EMETINE HYDROCHLORIDE AS AN AMEBICIDE AND HEMOSTATIC.

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I. EMETINE HYDROCHLORIDE.

Emetine Hydrochloride, or Emetinæ Hydrochloridum, is the hydrochloride, $C_{30}H_{44}N_2O_4$, 2HCL, $2H_2O$, of an alkaloid found in *Cephælis ipecacuanha*. According to "New and Non-official Remedies," published by the Council on Pharmacy and Chemistry of the American Medical Association (see Journ. A. M. A., July 5, 1913), it occurs as a white crystalline powder, soluble in water and alcohol. The aqueous solution of emetine hydrochloride is practically neutral toward litmus. The general alkaloidal reagents precipitate emetine, even from dilute solutions. Alkalies precipitate emetine from aqueous solutions of its salts. A freshly prepared concentrated solution of ammonium molybdate in concentrated sulphuric acid (Froehde's reagent) is colored green by emetine hydrochloride.

"If about 0.10 gm. of emetine hydrochloride be dissolved in water, the solution made alkaline with potassium hydroxide, shaken with ether till nothing more is extracted, then acidified and made alkaline with ammonia water and again extracted with ether, the second ether extraction on evaporation should yield a residue which, when treated with Froehde's reagent, should not become purple.

"If emetine hydrochloride be dried to constant weight at 100° C. the loss in weight should not exceed 8 percent of the original substance.

"*Actions and Uses.*—Emetine acts similar to ipecac but is relatively more nauseating and less emetic, and causes relatively less renal irritation, but more cardiac depression. Emetine hydrochloride in the form of injections has been reported to be of especial value in amebic dysentery.

"*Dosage.*—Expectorant, from 0.005 to 0.01 gm. (1/12 to 1/6 gr.). From 0.01 to 0.02 (1/6 to 1/3 gr.) causes emesis, but cephæline is preferred as an emetic. By hypodermic injection, 0.03 gm. (1/2 grain)."

Amebicidal dose, in amebic dysentery, for hypodermic medication: 1/2 to 2/3 grain, for adults; 1/3 grain for children of about eight years of age (Rogers). Amebicidal dose, in pyorrhea alveolaris, 1/2 of 1 percent solution to be injected into the pockets of infection daily for at least five days, then every other day until a total of about ten treatments have been made (Barrett); 1/2 grain daily for three to six days hypodermically (Bass).

II. EMETINE HYDROCHLORIDE AS AN AMEBICIDE IN AMEBIC DYSENTERY.

In 1902 and 1903 Rogers* reported in the British Medical Journal the common occurrence of amebic dysentery in India, where it had not previously been recognized, and established its role as the cause of tropical or amebic abscess of

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the liver, the relationship of which to antecedent bowel disease was up to then much disputed in the East.

In the course of his investigation he ascertained that ipecac has a definite specific action in the treatment of amebic disease, but is of little or no value in the bacillary type. In 1907, he demonstrated that the same drug will rapidly cure amebic hepatitis (amebic inflammation of the liver) in the pre-suppurative stage, and thus prevent the formation of amebic liver abscess if given in good time.

When analyzing a series of cases of amebic dysentery, treated with full doses of ipecac, from 30 to 60 grains a day, Rogers was struck by the fact that he had lost one-third of his cases, while another one-fourth had left the hospital uncured, declining to go on with the treatment. The great majority of his patients were either very acute or advanced chronic cases, while several died within two days of admission, being hopeless on their first arrival at the hospital. In some serious cases the good effect of the drug was very evident, but nevertheless in many it was clear that sufficiently large doses could not be administered by the mouth in time to save the graver cases. Recalling to mind Vedder's experiments in Manila with fluidextract of ipecac as an amebicide, Rogers tested the effects of the alkaloid, emetine, derived from ipecac, in the form of hydrochloride, on undoubted ameba dysenterica in the mucous stools of amebic dysentery patients, and found in a dilution of 1:100,000, that the emetine hydrochloride kills them. He therefore determined to try emetine hydrochloride hypodermically in severe amebic inflammation of the colon. The results were most remarkable and thoroughly demonstrated its superiority over ipecac as a remedy for amebic dysentery.

