

THE WASSERMANN REACTION AND THE KAHN TEST IN LEPROSY¹

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INTRODUCTION

The specificity of the laboratory tests for syphilis when applied to the sera of individuals infected with Hansen's bacillus is still a moot question. The Wassermann reaction in its many modifications, and the various precipitation or flocculation methods, which have been developed to serve as aids in the diagnosis of syphilis are often positive in leprosy. However, it is gratuitous to consider that any leprologist or serologist entertains today a belief that the two diseases have a common origin and thus a similar immunologic response.

The changes elicited in the skin by a luetic infection, or the cutaneous lesions of tertiary yaws—a disease which is closely related serologically with syphilis—are as a rule not difficult to distinguish clinically from leprosy, because of the absence of anesthesia, nerve thickening and acid-fast organisms. On the other hand the unequivocal recognition of syphilis superimposed upon a background of leprosy is in many instances practically impossible. This uncertainty has given substantial support to the conclusion that a positive reaction with the serum from a case of leprosy is indicative of an accompanying infection with syphilis or yaws.

The statement has been made that leprosy is most prevalent among those social and economic classes in which syphilis is relatively widespread. This view finds some basis in the fact that the first signs of leprosy frequently appear shortly after the initial or secondary manifestations of a spirochaetal infection. But is it sound to

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conclude from the evidence available, as several authors (16) have, that the Wassermann reaction is not positive in uncomplicated leprosy if a suitable antigen is used, and that the Kahn test is usually negative in pure leprosy? Stated in other words, the explanation of the positive reactions would lie: "in the simultaneous occurrence of syphilis or yaws with leprosy and in mistakes in clinical diagnosis" (22).

Such deductions have been questioned on several occasions by prominent leprologists who have had the opportunity during the past few years to give this phase of their work serious consideration. One individual in a personal communication recently stated:

"When you send the blood of a leper to a laboratory to be tested serologically for syphilis or yaws you may expect any type of a report; the test is without significance. Yet in the routine of the clinic with the nonlepers we expect the laboratory tests to be of considerable aid in the diagnosis of syphilis."

The following quotation from a recent publication of Ryrie (19) is quite pertinent:

"The sera of 690 patients were tested by both the Wassermann and Kahn reactions. Of these, 300, or 43.5 per cent, gave positive reactions with both tests. Further investigation is being made on this matter, but at present it is considered that it is unlikely that this large percentage of positive reactions is definitely luetic."

As long as the purposeful amelioration of leprosy appeared to be hopeless, there was little need for more than passing, scientific interest in the part that the disease might play in nonspecific serological reactions. However, evidence has been accumulating, as manifested by the distinct spirit of optimism prevalent among those in attendance at the Leonard Wood Memorial Conference (15), that chaulmoogra oil and its derivatives have definite therapeutic value in leprosy. This confidence is being confirmed in fact, since there is a decided increase in the number of patients discharged annually from leprosaria with the malady arrested, following intensive treatment with these compounds. It now becomes increasingly important for the serologist to be able to furnish the clinician with data which will aid him in the interpretation of the reactions for syphilis in the presence of leprosy. The present investigation was undertaken with this end in view.

The sera from 669 cases of leprosy were tested by means of the Kolmer-Wassermann complement-fixation reaction (10) and the Kahn

precipitation test (9). The selection of these two procedures was the natural outcome of a more or less intimate familiarity with them. Experience on the part of many workers has also emphasized the desirability of employing a complement-fixation technique along with a precipitation test of proven sensitiveness and specificity.

HISTORICAL

The literature on the subject of the Wassermann reaction and, recently, the Kahn test with the sera of patients with leprosy has been extensively reviewed by several authors.

Cooke (4) made a rather careful survey of the reports of forty-two investigators, published from 1908 to 1916, and concluded that positive Wassermann reactions may occur with the sera of individuals suffering from leprosy but free from syphilis. Hasseltine (8) extended the work of Cooke and included some data on the Kahn test, which had recently been developed. He seemed to think that there was ample foundation for the assumption that such sera may give a positive Wasserman reaction in the absence of syphilis. His experience with the Kahn test did not permit him to make a definite commitment concerning it.

A careful notation, which it would be fruitless to include here, of the many reports on this subject shows that only a few have failed to record positive reactions in the apparent absence of syphilis or yaws. However, Bloombergh (3) early explained these seemingly erroneous results as due to an unrecognized concurrent syphilitic infection. Mathis and Baujean (14) definitely agreed with this point of view. Lloyd, Muir and Mitra (13) in their study of the effect of antisyphilitic treatment on the fixation of complement in leprosy found that many of the cases were suffering from syphilis; the influence of the luetic infection in these instances was quite great. Information is not available as to whether Muir believes syphilis or yaws to be unequivocally involved when the tests are positive with the sera of patients with leprosy. Uniformly negative reactions with the sera of nonsyphilitic cases of leprosy have been reported by Kolmer and Denney (11) using the improved Kolmer-Wassermann technique, and by Yagle and Kolmer (21) employing the Kahn test.

Several important and comprehensive studies have been made by workers in the Philippines in an attempt to evaluate these tests. Goodpasture (7), in Manila, used the Wassermann reaction and obtained 8 positive results (61.5 per cent) in 13 clinically and bacteriologically active cases, all of which were undergoing treatment with chaulmoogra derivatives. In 16 individuals in whom the disease had become arrested as a result of the administration of the drug, he found the test uniformly negative. This writer believed that a positive Wassermann reaction in leprosy is due to the presence of Hansen's bacillus, and that the disappearance of the reaction is a specific phenomenon associated with clinical improvement and diminution in the number of acid-fast bacilli. He envisaged the complement-fixation test with an acid-fast antigen as holding

promise of a means of measuring the response of leprosy patients to chaulmoogra therapy.

Schöbl and Basaca (20), also in Manila, performed the Wassermann reaction in leprosy and obtained 35 per cent of the tests weakly positive.

Pineda and Roxas-Pineda (17), stationed at Culion, applied the standardized Wassermann technique of Kolmer to sera from 500 patients. Of these, 300 had had careful physical and historical examinations, and of this group 250 were without evidence of syphilis or yaws; 18 of these (7.2 per cent) gave reactions that were positive to some degree. Of the remaining 200 cases, 9 were positive without a history or clinical sign of spirochaetosis. These investigators were unusually fortunate in that they had the opportunity to study an additional number (82) of sera from patients undergoing lepra reaction; 16 of this group gave positive tests. They became convinced that there are two reasons for positive Wassermann reactions in cases of leprosy without accompanying clinical evidence; one is unrecognized syphilis or yaws and the other is lepra reaction.

Later Pineda and Roxas-Pineda (18) reported the outcome of the Kahn test in 250 sera. Of this series 54 cases were influenced by lepra reaction; each one proved to be negative. They concluded that the Kahn test is preferable to the Wassermann reaction for the detection of complicating treponematous infections in lepers, and, furthermore, that it is specific.

Arguelles (1) at the San Lazaro Hospital in Manila investigated the response to both tests with sera from 100 lepers and leprosy suspects, specimens from 100 nonlepers serving as controls. The results of the two tests agreed to the extent of 93 per cent. One per cent of the sera of the leprosy cases, after ruling out syphilis, were positive to the Wassermann reaction, whereas the Kahn test was positive in 5 per cent. It was obvious to this author that in uncomplicated leprosy the two procedures employed are generally negative.

Badger (2), in 1931, found in the more recent papers a perpetuation of the inferences and marked inconsistencies of earlier investigators. Working in Hawaii, where as in the Philippines the cutaneous type of the disease predominates, he selected 207 patients under treatment, all over 10 years of age, whose histories and clinical findings gave no indication of syphilis. A positive Wassermann test was observed with the sera of 42 (20.2 per cent), and a positive Kahn test with 57 (27.5 per cent). A comparison of these figures with those for a group of 1,212 ordinary hospital patients of comparable social and economic station and racial origin showed the incidence of positive reactions to be three times as frequent among lepers as nonlepers. This led Badger to postulate that, if a positive Wassermann or Kahn test in leprosy were conclusive evidence of the presence of an infection with the *Treponema pallidum*, it would follow that:

1. One in three of the patients studied was afflicted with both leprosy and syphilis;
2. Syphilis occurs three times as frequently in the leper group as in the control group;
3. Syphilis occurs almost twice as frequently among the females as among the male patients; and
4. The incidence of syphilis is greater in the patients under than in those over 20 years of age.

Experience with syphilis rendered such conclusions highly improbable, Badger believed, and he concluded that:

The results of the Wassermann and Kahn tests are variable during the course of the disease. Variations occur with the sera of patients who have received no antisyphilitic therapy. They bear a definite relation to changes in clinical manifestations of the leprosy. It is believed, therefore, that this study shows further evidence that a positive Wassermann or a positive Kahn test with the sera of lepers does not necessarily signify the presence of a syphilitic infection.

To an outsider the contributions from the Philippines lend themselves to but one interpretation, namely, that the serologists there are convinced that leprosy *per se* does not interfere with the specificity of the tests for syphilis. However, on personal inquiry in the Philippines it was found that this belief, while firmly entrenched with the laboratory workers, was viewed with considerable skepticism by many of the clinicians. Several of the later group at Culion kindly volunteered their service in the selection of the patients for the present study.

METHODS

The majority of the patients were chosen as they presented themselves at the clinics for antileprosy treatment. The others, examined in the wards, had been hospitalized because of severe lepra reaction, which was evidenced either by a general exanthematous eruption or by a sudden marked increase in the severity of the existing lesions and toxic manifestations. Approximately 0.5 per cent of the 6,700 patients at Culion are undergoing this unusual condition at any one time, and advantage was taken of this wealth of material to include a goodly number of such cases in the present study.

The nature and extent of the leprous infection was carefully noted in each instance. A special effort was then made to establish the presence or absence of syphilis and yaws. Each individual was carefully questioned by a staff physician and if the history was suggestive of a previous venereal infection or of framboesia the patient was excused. Those with negative histories were then given a physical examination to confirm the absence of these diseases.

A total of 669 patients was accepted. It is realized that the low mental development of many of them, and the difficulties of finding clinical manifestations of syphilis, are of paramount importance and subject the methods of selection to criticism. In the final analysis, however, it is the clinician who must establish the presence or absence of a spirochaetal infection. At the Copenhagen competitive conference and at the Montevideo conference, both arranged

by the League of Nations Health Committee (12) to permit of practical demonstrations by prominent serologists, the most sensitive test employed detected in the former instance only 63.5 per cent of the positive syphilitic cases, and in the latter 75 per cent.

The right arm of each patient was thoroughly scrubbed with alcohol over the median basilic vein, and tincture of iodine was applied. A tourniquet was then placed above the elbow and with a sterile Luer syringe 10 cc. of blood was withdrawn from the vein. Only one specimen was taken from each patient. The blood was immediately discharged into a sterile plugged centrifuge tube and placed in a refrigerator. The serum, freed from blood cells (by centrifugation when necessary) was divided between two sterile ampules (2 to 3 cc. in each), the mouths of which were sealed in the blast lamp. The specimens to be used for the Kolmer-Wassermann reaction were heated at 55° C. for 20 minutes; those to be examined by the Kahn method were heated at 56° C. for 30 minutes. The tests were made several months later, in the United States.

Each serum was examined, as stated, by both the standardized Kolmer-Wassermann test, employing a plain alcoholic antigen with a prolonged (18 hour) period for fixation at 6° C., and the regular Kahn test. All glassware was chemically clean and sterile. The saline solutions were prepared by the addition of sodium chloride (C.P., Kahlbaum) to sterile, double distilled water. A separate pipette was used for each specimen and for each reagent. The readings with both tests were recorded as agreed upon by the Copenhagen conference.

RESULTS AND DISCUSSION

ORDINARY CASES

The results obtained³ in 615 cases without lepra reaction are presented in Table 1, from which it will be noted that with the Kolmer-Wassermann reaction 18.5 per cent were definitely positive if the doubtful reactions are not included, and 81.5 per cent were negative, while with the Kahn test 31 per cent were positive and 69 per cent negative. There was absolute agreement of the two procedures with the same sera as follows: 100 were strongly positive, 5 positive and 407 negative; these total 512 out of the 615 sera, or 83 per cent. Naturally, it is impossible to estimate the relative sensitiveness of the two tests because the patients were considered free from syphilis or yaws.

