

FLUMERIN—A NEW MERCURIAL FOR
THE INTRAVENOUS TREATMENT
OF SYPHILISFIRST REPORT OF CHEMICAL, ANIMAL AND
CLINICAL EXPERIMENTS AND RESULTS *

EDWIN C. WHITE, PH.D.

JUSTINA H. HILL, M.S.

JOSEPH EARLE MOORE, M.D.

AND

HUGH H. YOUNG, M.D.

BALTIMORE

Experience in recent years has made it increasingly evident that the present day treatment of syphilis is not entirely satisfactory, partly owing to the fact that our attack on the disease is not sufficiently varied. It is generally agreed that efforts to improve on arsphenamin and neo-arsphenamin have been so far unavailing. It is also admitted that these drugs, either with or without mercury, constitute our most powerful anti-syphilitic remedies, especially in early syphilis. In most cases (and in all instances of late syphilis) mercury in some form must be employed. A few patients, moreover, fail to tolerate the arsphenamins, and complete reliance must then be placed on mercurial treatment.

The four common methods of administration of mercury, by ingestion, intravenous injection, intramuscular injection, or inunction, are open to various objections. All these methods are of value, but all fall short of the desired ideal. As far as intravenous injection is concerned, the compounds of mercury in common use (mercuric chlorid, cyanid, oxycyanid, benzoate, succinimid) are limited in value either by comparatively high toxicity or by their local corrosive action.

We have attempted, therefore, to develop a mercurial drug suitable for intravenous injection, in which would be combined the three factors of therapeutic value in animal and human syphilis, low toxicity and absence of local irritating qualities. The drug which forms the subject of this paper has these advantages. It is well to state that we do not believe that this drug, or any mercurial so far developed, can supplant the arsphenamins. We attempt to demonstrate only the three advantages mentioned and to suggest that further experience may show this drug to be of more value than other mercurials now in use by the intravenous route. We do not suggest that the intravenous route is the best method of administration of mercury, and we do not wish to be interpreted as advocating any special plan of treatment for syphilis.

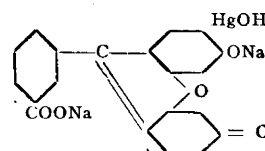
CHEMISTRY OF FLUMERIN

The field of search lay obviously among the organic mercurials, substances in which the mercury atom is bound directly to a carbon atom. In solutions of such compounds, the mercury is in a nonionic condition. In an earlier research on penetrating disinfectants, which led to the development of mercurochrome,¹ a number of mercury derivatives of various phthaleins were prepared by one of us (E. C. W.). Laboratory tests on

these compounds included, of course, determinations of their toxicity for animals; and from this standpoint the substance described in this paper stood out as having very low toxicity, although it was discarded as a local disinfectant because it did not show as marked penetration of tissue as did the other members of the series, and because it was comparatively low in bactericidal power.

Although low toxicity is perhaps the best lead in selecting a mercurial drug from a series for study in the treatment of syphilis, it must be pointed out that this property does not of itself mean that the drug will have practical usefulness. Only if it can be shown that there is a concomitant marked therapeutic effect in animals are we justified in believing that the low toxicity will be an asset of clinical value. For this reason, the present study has included a description of chemistry of the drug, toxicity determinations, a study of the effect of the drug on rabbit syphilis, and finally a careful clinical study.

Description of the Drug.—The drug is the disodium salt of hydroxymercurifluorescein² (whence the simplified name flu-mer-in) whose chemical formula is:



It forms a dark red powder with greenish iridescence and is easily soluble in water, especially hot water, up to about a 10 per cent. solution. The solution used clinically (2 per cent.) is stable to the air and to heat; in fact, solution of the powder is best effected by using hot water, although it is easily, though less rapidly, soluble in cold water. The powder is stable indefinitely in air, except that it is somewhat hygroscopic and should, therefore, be kept in well stoppered bottles or in ampules. As the drug has disinfecting value about equal to that of phenol, the solution may be considered self-sterilizing. Although we have used, clinically, solutions as old as 3 or 4 days, it is best to use only freshly prepared solutions made up in sterile, freshly distilled water. Exposure to the air for several hours does not alter the solution chemically. On long standing (one week or more), a slight precipitate of metallic mercury as a gray powder is sometimes seen.

Solutions of the drug give no precipitate with caustic alkali, iodids or ammonium sulphid, with the exception that the latter forms mercuric sulphid on long standing in the cold or in a short while on boiling. There is complete absence of precipitation when the solution is mixed with serum. This nonprecipitating action on protein accounts for the blandness of the drug toward tissues.

The drug contains about 32.5 per cent. of metallic mercury, as against the theoretical content of 33.8 per cent. required by the formula $C_{20}H_{10}O_6Na_2Hg$. The difference is due to moisture and a small amount of unmercurated fluorescein salt, which is quite inert.

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¹ From the James Buchanan Brady Urological Institute and the Syphilis Department of the Medical Clinic, Johns Hopkins Hospital.

² Read before the Section on Dermatology and Syphilology at the Seventy-Third Annual Session of the American Medical Association, St. Louis, May, 1922.

1. Young, H. H.; White, E. C., and Swartz, E. O.: A New Germicide for Use in the Genito-Urinary Tract: "Mercurochrome-220", J. A. M. A. 73: 1483 (Nov. 15) 1919.

2. To avoid misunderstandings, reference is made to two German patents, Nos. 201903 and 308335, dealing with mercury derivatives of phthaleins. At this time, it is only necessary to say that the process employed in the preparation of flumerin is fundamentally different from those of the patents mentioned, and leads to an essentially different product. Discussion of the technicalities involved would be out of place here, but will be entered into in detail in a later chemical paper. It is interesting to note that Klages and Schreiber (Seventeenth International Congress of Medicine, 1913, Transaction of Section of Therapeutics, pp. 65-71) made a clinical trial of some of the patented substances, including the derivatives of fluorescein. The therapeutic effects were so slight that further clinical use was not considered.

The 2 per cent. solution is hypotonic, showing a freezing point lowering of 0.14 C. as against an average value of 0.56 C. for normal blood serum.

TOXICITY OF FLUMERIN FOR ANIMALS

Toxicity has been determined on rabbits and dogs, always using intravenous injection. Rabbits uniformly tolerate a single dose of 30 mg. per kilogram. This is often followed by the appearance of albumin or casts, or by a decrease in phenolsulphonephthalein output, or by all three. The damage is transient, and usually within a week the phenolsulphonephthalein excretion, if lowered, returns to normal, and the urinary abnormalities disappear. This dose is usually followed by definite loss in weight. Of four rabbits receiving 40 mg. per kilogram, two died within twenty-four hours, and two survived. Fifty mg. per kilogram was fatal in all cases. Repeated small doses of 5 or 10 mg. per kilogram have been given in a series of as many as twenty doses, at intervals averaging two or three days. This rarely led to any urinary abnormality or phenolsulphonephthalein decrease, although some animals lost weight under continued medication. In this respect, there is great variation among individuals. Likewise, diarrhea has been observed occasionally, but its incidence has been so variable that it cannot be linked with size or number of doses.

The toxic limit is about the same in dogs, which usually die within twenty-four hours after a single dose of 50 mg. per kilogram, although a few have survived this amount. This dose always causes violent retching and diarrhea shortly after the injection, and the animal appears very sick. Blood in the rectum and mouth has been observed in some animals dying from such an injection. Thirty mg. per kilogram is well tolerated, although there is sometimes transient evidence of kidney damage. Loss in weight is less frequent and less marked than in rabbits receiving the same dose. Repeated doses, at average intervals of two or three days, of 10 mg. per kilogram are well borne, and as many as twenty doses of 5 mg. per kilogram are well tolerated by strong, healthy dogs, with no loss in weight and no evidence of kidney injury.

On the basis of the figures given by Schamberg, Kolmer and Raiziss³ as to the toxicity of various common mercurials suitable for intravenous injection, it is apparent that, by this route flumerin is tolerated by animals in amounts more than six times as great as any of the usual preparations; as utilized clinically, the average dose is twenty times that of the cyanid, benzoate, mercuric chlorid or succinimid, and in equivalent mercurial content is about eight times as large.

Pathologic studies on animals experimentally killed by large single doses, and sacrificed after repeated small doses, have been carried out by Drs. W. A. MacCallum and J. R. Cash. These studies, as yet incomplete, will be reported in detail in connection with a series of experimental and clinical papers to appear later.

THE VALUE OF FLUMERIN IN EXPERIMENTAL SYPHILIS

The chemotherapeutic investigations of Brown and Pearce on arsenicals, and of Schamberg, Kolmer and Raiziss on mercurials, have conclusively demonstrated that the therapeutic ratio of a given drug in protozoan infections other than syphilis, for example, trypano-

somiasis, relapsing fever or chicken spirillosis, cannot be considered accurate for syphilis. Mercurials have in general little or no effect on trypanosome infections. We have, therefore, confined the testing of the therapeutic action of flumerin to syphilis in the rabbit.

This method of therapeutic experimentation has fortunately become much more accurate than formerly, because inoculations of animals with infectious material are always successful, the incubation period is well defined and a complicating cause of resolution of lesions may be eliminated by avoiding their aspiration. Most important, the former indefinite end-point of therapeutic activity, namely, the resolution of lesions and prolonged observation of the animal for relapse, has been replaced by the method of transfer of lymph nodes from treated animals to normal rabbits. This offers not only a definite end-point, but also provides more rigid criteria of cure.

Method.—Through the kindness of Dr. Wade Brown, a rabbit was secured with a testicular infection of the Nichols strain of *Spirochaeta pallida*.⁴ From this rabbit, the strain has been continued by two methods. By the first,⁵ an infected testicle was excised under ether anesthesia, emulsified in a small amount of sterile 0.85 per cent. salt solution, the presence of spirochetes determined by dark-field examination, and normal rabbits injected intratesticularly, in most instances unilaterally, with not more than 0.5 c.c. each of this emulsion. By the second method,⁶ under ether anesthesia, the popliteal or inguinal nodes were excised, emulsified in a small amount of sterile salt solution, and, regardless of dark-field findings, normal rabbits were injected intratesticularly with not more than 0.5 c.c. each of the emulsion.

Treatment with flumerin was carried out in animals with fully developed lesions. A study of the action of the drug on very early lesions, at present in progress, indicates that it is more difficult to influence the infection at the time of first appearance of lesions than later. Treated animals, in which resolution of lesions occurred, were held under observation to allow the infection to become reestablished. If no relapse took place, transfers of the popliteal nodes were then made to the testicles of normal rabbits, which were observed for an average of seventy-nine days. If the transfer animals failed to develop lesions and if organisms could not be found in popliteal or inguinal nodes at the end of the period of observation, we felt justified in concluding that the action of the drug had been sufficient to destroy the organisms in the regional lymphatics, where Pearce and Brown⁷ have shown that spirochetes may be found on and after the second day after inoculation in untreated animals. Careful controls were made on every series of experiments.

Experiments.—Our experiments have fallen into two groups: animals treated with repeated small doses, and those treated with single large doses. In every case, the drug was given intravenously. The tolerated single dose of flumerin for rabbits by this method is, as has been stated, 30 mg. per kilogram.

4. Nichols, H. J., and Hough, W. H.: Demonstration of *Spirochaeta pallida* in the Cerebrospinal Fluid, J. A. M. A. **60**: 108 (Jan. 11) 1913.

5. Brown, W. H., and Pearce, Louise: Experimental Syphilis in the Rabbit. I. Primary Infection in the Testicle, J. Exper. Med. **31**: 475 (April) 1920.

6. Brown, W. H., and Pearce, Louise: Latent Infections with the Demonstration of *Spirochaeta pallida* in Lymphoid Tissues of the Rabbit, Am. J. Syph. **5**: 1 (Jan.) 1921.

7. Pearce, Louise, and Brown, W. H.: A Study of the Relation of *Treponema pallidum* to Lymphoid Tissues in Experimental Syphilis, J. Exper. Med. **35**: 39 (Jan.) 1922.

3. Schamberg, J. F.; Kolmer, J. A., and Raiziss, G. W.: A Study of the Comparative Toxicity of the Various Preparations of Mercury, J. Cutan. Dis., December, 1915.

Series I: Using Repeated Doses of 10 Mg. per Kilogram.—Five animals were given from four to eight doses of 10 mg. per kilogram, the drug being given every other day. In four, there was prompt resolution of lesions; the fifth, in which the local lesions had resolved, but which was known to be syphilitic, was treated during the latent period. These animals were held an average of thirty-five days after the last dose. At the beginning of these experiments, the value of lymph node transfer had not been demonstrated, but transfers of the popliteal nodes of two of this series failed to produce lesions in the transfer animals during eighty days of observation.

Series II: Using Repeated Doses of 5 Mg. per Kilogram.—Five animals were given an average of ten daily doses of 5 mg. per kilogram. Resolution began promptly and was complete in an average of eight days. At an interval of thirteen days after the last dose in four animals, and twenty-five days in the other, popliteal node transfers were made. One of the transfer animals failed to develop lesions during fifty-seven days' observation, the others remaining negative during seventy-seven days.

Series III: Using Repeated Doses of 3 Mg. per Kilogram.—Five rabbits were given twelve daily doses of 3 mg. per kilogram. The results of this treatment varied strikingly. In one animal, lesions resolved, and node transfer made forty-nine days after the last dose was negative during fifty-three days of observation. In a second, there was resolution of lesions, but node transfer made the fifteenth day after the last dose was positive in thirty-five days. In the third rabbit, the lesions persisted, and though spirochetes could not be found on the thirtieth day after the last dose, a node transfer was then made which proved positive in thirty-four days. In the other animals, lesions were not resolved, spirochetes being found in one the sixty-fifth day after the last dose. The remaining animal died by accident during the night, and although spirochetes could not be found at necropsy in the morning, the large lesions indicated the slight effect of the drug.

Series IV: Using a Single Dose of 30 Mg. per Kilogram.—Four rabbits were given this dose. In all, there was prompt resolution of lesions. Popliteal node transfers made twenty days after treatment were negative in three animals during ninety days of observation, and positive in one in forty-eight days.

Series V: Using a Single Dose of 20 Mg. per Kilogram.—Four rabbits were used in this series. In all, there was resolution of lesions. Node transfers from two animals made thirty days after treatment showed negative results during 101 days of observation in one, and positive results in the other in forty-three days. A third animal relapsed forty-five days after treatment, and spirochetes were found by dark-field examination. The fourth is still under observation.

Summary.—From four to eight doses of 10 mg. per kilogram, given on alternate days to a series of five rabbits with well established infection, caused resolution of lesions in every case, and in two instances in which node transfer was made no infection resulted in the transfer animals. An average of ten daily doses of 5 mg. per kilogram to a series of five rabbits caused resolution of lesions in every case, and popliteal node transfers were consistently negative. Twelve daily doses of 3 mg. per kilogram to a series of five rabbits gave conflicting results. In two animals, lesions resolved, and node transfer was negative in one, but positive in the other. In the remaining three, lesions persisted. A single dose of 30 mg. per kilogram caused resolution of lesions in four rabbits, negative node transfers in three cases and a positive node transfer in the remaining animal. One dose of 20 mg. per kilogram caused resolution of lesions in four animals, and later observation resulted in negative node transfer once, positive node transfer once, and relapse once; and one rabbit is still under observation.

In a single dose, therefore, the curative dose of flumerin, 30 mg. per kilogram, closely approaches the maximum tolerated dose; but a series of doses of 5 mg. per kilogram is uniformly effective. This is in sharp contrast to serial doses of 3 mg. per kilogram, which are usually ineffective.

CLINICAL APPLICATION OF FLUMERIN

The foregoing is a satisfactory demonstration that this drug is one of very low toxicity, and that in rabbit syphilis it has a definite curative effect. In single dose, its therapeutic ratio is, in common with that of other mercurials, 1:1; but repeated small doses are effective in eradicating rabbit infections, the standard of cure being based on rigid criteria. These data were considered sufficient to justify its use in human syphilis. Accordingly, a number of patients have been treated in the syphilis department of the medical clinic, under the direction of one of us (J. E. M.).

We have used flumerin alone in order that the results may not be obscured by the administration of arsphenamin.⁸ Treatment has generally been continued at two-day intervals, until a course of from twelve to sixteen doses has been given. In most instances, patients presenting open lesions have been chosen so that the effect of the drug on the healing of lesions could be followed.

In spite of the low toxicity of flumerin in animals, it was considered advisable to begin in the human subject with doses smaller than the demonstrated curative dose in rabbits, in order to avoid possible untoward effects. For this reason, the first dose was usually 2 mg. per kilogram, and subsequent doses 3 mg. per kilogram. For a man, this is about 0.2 gm. Recently, we have administered as much as 5 mg. per kilogram, or about 0.35 gm., to a small number of robust patients, without demonstrable ill effects. These patients are still under treatment, however, and are not included in the present discussion of therapeutic effect or reactions. The results of this larger dosage will be reported in a separate clinical paper.

Ninety-six patients have been treated. Of these, five patients with primary syphilis, twenty-one with secondary syphilis, and twenty-four with various lesions of tertiary syphilis, received five or more injections of the drug, sufficient to permit the formation of an opinion as to therapeutic and possible toxic results. In addition are included ten patients who were intolerant to arsphenamin, five who reacted badly to other methods of administration of mercury, four Wassermann-fast patients, and a few patients with latent or neurosyphilis. The remainder received only a few injections, and were then lost from observation.

The results on the whole have been good. In Table 1 are shown, in summary form, the data regarding the groups with open lesions.

Of the primary cases, three gave seronegative reactions on admission, the duration of the disease being three days, ten days, and seven weeks, respectively. (The last patient had received two doses of arsphenamin, beginning at the fifteenth day of his disease. He developed a typical arsphenamin dermatitis after the second dose, and was transferred to flumerin for this reason. At the time of transfer, his lesions were still unhealed.) In all three of these cases, the blood Was-

8. Since the toxicity of at least one of the halogen mercury compounds of fluorescein is much greater than that of flumerin, it is considered inadvisable at present to administer iodids concurrently because of the theoretical possibility of the formation of a toxic halogen mercurial compound in the body. A separate set of toxicity experiments, using an iodid and flumerin together, should be made.

sermann reaction remained permanently negative during and after treatment with flumerin. One patient had a seropositive reaction on admission which became permanently seronegative after the twelfth dose of flumerin fifty-three days after starting treatment, though a break in the Wassermann reaction was obtained eight days earlier. The length of time necessary to bring about this result is probably due to a long lapse in treatment, twenty-three days intervening between the first and second doses.

With one exception, the primary lesions were healed in an average of twenty-two days, the shortest time being fourteen days (after five doses of the drug), the longest thirty days (after four doses). The one case in which healing failed to occur was that of a man with a typical diphtheritic chancre of three days' duration, in which spirochetes were demonstrated. His blood Wassermann reaction was negative. After seven doses of 3 mg. per kilogram, the initial lesion was still unhealed and had definitely spread. At this time, sixteen days after starting treatment, no spirochetes could be found. A week later, two more doses of flumerin having been given without healing, this drug was discontinued, and a course of eight doses of arsphenamin substituted. The lesion healed very slowly, complete cicatrization occurring only after the sixth

TABLE 1.—SUMMARY OF TREATMENT OF FIFTY CASES WITH FLUMERIN

Stage of Syphilis	Number of Cases	Lesions Healed	Average Number of Days to Heal Lesions	Serologic Result (Blood)		Average Number of Doses to Reduce Wassermann
				Good	Poor	
Primary.....	5	4	22	4	1	3 remained 0
Secondary....	21	21 (relapse in 1 case)	19	11	10	1 case, 12 doses
Tertiary.....	24	19 (improved in 5 cases)	25	9	15	10

arsphenamin injection. At the completion of this series, he was put on mercury by inunction; but after three weeks of faithful application to this treatment, he returned with an ulceration in the indurated scar of the healed chancre. Many spirochetes were now demonstrated by dark-field examination. This case, therefore, is obviously resistant to arsphenamin, as well as to mercury, and can hardly be charged against flumerin as a failure.

In secondary syphilis, evidence of the therapeutic activity of the drug was also obtained. Of twenty-one cases, the blood Wassermann reaction was reduced to negative (in most instances permanently so) in eleven. This result was accomplished in an average number of eight doses (about three weeks of treatment). In another case, a break to suggestive negative was obtained after seventeen doses of flumerin. An additional patient, who had received numerous doses of antimony and potassium tartrate intravenously elsewhere because of the erroneous diagnosis of granuloma inguinale, had a negative reaction on admission, which remained so in spite of unmistakable lesions of early secondary syphilis. In the remaining eight patients, the blood Wassermann reaction remained positive throughout the course of treatment. Four of these, however, received only six injections or less.

All lesions were healed, the average time necessary (regardless of the type of lesions) being twenty-one days (seven doses of flumerin). In one patient, a man

with enormous condylomas, the behavior of spirochetes was studied. Five hours after the injection of 3 mg. per kilogram, no spirochetes could be found, though on admission they averaged one to the high power field. Twenty-two hours after the injection three spirochetes only could be found after exhaustive search, while, after twenty-five hours, none were present.

One case was of particular interest. This was that of a colored girl with annulopapular lesions on the face, and moist papules about the genitalia. She was given sixteen doses of flumerin, the average dose being 3 mg. per kilogram, at fairly regular intervals, though treatment was twice interrupted because of stomatitis, for a week and ten days, respectively. Her original lesions were completely healed in thirty-one days, after eight doses of the drug, and at the same time a beginning reversal of her blood Wassermann reaction had occurred. The remainder of her treatment was uneventful until the day of the sixteenth injection, when she drew attention to a lesion on her lower lip, of two days' duration. This was a typical papulo-erosive mucous patch about 2 cm. in diameter, containing an enormous number of actively motile spirochetes. Her blood Wassermann reaction was still negative. This represents a clinical recurrence while under treatment, such as are practically never observed under arsphenamin therapy, though similar instances after administration of various types of mercurials are not uncommon.

To sum up with regard to primary and secondary syphilis: evidence is provided that in the dosage employed, 3 mg. per kilogram, flumerin is therapeutically active in the sense that it will cause spirochetes to disappear from lesions, will bring about the resolution of lesions, and, in about half the cases treated, will change a positive blood Wassermann to negative.

Twenty-four cases of tertiary syphilis, mostly gummatous or nodular skin lesions, have been treated. Several cases of bone syphilis are included in this total. All lesions were healed in nineteen cases, and in the remaining five were greatly improved. The average time of healing was twenty-five days. Nodular syphilids healed more promptly, the average being fifteen days; while skin gummas, ranging in diameter from 1 to 10 or 15 cm., took an average of thirty days to heal. A break in the blood Wassermann reaction, not always to a complete negative, was obtained in nine of the twenty-five cases, while in sixteen the test remained positive.

The groups of patients who tolerated arsphenamin or other forms of mercury badly are of interest, and the cases may be briefly summed up. Ten patients who had had an arsphenamin dermatitis have been treated with flumerin and have in every instance tolerated the drug well. The results are obscured by the previous treatment, but in two cases it has been possible to reduce a positive Wassermann reaction to negative. It is suggested that in patients of this type flumerin may prove a valuable addition to our insufficient armamentarium.

Five patients who tolerated badly mercury in other forms have been treated. Three of these, all patients with late syphilis, had repeatedly shown their inability to tolerate mercury by inunction. In each instance, after a week or two of rubs, salivation, headache or severe bone pains always occurred. Each of these persons tolerated from eight to twelve doses of flumerin, 3 mg. per kilogram, without reaction of any kind. The remaining two suffered from recurring eye lesions each time mercury by inunction was attempted, though ars-

phenamin promptly controlled the lesions. In the first, a case of recurrent iritis and neuroretinitis, flumerin was begun after the third course of arsphenamin, in the attempt to avoid the recurrences of the first and second course of inunctions. The result was satisfactory—no recurrence developed. The second patient was put on flumerin during his fifth recurrence of iritis, which healed promptly—a result never obtained in that patient by inunctions.

Reactions.—There were no local reactions observed from the use of this drug. It is nonirritating to veins, and thrombosis has never occurred, even after many injections. In a few instances in which the drug has

TABLE 2.—GASTRO-INTESTINAL REACTIONS FROM FLUMERIN

Total Number of Doses Given	Number of Injections Followed by				
	Immediate Nausea or Vomiting		Cramps	Diarrhea	
	Mild	Severe		Mild	Bloody
	22 (2.3%)	19 (2.01%)		10 (1.0%)	8 (0.9%)
945	41 (4.3%)		7 (0.7%)		

been injected outside the vein, a moderately painful swelling, lasting about twenty-four hours, has resulted. No sloughs have been observed.

The general reactions observed may be separated into three groups: (1) gastro-intestinal; (2) stomatitis, and (3) renal irritation. In Table 2, it is shown that, of 945 doses of the drug, 66 injections (6.9 per cent.) have been followed by a reaction of the first group. For the most part they have been negligible, but occasionally a very severe reaction is observed. Fairly commonly, a patient complains of nausea, either actually during the injection of the drug or within five minutes afterward. This is usually mild in character and lasts only a few moments. Less frequently it is quite marked and is associated with very severe retching and vomiting. Even in these cases, however, the discomfort disappears spontaneously within half an hour, and usually there is no after-result. In a few patients, such reactions have tended to recur after succeeding injections, and twice it has been necessary to discontinue the drug for this reason. The rapidity with which the reaction appears suggests that it may be central in origin. Four per cent. of all injections have been followed by reactions of this type, equally divided between mild and severe. Dosage, the number of injections given, the concentration of the solution, or the speed of administration, seems to play no rôle in the development of these reactions.

Seven injections were followed in a few hours by abdominal discomfort or cramps, and eighteen (1.9 per cent.) by diarrhea, which in eight instances, according to the patient's report, contained blood. Two patients had to be transferred to arsphenamin because of bloody diarrhea.

Of the total number of ninety-six patients treated, more than one third complained, at some time during the course of treatment, of sore mouth, gums or teeth. In the majority of cases, this was subjective only. Nothing could be seen on examination, and the continued administration of more drug did not make the condition worse. On the contrary, it usually cleared up spontaneously, even when further injections were given. In six cases, an actual stomatitis, with swollen, bleeding gums, ulceration behind the last lower molar, etc., occurred. In all instances, this was comparatively mild, and cleared up as soon as the drug was stopped.

Aside from this, and the gastro-intestinal reactions already detailed, the use of flumerin has been attended by practically no subjective complaint. These reactions are less frequent than after the arsphenamins or an equivalent amount of other mercurials.

Particular attention has been paid to the possibility of renal damage. Urine examinations have usually been made at every visit, phenolsulphonephthalein tests have been made before and after treatment, and, in a few cases, the blood chemistry has been studied. Of seventy-seven patients in whom adequate urine examinations had been made, the urine showed no change in fifty. In ten instances (12 per cent.), albuminuria or cylindruria present on admission was cleared up by the end of treatment with flumerin. In seventeen cases (22 per cent.), a transient albuminuria or cylindruria developed during treatment, but cleared up promptly on cessation of the drug. In four instances, both albumin and casts appeared, in nine cases albumin only, and in four casts only. These figures are based on a dosage of 3 mg. per kilogram. Recent experience, using 4 or 5 mg. per kilogram, shows no higher incidence of urinary abnormalities, though the data regarding these dosages are not included in this paper. Judging from the urine examinations, therefore, no permanent renal damage was done by flumerin.

Confirmation of this is afforded by the phenolsulphonephthalein results. In thirty-six of sixty-one patients, the last test was the same as the first. In nine instances (14.7 per cent.), the phenolsulphonephthalein output was fifteen or more points higher at the end than at the beginning of treatment, while in three cases (4.9 per cent.) only was there a drop of fifteen or more points (—25 once [artefact?], —15 twice). Blood chemistry studies before and after treatment have also been negative. Not only is evidence of nephritis lacking, but it is also apparent that the

TABLE 3.—REACTIONS FROM FLUMERIN

Total Number of Patients	Stomatitis		
	Total Cases	Mild	Severe
96	36 (37.5%)	30	6 (6.2%)
77	Urine Examinations		
	Existing Abnormalities Cleared up Under 205		Transient Albuminuria or Casts During Treatment
	No Change	50	10 (12.9%) 17 (22%)
61	Phenolsulphonephthalein Output		
	Increased Plus 15 or More		Decreased Minus 15 or More
	No Change	49	9 (14.7%) 3 (4.9%)

functional renal abnormalities caused by syphilis have frequently disappeared after the administration of flumerin.

This drug is, therefore, singularly free from serious reactions in the dosage which we have employed.

COMMENT

The evaluation of the worth of any new drug in medicine, and particularly in the treatment of syphilis, is a difficult problem, which must be approached with the utmost caution. In this instance, it is fraught with special difficulties. It is obvious that flumerin cannot be compared with the arsphenamins. No strictly comparable studies with other mercurials, especially so far as rabbit syphilis is concerned, have been carried out. It is not permissible to conclude, because the single dose

therapeutic ratio of this drug is the same as that of other mercurials, and because a quantity of flumerin from eight to twenty times greater than other mercurials can be safely employed, that the actual therapeutic activity of flumerin is, therefore, proportionally greater. Therapeutic activity depends on many other factors, chief among which may be mentioned the penetrability of a given drug, and its ultimate fate in the body. No comparisons are therefore attempted, and it is given only as our clinical impression that flumerin is, from the standpoints of toxicity and therapeutic activity, superior to the soluble mercurial salts in general use by the intravenous route.

No attempts have as yet been made to employ the drug by the intramuscular route. For the present, and until adequate experimentation shall have demonstrated the limitations of toxicity, the factor of freedom from pain and the relative value of this route as compared to the intravenous route, we do not advise its use.

From the standpoint of the clinical results, it should be pointed out that, as yet, we have given only small doses of the drug. The results obtained in rabbit syphilis indicate the desirability of employing doses larger than 3 mg. per kilogram. The few instances in which we have recently administered 4 or 5 mg. per kilogram indicate that the effect of the drug on lesions and on the Wassermann reaction is enhanced. Attempts to increase the dosage must, however, be carried out cautiously and under adequate control.

No attempt is made to suggest the ultimate place which this drug may attain in the treatment of syphilis. It is not available for general distribution, and, for the present at least, permission will not be granted for its commercial manufacture.

SUMMARY

This paper deals with a new soluble mercurial drug of low toxicity and of remarkably nonirritating character when injected intravenously. The complete chemical name—hydroxymercurifluorescein—has been shortened to flumerin. This drug is effective in eradicating experimental syphilis in rabbits in doses which are well tolerated. Even in large doses, it causes little or no clinical injury to the kidneys of animals. In ninety-six human cases, definite proof of its value as an antisypilitic drug has been given.

Doses containing from eight to twenty times the amount of mercury present in the therapeutic dose of other mercurial drugs commonly used intravenously have been given with impunity, and the maximum dose which may be employed serially in the human being has not yet been determined.

The therapeutic effect of the drug has been shown in primary, secondary and tertiary syphilis by the resolution of lesions and the reversal of positive blood Wassermann reactions. The number of cases treated is sufficient to demonstrate that this mercurial is of value, but is too small to permit the allocation of the drug to a definite place in the therapy of syphilis.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. KEIM AND WILE, KEIDEL, AND WHITE, HILL, MOORE AND YOUNG

DR. UDO J. WILE, Ann Arbor, Mich.: I can add very little to what Dr. Keim has said about this test, except to emphasize that it embodies certain features that are simplifications of our standard Wassermann reaction. It commends itself by the fact that all those tests which would ordinarily be

4 plus with the standard Wassermann reaction can be read within one hour after the blood has been drawn. Secondly, the use of a single substance in the performance of the test, together with a small quantity of blood serum, leads certainly to the hope that we are on the way toward a possible standardization of this test. Surely, if a test is so simple that it requires only a single substance plus the suspected blood serum and the complete elimination of the many details and sources of error which are found in the employment and nomenclature of the hemolytic system, that test is deserving of careful scrutiny for general application. It must be remembered that we have used this test in only a small number of cases. Three hundred cases tested clinically is really a very small number on which to base conclusions. This test has been used about 8,000 times, not clinically but in the department of health in Lansing, where its author, Dr. Kahn, compared it from the serologic standpoint with the Wassermann reaction, and I believe that it is on the way to a permanent place in the serology of syphilis.

DR. R. L. KAHN, Lansing, Mich.: The limited time at Dr. Keim's disposal necessarily did not give him an opportunity to discuss the principle of the reaction. I will therefore take the liberty to say a word about it. Briefly, the antigen is so prepared that it contains a concentrated amount of antigenic substance and is diluted with physiologic sodium chlorid solution for the tests, with a view to rendering the final mixture as unstable as possible. This instability is brought about by adding as little salt solution to the alcoholic antigen as possible, rendering the diluted mixture on the verge of precipitation. This mixture is opalescent and clear, and will remain so at warm room temperature; but placed in the icebox, it will precipitate. The antigen is thus quite sensitive to precipitation. Therefore, when properly mixed with syphilitic serum, the antigen molecules readily react with the combining molecules of the serum, and marked precipitation results. Dr. Wile said that in the state health department at Lansing, about 8,000 tests had been made. This, I think, is based on a statement made months ago. We have now a record of more than 12,500 precipitation tests in the state laboratory. Most of these tests, however, lack definite clinical histories. The combined laboratory and clinical study of Dr. Keim and Dr. Wile, therefore, is of the utmost importance. For my part, it can only serve as a stimulus to try to perfect the test as much as possible, with a view to rendering it an important aid in the diagnosis of syphilis. With regard to spinal fluids, we are still in the experimental stage. We hope, in the course of months, to have this test apply to spinal fluids as well. The paper presented by Dr. Keim and Dr. Wile is based on the third communication of this precipitation test, which is to be published.

DR. JAMES HERBERT MITCHELL, Chicago: I should like to emphasize the importance of gland puncture in the early diagnosis of syphilis. Until about a year ago I thought very little of this, not having carried it out in any series of cases. Recently, however, I have carried this out as a routine procedure in all early cases of syphilis. Many times the chancre has been treated locally with various antiseptics, and often we do not see the chancre in public practice until three or four weeks have elapsed. At that time, especially after the application of antiseptics, it is very difficult to find spirochetes in the serum from the surface. Formerly we used to puncture the chancre at the root, but now we are puncturing the lymph glands. At first I used a small needle, believing that I obtained a better serum in that way; but now I use a large needle and leave it in the gland for two or three, or sometimes five, minutes, moving it about quite a little. Then with a very tight fitting syringe we aspirate gently. In practically all cases in which the glands in the region are large it is possible to get the organism.

DR. RICHARD L. SUTTON, Kansas City, Mo.: Dr. Driver referred to the importance of repeated Wassermann tests in cases that are negative to examination by dark field illumination. At times, it is extremely difficult to diagnose a suspicious primary lesion, and in many instances, only time and a number of serum tests will solve the problem. Should material from the lesion itself fail to contain spirochetes,

serum, obtained by puncturing a contiguous lymph node, may prove fruitful. I believe that much of the criticism of the Wassermann test is due to the fact that in about 50 per cent. of cases the test is improperly or carelessly made. If it is too sensitive, we not infrequently get a false positive in a patient who is innocent of syphilis; if lacking in sensitivity, a weak positive will be reported as negative. In one of our Kansas City laboratories, Dr. W. W. Duke and his laboratory chief, Miss Elizabeth Lease, have formulated a standard Wassermann test, or rather series of tests, in which I have grown to have great confidence. I cannot too strongly emphasize Dr. Keidel's plea for early and repeated examinations of the spinal fluid in patients with tertiary syphilis and neurosyphilis. It is a serious mistake to release a patient as "cured" until a careful examination of the spinal fluid has been made. I was also interested in Dr. Keidel's statement regarding the absence of gross skin manifestations in many, if not the majority of cases of syphilis of the nervous system. Dr. Charles White has called attention to the great frequency with which persons suffering from tabes and paresis give a negative history of skin syphilis, and I must acknowledge that I belong to that rather old fashioned school, the pupils of which believe that there exist certain strains of spirochetes which possess an affinity for certain tissues, such as the skin and the spinal cord. Dr. Moore and his associates have done an interesting and, I believe, valuable piece of work, and the remedy which they have introduced should find a broad field in the treatment of those patients who are very susceptible to arsenic.

DR. JOHN E. LANE, New Haven, Conn.: I was particularly interested in the relatively high percentage of ulcerative and gangrenous balanoposthitis found in Dr. Driver's series of penile lesions. Attention has not been called to this disease sufficiently, although Donovan's paper on the subject a year or two ago attracted considerable attention. The extremely rapid destruction of tissue which takes place when this condition is not recognized early makes its early diagnosis of the utmost importance, whether it exists alone or in combination with a chancre. I have found that this condition does not respond as well to intravenous injections of arsphenamin as does the Vincent infection in the mouth. I should like to know whether others have had the same experience. I was much interested in Dr. Moore's paper, but was rather disappointed that he did not compare the toxicity, therapeutic results and accidents following the use of the new compound, with those of the best mercurial compound we have previously used intravenously, mercuric cyanid. It would seem that a comparison of this sort should be made and that a probable superiority of the new compound should appear from the comparison in order to make a convincing argument for the adoption of the new compound. I should like to hear Dr. Moore's impression of this, even though he may have no experimental data on the cyanid. From the minor accidents following the injection of the new mercurial as described by Dr. Moore, I should infer that they are more frequent and somewhat more troublesome than they are following the use of mercuric cyanid.

DR. HARRY G. IRVINE, Minneapolis: The figures of Dr. Driver on the difficulty of making an early diagnosis in syphilis are not only very interesting but also of extreme importance. I was much interested in the failure with results after something had been used on the chancre in the way of antiseptics. I should like to call attention to the work of Kolmer on the Wassermann test of serum from the chancre. For the past year we have been doing some work along this line, and have confirmed his work with forty or fifty cases. These have been proved later, either by clinical symptoms or finding of spirochetes, and so far as we have gone we have been able to show the presence of a positive Wassermann reaction in the serum from the initial lesion. I think this is important, and it may be that before long physicians will be able to send in serum from the lesion as they now send the blood for a test, and we may then make the diagnosis much earlier.

DR. WILLIAM ALLEN PUSEY, Chicago: One of the points Dr. Keidel made should not pass without more comment than it has had, and that is the importance of the early immunity

produced when syphilis is allowed to run its course. It is interesting to find that this work is confirming the early view that the uncured early treated case of syphilis was in worse shape than the patient who had been allowed to go on and develop his immunity. The experiments of Moore and Pearce are along the same line as the experiments reported today, and we should not let pass the importance of the observation that was made.

DR. JOSEPH GRINDON, St. Louis: In reference to the intravenous use of mercury in syphilis, I wish to call attention to the fact that in the medical history exhibit at the library of the St. Louis Medical Society, among many other interesting things, there is a copy of the *Acta Philosophica* of the British Royal Society, published in 1674, giving an account of the treatment of syphilis by the intravenous injection of a mercurial solution, done in 1668. Also an English translation of the Latin original by Dr. L. C. Boisligniere of this city.

DR. V. G. VECKI, San Francisco: I am really glad to see that the glands are being a little more appreciated as a pathognomonic symptom, for even in late syphilis the glands sometimes will tell us stories that the blood test cannot. Ravogli recently named the two different strains of spirochetes, the neurotrope and the dermatrope. I had the opportunity to see the Molzer experiments in Munich. One strain he called his own, and another he got from Italy. With Plaut's system to obtain the spinal fluid of the rabbit without any admixture of blood, it was proved in many experiments that the Italian strain caused an increased cell count in the spinal fluid before any other symptom of syphilis appeared, or even any symptom to show that the inoculation was successful. That would prove that there are neurotrope strains; but if the German strain and the Italian strain show such a difference, how shall we explain the difference here in America? There are many questions to answer and one really does not know where to begin or where to stop. Of course, I also had my troubles with the Wassermann reaction, and I only hope that the Vernes colorimetric test, which is being investigated at the Columbia Hospital and which I have closely studied, and which, though fought for many years by the French medical profession, is now being endorsed by the president of the Pasteur Institute, Professor Brock and many other syphilographers, is going to solve the problem and enable us to make a periodic quantitative diagnosis and always receive the proper answer: Is there any syphilis or not?

DR. JAMES R. DRIVER, Cleveland: I am glad to hear Dr. Mitchell speak of gland puncture in making dark-field preparations. This procedure, especially in cases having had previous local treatment, should increase greatly our percentage of positive results. Our results so far by this method have not been very flattering, but with Dr. Mitchell's suggestions in mind we will try to improve our technic. Dr. Lain spoke of Vincent infections in the mouth reacting better to treatment than those on the genitalia. This has been our experience, if the infection involves the deeper tissues. What I wish to emphasize about erosive gangrenous balanitis is the early diagnosis, before the deeper structures are involved. In one of our cases there was almost complete destruction of the penis in one week's time, and in another there was total destruction of the scrotum in less than a week. We put these cases on soaks of hot potassium permanganate, 1:5,000 solution, for thirty minutes every four hours, alternating with hydrogen peroxid as a wash. The process clears up in a few days, but in the cases with extensive destruction a much longer time is necessary. Dr. Irvine's suggestion of early Wassermann tests on the serum from genital lesions is quite timely. This, in addition to our dark-field examination from the lesions, and from serum obtained by puncture of the regional lymph glands, I think, should make it possible to diagnose almost 100 per cent. of our primary lesions before the Wassermann reaction on the blood becomes positive. This would mean the possibility of curing practically all of our primary syphilitics if adequate therapy is given.

DR. H. L. KEIM, Ann Arbor, Mich.: We suggested that the tests should be read on the following morning without

shaking. However, I noticed that immediately when the tubes were received in the audience, they were shaken; while this does not dissolve the precipitate, it does break it up and make it less perceptible to the naked eye. We are planning further studies with this test, and hope at a later date to add more data on its clinical application.

DR. ALBERT KEIDEL, Baltimore: Whether or not we shall have to change our conceptions of immunity will be told by the future, but it seems today that our original ideas about immunity in parasitic diseases are about to undergo some rather fundamental changes, particularly getting away from the idea of the more or less graphic conception which we carry in our minds of Ehrlich's side-chain theory. We are approaching the chemical solution rather than the biologic solution of these theories. The question of strains has a bearing on the problem I presented, but as it is such a controverted point I wish only to say that my attitude toward the existence of strains, the neurologic strain, for example, is not one of great enthusiasm. I think the arguments against the existence of strains are very much more sound and practical than those in favor of them.

DR. J. E. MOORE, Baltimore: In reply to Dr. Lane, I did not attempt to make any very definite comparison with cyanid or other mercurials used intravenously. Cyanid contains by weight about 83 per cent. of mercury as against 32 per cent. for the new drug. The maximum therapeutic dose of cyanid is about 0.02 gm., whereas the therapeutic dose of flumerin is from 0.2 to 0.3 gm. On the basis of mercurial content, that means about seven times as much mercury in flumerin as in cyanid. The therapeutic ratio of both drugs is 1:1. The single curative dose in animals is practically the maximum tolerated dose. In order to cure the disease one has to kill the animal. No experiments have been carried out with node transfer for other mercurials, so far as I know, so that we feel we have a better criterion of cure for flumerin than for other preparations. I am not familiar with any recent literature on the use of cyanid alone. I am familiar with much literature in which cyanid has been used in connection with other drugs, and I feel that such work is absolutely of no value in estimating the worth of cyanid. This drug has been supplied to four or five clinics, notably those of Dr. Fordyce, Dr. Schamberg, Dr. Stokes and Dr. Wile, who I hoped would say something about it. Dr. Schamberg has been particularly interested because of the work he and Dr. Kolmer had done on the mercurials.

CALCIUM AND PHOSPHORUS METABOLISM IN PATIENTS WITH FRACTURES*

FREDERICK F. TISDALL, M.D. (TOR.)

Attending Physician, Pediatric Service, Hospital for Sick Children
AND

ROBERT I. HARRIS, M.B. (TOR.)

Attending Surgeon, Hospital for Sick Children
TORONTO

The exact mechanism by means of which calcium salts are deposited in areas of bone growth or bone repair is to a large extent unknown. While part, at least, of the process must take place at the site of growth or fracture, there is reason to believe that changes in the inorganic metabolism of the body may accompany and perhaps determine the deposition of bone salts. During the last three or four years, many investigations have been undertaken in the study of one of the frequently encountered diseases of childhood which produces marked changes in the osseous system; namely, rickets. These investigations included not only the experimental production of

rickets in animals, but also the study of the inorganic metabolism in children with this disease. Howland and Kramer¹ have shown that in rachitic infants the inorganic phosphate content of the blood serum is markedly reduced, and that when healing occurs, with the deposition of bone salts, the phosphate content of the serum again

TABLE 1.—CONCENTRATION OF PHOSPHORUS IN SERUM OF PATIENTS OF VARIOUS AGES FROM A FEW MONTHS TO FORTY-FOUR YEARS

Serum No.	Age, Years	Inorganic Phosphorus per 100 C.c. of Serum, Mg.	Serum No.	Age, Years	Inorganic Phosphorus per 100 C.c. of Serum, Mg.
53	4 mos.	5.7	29	21	4.1
22	10 mos.	5.3	42	21	3.9
10	1 yr.	5.2	33	23	3.5
20	1 yr. 2 mos.	5.8	53	23	3.7
55	3	6.4	40	24	4.0
61	5	5.7	50	24	3.7
58	7	4.8	45	25	3.8
69	9	6.0	46	25	3.7
59	10	5.2	51	25	3.8
62	11	5.7	47	26	4.3
68	12	5.5	36	27	3.6
64	13	5.4	35	28	3.7
397	14	4.4	49	28	3.6
411	15	4.4	44	29	3.7
395	16	6.0	48	30	4.0
412	17	5.1	31	31	4.0
396	19	5.2	30	32	3.7
413	19	4.5	32	32	3.7
25	19	4.2	34	32	3.7
28	20	4.1	41	34	3.2
39	20	3.7	42	44	3.9

reaches a normal level. These authors have advanced a theory to explain the deposition of bone salts, and have given considerable evidence in support of it. Briefly, the theory is that the serum (and tissue fluids) of normal infants contains calcium and phosphate in a nearly saturated solution; slight reduction of the acidity of the tissue fluid at a point at which the cartilage is in close contact with the circulation from the bone marrow reduces the solubility of these salts, and results in their precipitation. As a result of the foregoing work, and also of the study of the calcium and phosphate concentration in the serum of rachitic infants undertaken by one of us, we have endeavored to determine whether some of the fundamental principles which apparently apply to the deposition of bone in rickets also apply to the deposition of calcium salts in the union of fractures.

While we by no means have solved the problem of deposition of bone in fractures, we have found that certain definite and important changes in the inorganic metabolism of the body almost invariably accompany the process of bone repair.

The inorganic constituents of bone consist largely of calcium phosphate, with a small amount of calcium carbonate and a trace of magnesium phosphate. These elements must be carried to the site of growth by the tissue fluids, which in turn receive their calcium, phosphorus and magnesium from the blood serum. As it is not feasible to examine tissue fluids, our studies have consisted in the determination of the calcium and phosphorus in the serum of normal persons and of patients with fractures. The methods used have been described elsewhere.² After making several hundred determinations of both calcium and phosphorus by these methods, we are convinced that the results recorded here are accurate within 2 or 3 per cent.

* From the Nutritional Research Laboratory of the Hospital for Sick Children and the Departments of Pediatrics and Surgery, University of Toronto Faculty of Medicine.

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2. Kramer, B., and Tisdall, F. F.: *J. Biol. Chem.* 47: 475 (Aug.) 1921. Tisdall, F. F.: *Ibid.* 50: 329 (Feb.) 1922.