Rogers' brilliant discoveries were the cause of a decrease in the annual death rate from abscess of the liver in the British Army in India, to only 30 percent of its former steady number within three years, and a similar decrease in the death rate from abscess of the liver in the Calcutta General Hospital.

Until more recently ipecac did not find favor among American physicians. However, in 1909, Simon, of New Orleans, advocated its use in large doses in amebic bowel disease, and further verification of its value was furnished by the experience of Dock, Roberts, Brown, Zeiler, Allan, Lyons and other competent observers. From this time onward, ipecac and its alkaloid, emetine in the form of hydrochloride, grew in favor and became popular throughout the world. At a meeting of the Academie de Medicine of Paris on February 25, 1913, Chauffard reported a case of dysenteric abscess opening into the bronchi, in which rapid recovery took place. At a meeting of the Societe Medicale des Hopitaux of Paris on April 11, M. S. Costa reported a case of amebic abscess of the liver cured by the same treatment, but aspiration was also performed. In the China Medical Journal for March, Dr. J. Preston Maxwell reported ten cases of amebic dysentery treated with great success by injection of emetine. Later Chauffard reported to the Societe Medicale des Hopitaux de Paris another case of dysenteric abscess successfully treated with emetine. Dr. Rouget reported that he had suppressed an amebic abscess of the liver by a subcutaneous injection of emetine. Dr. Flandin reported the case of a woman who had contracted amebic dysentery

in Madagascar, and presented sometime later an abscess of the liver which opened into the bronchi and necessitated an operation. The patient was cured by subcutaneous injections of emetine hydrochloride in 0.08 gm. (13/16 gr.) doses per day.

Dr. Dopter gave an interesting account of a case of amebic dysentery which had resisted the usual methods of treatment and was completely cured by three injections of emetine hydrochloride, the first dose 0.02 gm. (5/16 gr.) and the other two in doses of 0.04 gm. (⅝ gr.) each.

Dosage in Amebic Dysentery.—Rogers, in commenting upon the administration and dosage of emetine hydrochloride in amebic dysentery, advises that solutions should be made by adding the emetine hydrochloride to previously boiled water or normal salt solution, but prefers doses put up in sterile glass ampoules ready for use. The solution should be isotonic with the blood. In the treatment of amebic dysentery, he began with one-third grain doses, equal to 30 grains of ipecac, but now uses one-half or two-third grain doses in adults, while one-third of a grain may be given with perfect safety in children of about eight years of age. He says that he has several times given as much as a grain at once, two or even three times a day in adults, and has never seen any depression or other alarming symptoms follow its use. Very occasionally, severe pain may result at the seat of injection, but this is quite exceptional, and there is usually no sign of any local reaction. Half a grain twice a day give uniformly good results, or a larger dose once a day may be used if this is more convenient.

Quite as striking is the rapidity of the cure by emetine. Thus in a series of cases, the average stay in hospital of the recovering ipecac cases was 16.4 days, and of the emetine ones 7.2 days, including one day they were kept under observation, if not urgent cases, before the treatment was begun. Further, the average number of days under ipecac before the stools became finally normal was 11.4, and the average amount of the drug given amounted to 406 grains; while the corresponding figures for the emetine treatment were respectively 2.35 days and 2 grains of the drug, equal to 180 grains of the powdered ipecac.

Diagnostic Value of Emetine Injections.—Another interesting and valuable fact in connection with the use of emetine hydrochloride in curing dysentery and amebic abscess is that the action is specific. So thoroughly specific is this action that Rogers believes that where clinical microscopic facilities are not available the response to the use of emetine is diagnostic. Where the dysenteric symptoms are not affected by a few injections of the drug, the conditions have always been found to have been due to some other cause than the ameba. The blood and mucus nearly always finally disappear from the stools of an amebic dysentery patient within two or three days, four days being the longest period he has observed. In bacillary dysentery, on the contrary, the drug exerts little or no effect, so that the failure of the emetine injections to produce a very material improvement in the stools within two or three days affords very strong evidence that the disease is not amebic in origin.

III. EMETINE HYDROCHLORIDE AS AN AMEBICIDE IN PYORRHEA ALVEOLARIS.*

Barrett, in 1914, working in collaboration with Allen J. Smith, Professor of Pathology in the School of Medicine, University of Pennsylvania, announced the discovery of the Endameba buccalis as the primary etiological factor of pyorrhea alveolaris. The report was founded upon 45 cases of suppurative affections of the gums and pericemental tissues, in all of which without a single exception, parasitic amebas were discovered in active motility.

While confident of the actual pathogenic importance of these parasites from their uniformity of occurrence and distribution and from the evidence of their ingestion of leucocytes and erythrocytes, the authors did not feel justified in attempting inoculating experiments. They applied another test for pathogenicity which seemed conclusive. Resource was had to the use of emetine, a specific against the endamebas of dysentery. Accordingly, 13 cases of pyorrhea alveolaris, or Rigg's disease, were treated locally by injecting into the pockets of infection (which in that disease occur at the margin of the gums) one-half of one percent of emetine hydrochloride. In several of these 13 cases, the pus disappeared from the pockets completely to gross inspection in twenty-four hours after application. This result was attained in all the cases after three daily local treatments.

Dr. C. C. Bass and F. M. Johns, Tulane University, College of Medicine, New Orleans, La., working independently of Barrett and Smith and without knowledge of their investigations, arrived at the same conclusions. Their first paper on the subject, "The Specific Cause and the Prompt Specific Cure of Pyorrhea Alveolaris or Riggs' Disease," appeared in the New Orleans Medical and Surgical Journal, November, 1914. Another contribution by the same authors appeared in the Journal of the American Medical Association, February 13, 1915, entitled "Pyorrhea Dentalis and Alveolaris—Specific Cause and Treatment."

Dosage in Pyorrhea Alveolaris.—Microbic invasion of the tissues of the mouth is now considered the determining etiological factor. The microbes associated with pyorrhea alveolaris are of two kinds, namely, protozoa and bacteria. Bacterial infection as an etiological factor has been recognized for a number of years. It is only within the last year that the part played by the protozoa has attained importance in the etiology of the disease. To Barrett, Smith, Bass, Johns and their co-workers, we are indebted for our present knowledge concerning endameba buccalis as a causative factor in producing Riggs' disease.

In the treatment of pyorrhea alveolaris the objects are, first, to destroy the infecting micro-organisms; second, to get rid of the pockets of infection existing between the gums and the teeth; third, to prevent re-infection; fourth, to restore the tissues to a normal condition as far as possible; fifth, to meet the indications arising from systemic infection, for it is now known that an infected mouth may infect the system, and systemic infection predisposes to lowered tissue resistance and a continuance of the local condition.

This paper only deals with the use of ipecac (and its alkaloid, emetine) which, properly employed as an amebicide, is capable of killing out the ameba buccalis.

* Paper entitled "The Protozoa of the Mouth in Relation to Pyorrhea Alveolaris," read before the Pennsylvania State Dental Society, Philadelphia, July 1, 1914, and afterward published in the Dental Cosmos for August, same year.

The employment of operative procedures is also essential to the cure of Riggs' disease, and the use of bacterin treatment may also be necessary.

Emetine hydrochloride may be used locally or systemically in the treatment of pyorrhea alveolaris. Barrett recommends its employment locally in one-half of one percent solution. Stronger solutions are apt to provoke inflammatory reactions in the gums. Care should also be taken to use a neutral salt, as free hydrochloric acid is liable to irritate the gums and adjacent surfaces. The solution should also be isotonic with the blood for it may prove irritating if used in stronger or weaker solutions.

The solution is introduced into the pyorrhea pockets by means of a hypodermic syringe, preferably with a curved, blunt-pointed, needle. Treatments which include all recognizable pus pockets, and especially parts under suspicion, should be repeated daily for at least five days, and thereafter every other day, until about ten treatments as a total have been made. Microscopic examination of scrapings from the pockets should be made from time to time for persisting endamebæ as the treatment progresses, and this, together with the general appearance of the lesions, will determine the appropriate duration of treatment. In some of the less marked and less chronic cases, a total of five or six applications or even less may be sufficient, while in the more stubborn instances, treatment may be continued even longer.

Barrett further states that coincident with the disappearance of the endamebæ, the soreness, pain or discomfort, and the amount of pus formed, rapidly decreases. The tendency to bleed from slight trauma usually ceases within forty-eight hours, and in almost all cases the patient recognizes and feels confident of the beneficial effects within a few days.

Bass and Johns find that the endamebæ may be destroyed in cases of pyorrhea alveolaris by the subcutaneous injection of emetine hydrochloride. According to these investigators the endamebæ disappeared from the lesions following from one to three days of hypodermic treatment in more than 90 percent of all cases. Injections of one-half grain up to three grains were sufficient. All cases should be treated at least three days and none need more than six. Usually one-half a grain daily for three to six days, depending upon the case and the stage of the disease, is all that is required to accomplish the purpose.

To Prevent Re-Infection.—Barrett says with truth that every unhealed lesion must be regarded as a source of re-infection which will certainly promptly occur just as long as endamebæ are being constantly thrown off from the pockets of infection. Therefore these pockets of infection should be healed and permanently abolished, first by proper operative procedures, including scaling off the tartar from the teeth (which can be greatly facilitated by the use of bifluoride of ammonium solution as recommended by Dr. Joseph Head, of Philadelphia); and, second, by the employment of emetine hydrochloride and ipecac. Bass first recommended rinsing the mouth thoroughly with a solution of fluidextract of ipecac—two or three drops to a half tumbler of water—which he believes protects against reinfection. Later he recommended the use of emetine hydrochlor-

ide dissolve in alcohol,—strength 1 to 10—one drop of which should be applied to a wet tooth brush, and used for brushing the teeth every night before retiring.

A valuable mouth wash containing ipecac to be used as a preventive of reinfection and as a cure for pyorrhea alveolaris in mild cases, to meet the suggestion of Bass may be prepared by combining the following:

Fluidextract Ipecac	8 min.
Zinc Chloride	2 gr.
Beta-naphthol	½ gr.
Solution Formaldehyde (40%)	⅓ min.
Menthol	⅛ gr.
Oil Gaultheria, q. s.	
Alcohol, 55 percent, q. s. to make one fluid ounce.	

Directions: Cleanse the teeth and gums with the solution undiluted, using a soft tooth brush. As a mouth wash, add 20 drops to about two tablespoonfuls of water.

IV. EMETINE HYDROCHLORIDE AS AN HEMOSTATIC.

C. Flandin,[1] impressed by the prompt disappearance of blood from the stools in cases of amebic dysentery treated by hypodermic injection of emetine hydrochloride investigated its action as an hemostatic in hemorrhage from the lungs. He applied the remedy by the same technic as for dysentery, injecting into the thigh 1 cc. of distilled water containing 0.04 mg. (about 5/8 gr.) of the salt. The result of the injection was surprising, the hemorrhage stopping immediately.

In about twenty cases in which this treatment was used, the hemotysis was regularly arrested, even where copious hemorrhage had been taking place but a short time before. With the exception of one case of galloping tuberculosis, the tendency to pulmonary hemorrhage seemed definitely arrested. However, in the more threatening cases he repeated the injection twelve hours later and once on the following day, and if necessary on the fourth and fifth days.

The injection causes temporary pain only in the most sensitive individuals. No disagreeable sensation was experienced, no palpitation, dizziness or nausea. In some cases there was no longer a trace of blood in the sputum, but occasionally blackish stools were present and persisted for a time.

Why does emetine arrest pulmonary hemorrhage? The reason is obscure. H. C. Wood, Jr.,[2] says: "The alkaloids of ipecac seem to have some peculiar predilection for the lungs. A number of investigators have observed areas of pallor and of intense hyperemia in the pulmonary tissue."

The effect was not due to a lowering of blood pressure, for the author's sphynmomanometric measurements showed the pressure to remain the same; nor could he detect any effect on the coagulability of the blood or the number of red cells, leucocytes, and platelets. The measure seems to be entirely harmless and has succeeded when all others have failed. In but a single case was permanent arrest of hemoptisis not obtained with emetine.

Can Emetine Hydrochloride Be Used by Mouth?—As the hypodermic method is not always convenient in practice, Rogers has tried giving one-third of a grain of emetine hydrochloride in tablets by mouth on an empty stomach, and finds that two-thirds of a grain can generally be taken without producing any material

[1] Presse Medicale, September 24, p. 777, Jour. A. M. A., November 1, 1913.

[2] Pharmacology and Therapeutics. By H. C. Wood, Jr., M. D., J. B. Lippincott Company. London and Philadelphia, 1912.

sickness and with much more favorable results than with ipecac by the mouth. However, the action is slower and less effective than by the hypodermic method, and in one patient blood and mucus reappeared in the stools after three days absence, although he had taken a total of two grains by the mouth; but all symptoms finally vanished after two more days of hypodermic medication.

Tablets of ipecac and of emetine are now used by mouth in the treatment of pyorrhea alveolaris. Bass and Johns recommend a tablet of ipecac, each representing 10 grains of the powdered drug. "One tablet three times a day does not destroy the endamebas in the mouth in many cases in a week or ten days. Two tablets three times a day destroys all demonstrable endamebas in six days or less in practically all cases. Three tablets three times a day destroy all demonstrable endamebas in from four to six days." The authors say that this tablet does not cause nausea, but there is frequently more or less abdominal discomfort and also some looseness of the bowels. However, members of the West Virginia Dental Society reported to me their experience and stated that nausea is sometimes produced by the tablets and their use must under such circumstances be dropped until the symptom disappears. Bass says that he would expect to find an individual occasionally who could not take the tablet satisfactorily and also those who would not absorb enough of the drug to destroy the endamebas on account of the diarrhea produced carrying it through the intestinal canal too rapidly.

CAN EMETINE HYDROCHLORIDE BE SAFELY INJECTED INTRAVENOUSLY?

Rogers has found that emetine hydrochloride can be safely injected intravenously in considerable doses. In one severe case of amebic dysentery he gave first, half a grain of the drug dissolved in 5 cc. of normal saline, injected very slowly into the median basilic vein, without the slightest depressing effect on the pulse, while the same evening he gave two-thirds of a grain and a day later, a one-grain dose in the same way, in addition to several subcutaneous ones. The favorable results in this case,—an extremely severe one—justifies him in advising the intravenous method in such acute attacks of amebic disease.

DO EMETINE INJECTIONS KILL ALL THE AMEBÆ AND PREVENT RELAPSES?

This question is discussed quite at length in Rogers' papers, and while, in his opinion, it is still too early to give a final answer, yet some important evidence regarding it has been accumulated, sufficient in amount to justify him in believing that this method of treatment can completely sterilize the whole of the tissues of the body as far as pathogenic amebæ are concerned, and afford good ground for hoping that at last a simple drug has been found which will absolutely rid the human system of a deadly protozoal parasite.