A number of general considerations not given in the table are now mentioned as they are pertinent in connection with the work of others. The individuals examined would all be rated as adults

³ A representative group of duplicate sera were tested in the laboratories of Drs. H. Eagle, F. W. Hartmann, S. Ide, R. L. Kahn and J. Kolmer, and their cooperation is gratefully acknowledged.

inasmuch as the lower age limit was 18 years. The group was composed of 526 males and 89 females. The frequency of positive reactions was 3.2 per cent greater among the males than the females with the Kolmer-Wassermann reaction and 1.8 per cent with the Kahn test. These differences in sex distribution, while real, should be interpreted in terms of the relative disproportion of numbers in the two groups. The patients all showed leprotic lesions in the skin and were classified as C2 and C3 at the time of the physical examinations, this indicating the degree of severity of the infection. They were all bacteriologically positive, and were undergoing regular treatment with the iodized ethyl esters of chaulmoogra oil (*Hydnocarpus wightiana*), though the drug had been temporarily withheld from those having lepra reaction. The findings with the sera of this reaction group, which included 47 males and 7 females, have been placed in Table 2 and will be discussed later.

TABLE 1.—*The Kolmer-Wassermann and Kahn reactions with sera of Filipino patients without lepra reaction and presenting no evidence of syphilis or yaws.*

Test	Number of sera tested	Results					
		Strongly positive	Positive	Doubtful	Negative	Per cent negative	Per cent positive
Kolmer	615 *	109	5	14	487	81.5	18.5
Kahn	615	121			424	69.0	31.0
Sera in which the two reactions were identical .		100	70		407		

* 526 males and 89 females.

Before attempting to evaluate the figures presented in Table 1 it would be well to recall the data cited, particularly those from the Philippines. Pineda and Roxas-Pineda found the Kolmer-Wassermann reaction positive in 17 per cent of 500 Culion patients, which is quite in keeping with my 18.5 per cent. However, they ascribed most of their positive results to syphilis or yaws, the exceptions being a limited number of uncomplicated cases with lepra reaction. (These instances will be commented upon in connection with Table 2.) With the Kahn test they detected 14.4 per cent reactors, much below my 31 per cent. Again they were able to satisfy themselves that syphilis or yaws was involved in all of these reactions. Arguelles, in 100 sera, found only one positive specimen by the Wassermann technique and five by the Kahn test. He endorsed the interpretation of Pineda and Roxas-Pineda that these tests are negative in uncomplicated leprosy. On the basis of the clinical findings the figures in Table

1 are not open to such a simple interpretation, and the explanation must be found elsewhere.

Goodpasture's results with the Wassermann reaction—61.5 per cent reactors among 13 untreated patients and 84.5 per cent among 14 patients undergoing treatment—are strikingly at variance with the figures of Pineda and Roxas-Pineda and also with those in Table 1, but it is probable that an extension of his experiment would have affected materially the relative proportions. Goodpasture was quite firm in the conviction that the values he obtained were not the result of spirochaetosis, but of the presence of Hansen's bacillus.

These references include the more extensive studies from the Philippines and it would be futile to review here the conflicting data from other sources. It will suffice to recall that Badger tested the sera of 207 selected, nonsyphilitic Hawaiian cases and found the Wassermann reaction positive in 20 per cent and the Kahn test positive in 27 per cent. He also found that the results varied during the course of the disease, having a relation to the changes in its clinical manifestations. The frequency of positive reactions, three times as great as in a large control group, and considerations with reference to age and sex, forced him to interpret his findings as substantiating the view that a positive Wassermann or Kahn test in leprosy does not necessarily signify the presence of a complicating syphilitic infection.

REACTION CASES

In Table 2 are given data referring to the 54 individuals (not included in Table 1) who at the time the blood specimens were obtained had lepra reaction with generalized disturbance severe enough to warrant their hospitalization. Comparison of the figures reveals that the two methods gave practically identical results. There was

TABLE 2.—*The Kolmer-Wassermann and Kahn reactions with the sera of Filipino patients having a severe lepra reaction but presenting no evidence of syphilis or yaws.*

Reaction	Number of sera tested	Results				
		Strongly positive	Positive	Negative	Per cent negative	Per cent positive
Kolmer	54 *	18	1	35	64.8	35.2
Kahn	54	18		36	66.8	33.4

* 47 males and 7 females.

only one exception to absolute agreement with the same sera, and in that instance the Kolmer-Wassermann reaction was positive and the Kahn test negative. On comparing Tables 1 and 2 it is seen that in the presence of lepra reaction the incidence of positive reactions with the Kolmer test increased from 18.5 per cent to 35.2 per cent, but with the Kahn test only from 31.2 per cent to 33.4 per cent.

Changes in ordinary cutaneous-type leprosy that are classified as "lepra reaction" vary widely in their degree of severity. Pheno-

mena ranging from simple "flare ups" of one or two pre-existing lesions to acute generalized involvement with exanthematous eruptions are all designated under this heading. It is only natural to infer that such a condition, at least in its more severe forms as in the cases tested, would have a profound effect on the relative proportions of the normal constituents of the serum, as well as being accountable for the introduction of foreign substances.

The influence of this poorly understood phenomenon on the Wassermann and Kahn tests was considered at some length by Pineda and Roxas-Pineda. It was obvious, in their first series of experiments, that the lepra reaction *per se* was in some manner responsible for serum changes which tended to cause non-specific binding of complement in the presence of lipoidal antigens, although they were cognizant of the possibilities of an underlying treponematous infection. With the Kahn test the sera from lepra reaction cases gave uniformly negative results. These indications led them to reconsider the previous studies involving the fixation of complement, and they became convinced that the two tests are negative in uncomplicated cases of leprosy. Badger, on the other hand, records that subacute or acute leprosy reactions may be accompanied by changes in the serum response from negative to weakly or strongly positive.

DISCUSSION

The conclusions of Pineda and Roxas-Pineda, in view of the figures presented in Tables 1 and 2, are of considerable importance. One should recall that both their studies and my own were carried out at Culion, separated, however, by an interval of six or seven years. In the present investigation an attempt was made to obtain blood specimens from the same patients that were included in the earlier series, but there is no assurance that that was accomplished. Be that as it may, it can at least be said that the two groups were sufficiently large to be representative of the colony population (my cases constituted 10 per cent of it), and they were drawn from the same sources in the Islands and lived under practically the same conditions at the colony. Nevertheless, it would seem that with the passage of time a radical change has occurred in the blood serum responses of the patients at Culion. From typically negative reactions in a selected group of patients the incidence of positive reactors has reached in ordinary cases values of 18 and 31 per cent with the Wassermann and Kahn tests, respectively, and in reaction cases 35 and 33 per cent.

In an attempt to account for these differences several factors have been taken into consideration, the most important of which

is the intensive treatment of all individuals with the iodized ethyl ester derivatives of chaulmoogra oil. That the drug does influence the physical nature of the serum can perhaps be postulated from the data of Goodpasture. He showed that there was a difference of 23.1 per cent between a group of patients undergoing medication and a similarly untreated one. He felt that the increase in strength of complement-fixing substance during treatment was analogous to the so-called "provocative reaction" in syphilis, though Pineda and Roxas-Pineda did not concur in this interpretation since in their experience no such differences were noted.

However, it is to be said that when the Pinedas made their tests (1925-26) active treatment had been given to all of the colony inmates who could take it since the middle of 1922. That is not to say that all of their cases had been treated all that time, for through new admissions, discharges and deaths there is a certain degree of change of population, but unquestionably many of them had been treated that long and most of the others had had it for more or less prolonged periods. When we did our work, seven years and more later, the average duration of treatment of the patients tested was unquestionably much longer. Treatment of cases such as the average of these at Culion is notoriously a long affair, and though many of such cases have little chance of recovery the treatment does as a rule ameliorate their condition to a considerable degree, so that the lives of many of them are greatly prolonged. Another fact to be mentioned, though its effect in the present connection, if any, is quite unknown, is that the method of treatment has been changed. In the earlier days all injections were given intramuscularly, whereas for some years all skin lesions are injected intradermally, though intramuscular injections are given simultaneously as a rule.

