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DIDOQUIN FOR CHRONIC AMOEBIC DYSENTERY IN SERVICE PERSONNEL INVALIDED FROM INDIA

BY

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The problem of treating resistant amoebic dysentery cases is arousing great interest both in the Services and in civil life, and it is felt that a report on the trial of an amoebicide, new so far as this country is concerned, is worth recording, although it is realized that sufficient time has not yet elapsed to be sure of the prospects of a complete cure in the present series of cases. Two of them had received no previous specific therapy, but all the others had had repeated maximum courses of emetine injections (12 gr.), with or without any further gut-sterilizing treatment such as emetine bismuth iodide (E.B.I.) by mouth combined with yatren retention enemata, and all these cases had experienced anything from 3 to 9 relapses before treatment with didoquin. The majority had received carbarsone or stovarsol and numerous courses of sulphaguanidine or sulphapyridine. These cases had become resistant, and it was felt that the best prospect of cure was to try some other amoebicidal drug chemically as far removed from emetine, or one of the arsenicals, as possible. On discussing our problems the Director-General of Medical Services obtained for us a supply of didoquin (5,7-diiodo-8-hydroxyquinoline), a product of the Searle Laboratories of the U.S.A., which had been introduced in that country since 1935 and appeared to be the most promising of the oxyquinoline compounds. It had been reported on very favourably by Craig (1937) and D'Antoni (1942).

Properties of Didoquin

Didoquin is a tasteless non-toxic compound containing 63.9% iodine, while chiniofon and vioform contain 28.9% and 41.5% iodine respectively. Didoquin is extremely insoluble in water, dilute acids, or alkalis; because of its insolubility it does not produce the unpleasant purgation often experienced with the use of the other hydroxyquinoline compounds when given orally. The makers state that it is not absorbed, but David, Phatak, and Zener (1944) found that in some cases it gave rise to pruritus ani, which developed on the 4th to 5th day of administration and persisted for some days after the drug was stopped; no symptoms of iodism were observed, and increases in the blood iodine level were very irregular, varying from 45.6 micrograms to 437.25 mg. in man and experimental animals. Their conclusions were that the toxicity of an insoluble drug like didoquin may depend on such factors as hyperacidity or intestinal stasis rather than on the actual amount of drug administered. In the present series of 78 cases two cases of intolerance were observed and two patients complained of mild pruritus ani; in no case were there any serious after-effects, and the patients were pleasantly surprised, after their previous experiences with emetine and E.B.I., at the non-toxicity and efficacy of the new treatment. Didoquin is opaque to x rays, and radiographs show an even distribution throughout the large bowel. *Lambia* are not affected by didoquin, but Hummel (1940) states that *Balanitidium coli* responds well to treatment with the drug.

Treatment

Three tablets of didoquin, 3.2 gr. each, three times a day for 20 days, was the standard dosage adopted. In addition, in another series of cases the didoquin was combined with yatren retention enemata for 10 days, and a small series showing either amoebic hepatitis or other evidence of deep infections received emetine injections as well. A small control series treated

with the standard combined E.B.I. and yatren course is included for comparison; there was no selection of cases for this control course. All patients were sigmoidoscoped before and after treatment, and in 15 cases treatment was carried out on the typical sigmoidoscopic appearances alone, the stools being negative, although in all these 15 cases *Entamoeba histolytica* had been found previously.

Series I: Cases treated with didoquin alone by mouth.—26 cases were treated with didoquin alone—three tablets t.d.s. for 20 days. 17 cases were apparently cured, and follow-up examinations of 3 stools were negative two months after discharge from hospital. Two of these cases had received no previous treatment for dysentery. In addition, three cases with positive sigmoidoscopic findings but with negative stools were treated, and the lesions had healed at the end of the treatment. There were two relapses, and four cases were resistant to treatment. In one case active entamoebae were present at the end of the course. In another, ulcers were still unhealed at the end of one course. In a third, amoebic abscess of the liver developed three months later, although the stools were negative on readmission. One patient had an acute relapse, with active entamoebae. This was a very chronic case which had previously had nine relapses after E.B.I., yatren, etc. Another patient had petechial haemorrhages present in his rectum at the end of one course, although his stools were negative; these had disappeared after a second course. One case relapsed four months after treatment.

Series II: Cases treated with didoquin for 20 days + yatren retention enema for the last 10 days of the course. This treatment was initiated as it was felt that lesions in the rectum might not be exposed long enough to didoquin in the lumen of the bowel and that this was probably the cause of the relapse in the cases treated with didoquin alone by mouth. Logically, one should have treated these cases with didoquin retention enemata. This was done successfully in one case, but as supplies of the drug were restricted it was not possible to use this method in the other cases. 39 cases were treated. Enough time has not yet elapsed for a two-months follow-up in all cases, but the results to date are as follows: Cures, stools positive for *E. histolytica* before treatment, 22; cures, stools negative before treatment, but sigmoidoscopy typical, 8; resistant, 2; relapses, 7.

Series III: Emetine hydrochloride, 6 to 10 gr. by needle + didoquin concurrently by mouth for 20 days; the last 10 days the patient received yatren retention enemata without a preliminary bowel wash-out.—This treatment was carried out in those cases showing symptoms of hepatitis, gross deep ulceration of the rectum, or a marked leucocytosis. 13 cases were treated, but follow-ups are not yet due in all of them. Results: Apparent cures, stools positive for *E. histolytica* before treatment, 9; apparent cures, stools negative before treatment, 2; relapse, 1; resistant, 1. In one case petechiae were present in the rectum; after one course this patient was given E.B.I. and yatren, and a further sigmoidoscopy showed a normal mucosa.

Series IV: Emetine bismuth iodide + a cleansing bowel wash-out with 2½% sod. bicarb. solution, followed by 250 c.cm. of a 2½% solution of yatren as a retention enema and 10 days' carbarsone, 4 gr. b.d.—Standard combined course: Emetine bismuth iodide, 3 gr. in cachets by mouth, together with a

cleansing bowel wash-out of 2½% sodium bicarbonate, followed an hour later by 250 c.cm. of 2½% yatren, which is retained for 6 to 8 hours. This is carried out for 10 days and is then followed by carbarsone, 4 gr. b.d. for 10 days. In this series 24 cases were treated; 18 were cured, 6 relapsing. There were 3 primary cases, which were all cured. Two of the relapsed cases were cured with didoquin. In 5 cases examination of the stools was negative, but sigmoidoscopy showed either ulcers or active pits. Two cases were most resistant to all forms of treatment. One has since apparently recovered with a high-protein diet and vitamin B₂+liver injections, and is back to full duty but under surveillance. The second is still under treatment. A roster of cases is being kept, and a follow-up of stools at two-monthly intervals after treatment is being carried out as a routine in all cases of dysentery however treated.

Results

Series I and IV have been observed and had 3 stools examined two months or longer after discharge from hospital. Series II and III have not all completed their period of surveillance since discharge from hospital.

Series	Apparent Cures	Resistant at End of Course	Relapses	Approximate Percentage of Failures After One Course
I	20	4	2	23
II	30	2	7	23
IV	18	1	5	25

Results of Series III are not included owing to the small number of cases.

Intolerance to Didoquin

Two cases of intolerance to the drug were encountered.

Case 1.—A patient was being treated on his sigmoidoscopic appearances. Localized hyperaemia was present in his rectum, but stools and swabbings were negative. On the 14th day of treatment with didoquin he had abdominal pain, diarrhoea, and blood and mucus in his stools, which were full of *E. histolytica*. He responded well to emetine and a second course of didoquin and yatren enemata, with no further ill effects and apparent cure.

Case 2.—A severe case showing numerous ulcers with Dyak hair sloughs in his rectum and active *E. histolytica* in his stools. On the 14th day of the course he complained of abdominal pain, diarrhoea, and headache. The didoquin was stopped, and the symptoms were rapidly relieved by emetine. A further course of didoquin, E.B.I., and yatren was well tolerated, and sigmoidoscopy showed complete healing of the ulcers.

Records of Two Chronic Cases

The histories of two severe cases are given below; one was treated with didoquin alone, the other received a course of emetine+didoquin. These cases are worthy of record, as the first exemplifies how, by erratic and insufficient initial therapy, a case is rendered emetine-resistant, and how quickly it responds to treatment with didoquin. The second is of interest because of the long-standing and atypical nature of the symptoms and the rapid response to specific treatment once the correct diagnosis was made.

Case 3.—Man aged 29. The first attack started in July, 1942, in India, the patient having been over-seas since Jan., 1942. Typical onset, with abdominal pain and bloody diarrhoea; 10+ stools a day. