solution, we obtained only localized muscular clonus, generally weaker than that produced with more concentrated solutions. In some animals, the motor rhythmic reactions presented a transitory convulsive aspect, but they always remained restricted to the muscle related to the cortical "motor" point submitted to the action of thiamine, and no generalized convulsive reactions were observed.

Using the same technique, we tried diphosphothiamine (cocarboxylase) in 2 and 5 per cent solutions, identical results being obtained. All animals showed localized muscular clonus, and in 2 of the 5 dogs studied generalized epileptiform convulsions were observed.

Experiments were made with the two separate thiamine moieties: pyrimidine and thiazole. The cortical application of 2-methyl-5-ethoxy-methyl-6-aminopyrimidine (10 per cent sol.) and 4-methyl-5-beta-hydroxyethylthiazole (pure liquid substance) gave negative results, no motor reactions being observed. Each of the two substances was applied to the cerebral cortex for 30 minutes, the drug being renewed each 6 minutes.

Other hydrosoluble vitamins, pyridoxine hydrochloride (5 per cent sol.), niacinamid (5 and 10 per cent sol.), and ascorbic acid (5 and 10 per cent sol.), applied to the cerebral cortex for 30 minutes with regular renewal of the substance, proved to be ineffective in producing any kind of muscular reaction.

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Bacillary Dysentery and Chronic Ulcerative Colitis in World War II

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Bacillary dysentery has long been recognized as a major military disease. Next to malaria, it was the prevailing disease, during World War II, among the American forces in tropical areas and the second greatest disease threat in number of cases among overseas troops. Since 1933 a rather striking increase in incidence of the disease among civilians throughout the world has also been noted. In the United States the number of reported cases in 1944 was approximately 60 times greater than in 1933.

The subject of bacillary dysentery has been recently reviewed elsewhere (*1*). There is, however, a great paucity of data regarding the chronic manifestations of the disease. Evidence has been presented that these appear as diffuse cicatrizing, ulcerative, polypoid lesions of the small and large bowel known as regional ileitis (enteritis) and chronic ulcerative colitis. This view has met with considerable resistance in some circles, although typical chronic ileitis and ulcerative colitis have been demonstrated in many individuals followed from the acute to the chronic phase. The first extensive group follow-up was that of the atypical Flexner dysentery epidemic which occurred in Jersey City in 1934 (*2*). Of 210 patients hospitalized at the Medical Center, 122 were studied for periods varying from 9 to 12 months. Of the latter, 10.7 per cent developed chronic ulcerative colitis or ileitis. Subsequent studies elsewhere by other investigators have closely approximated this figure, so that we may reasonably assume that 1 of 10 patients with acute bacillary dysentery will probably develop the chronic form of the disease—usually ulcerative colitis. One of the major contentions of those opposing the bacillary dysentery etiology of chronic ulcerative colitis is that, if true, we should see many instances in connection with wars, since bacillary dysentery is largely a military disease.

The present communication concerns 61 cases of chronic ulcerative colitis occurring in American military personnel, including some war prisoners, of World War II. Of the total, 50 were studied from 5 to 30 months after the onset of diarrhea. In the remainder, the symptoms and signs were of slightly shorter or longer duration than the period specified. In 33 instances, the onset of the disease was definitely traced to outbreaks, 3 of them occurring aboard transports and 30 in military camps. Almost all patients incurred their initial acute bacillary dysentery in known endemic and epidemic areas, chiefly New Guinea, India, the Philippines, and North Africa. Accurate bacteriologic data during the acute phase was sparse, due to the lack of adequate laboratory facilities or the stress of combat service. In 5 of the outbreaks, *Shigella paradysenteriae* (Flexner's bacillus) was isolated. Confirmatory epidemiologic evidence was sometimes obtained in cases where initial cultural studies were not carried out. This consisted of positive cultures for *B. dysenteriae* in other military personnel who had diarrhea at the same time and place as those who were not studied bacteriologically. All cases were diagnosed as "dysentery," "GI's," "intestinal infection," "gastroenteritis," or "Delhi belly"—terms which, on the basis of previous studies, are now recognized as being practically synonymous with bacillary dysentery. All patients were treated with sulfonamides.

The general clinical picture during the acute phase in all patients included in this report was the abrupt onset of abdominal cramps, diarrhea, and fever. The bowel movements were watery, mucopurulent, or bloody. In 5–10 days these symptoms and signs subsided only to be followed by the characteristic postdiarrheal phase of constipation (healing phase). No sigmoidoscopic studies were made during the acute stage. There followed recurring episodes of bloody diarrhea, and in 8 patients the diagnosis of chronic ulcerative colitis was subsequently made in military hospitals. Fifty of the 61 patients were subjected to sigmoidoscopic study 5–30 months after their initial infection. All patients exhibited the typical hyperemic, granular mucosa or ulceration and purulent cytology of the mucosal exudate. Mural fibrosis and luminal stenosis were usually present only in cases of long duration (a year or more). Five patients in the present series also exhibited a concomitant distal ileitis, one confirmed by X-ray.

Of 12 patients receiving fecal cultures during the acute phase, 5 (41.6 per cent) were positive for *B. dysenteriae*. Of the 61 patients examined by us during the chronic phase, 6 (9.8 per cent) revealed *B. dysenteriae* by the mucosal crypt aspiration method. One patient exhibited positive cultures during both acute and chronic phases. Thus, out of a total of 61 patients with chronic ulcerative colitis, 10, or 16.4 per cent, exhibited positive cultures. This figure is significant since so few were studied initially, and the recovery of the dysentery organism in 9.8 per cent after 5–30 months appears in marked contrast to our control group where the incidence is 0.08 per cent.

The evidence presented is deemed to be of sufficient importance to lend additional support to our contention that chronic ulcerative colitis and ileitis are the result of acute bacillary dysentery. It is of particular relevancy at this time, since many of our veterans are finding it difficult to establish service-connected disability in chronic ulcerative colitis and ileitis because the initial acute phase has been forgotten or inaccurately diagnosed. It is quite probable that the present series of 61 cases forms but a small fraction of the actual number occurring in veterans of World War II.

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