It is unfortunate that it was not possible in the present study to obtain sera from any considerable number of untreated patients classified as C2 and C3 as regards the degree of infection. It is doubtful if such a group of individuals exists in the Philippines, so thorough have been the activities of the Bureau of Health in its antileprosy work. Such a control would have given pertinent information regarding the influence on the serological tests of the present-day treatment. However, a somewhat indirect control of this na-

ture is found in the data of Rylie (19), who employs solutions of dyes rather than chaulmoogra derivatives in treatment.³

No attempt will be made to delve into the theoretical aspects of the biological nonspecificity and the clinical specificity of these serological tests under ordinary circumstances. The tests are based upon the capacity of syphilitic sera to react with tissue lipoids, and their value as diagnostic measures in that malady has been established. Naturally, the activities of serologists directed at attempts to justify the specificity of the reactions, rather than in extending their sensitiveness, is of more than passing interest since the laboratory tests for syphilis must continue to play an important rôle in both the diagnosis and treatment of that disease.

When attempting to draw conclusions in the present study one is confronted with the specter of inapparent luetic infections. In this connection it is pertinent to note that a recent paper (6) gives the following results on 10,383 sera from known syphilitic cases. Three representative techniques detected as positive only 75 per cent, 58.7 per cent and 60.2 per cent, respectively. Such a marked discrepancy throws the burden of the proof on the clinician, and in the present instance the coexistence of syphilis or yaws was ruled out as far as was possible clinically. Therefore, the positive reactions are looked upon as the direct result of the infection with the germ of leprosy, together, perhaps, with that of its treatment with preparations of chaulmoogra oil. The serologist will naturally, and perhaps justly, state that this is presumptuous, and that under no considerations is it permissible to rule out a spirochaetal infection as long as the tests are positive. One deduces approbation for this contention from the article of Kolmer and Denney (11).

³ Since this paper was sent to press an article which bears on this subject has appeared [Monserrat, C. *Philippine Jour. Sci.* 54 (1934) 343]. In 84 cases Monserrat obtained positive results with the Vernes test in 21.6, the Kahn in 21.4, and the Wassermann (including weak reactions) in 38.1 per cent; all three were positive in 17.8 per cent. In 54.3 per cent of 46 untreated cases one or more test was positive, but in only 30.3 per cent of 33 treated cases. In 9 cases found positive before treatment and later treated for six months to a year, the reactions usually showed a decrease in intensity. A monkey which had been strongly positive for several years as a result of experimental yaws became almost negative after receiving 7.5 cc. of pure chaulmoogra oil during one month.

It is possible that the presence of yaws is responsible for many of these findings, as pointed out by Pineda and Roxas-Pineda in calling attention to the endemic nature of this disease in the rural districts of the Philippines. However, its distribution is far from general or uniform. The people most commonly exposed to this disease, the Moros, were represented by only three individuals in this study, but their sera gave negative tests.

The disintegration of the acid-fast leprosy bacilli, rich in fats, by the defensive mechanisms of the body has been postulated as responsible for non-specific serum changes. This view may be somewhat nebulous and hard to prove. Nevertheless, in the cutaneous manifestations of this disease, as in no other bacterial infection, the host is practically an over-grown culture medium for a long period of years, and such an effect may well occur.

The true answer as to whether the positive serological reactions are due to undiagnosed syphilis or yaws in the presence of leprosy, or to an influence of leprosy itself, will be found only as a result of the testing at frequent intervals, over a protracted period of time, of such individuals as are found positive. A number of workers are now engaged in this project. The outcome of the survey (5) under consideration by the United States Public Health Service will be awaited with interest by leprologists. In that study approximately 1,000 specimens of blood will be submitted to a representative group of participating serologists. The object is to appraise separately the various serodiagnostic tests for syphilis. Included among the donors selected will be individuals with leprosy.

SUMMARY

The sera of 615 patients with more or less advanced cutaneous leprosy, and 54 other cases with severe lepra reaction, were tested by both the Kolmer-Wassermann and the Kahn procedures for syphilis. The group had been carefully selected, and comprised only individuals whose clinical examinations and case histories failed to reveal evidence of syphilis or yaws.

Of the 615 sera from cases without lepra reaction the Wassermann test gave 109 strongly positive and 5 positive, a total of 18.5 per cent, as compared with 121 strongly positive and 70 positive, a total of 31 per cent reactors with the method of Kahn.

Of the 54 sera of patients undergoing severe lepra reaction 18 were strongly positive and 1 positive with the Wassermann test, and 18 strongly positive with the Kahn, 35.2 per cent and 33.4 per cent, respectively.

This study adduces considerable evidence that leprosy *per se* is responsible for the positive reactions.

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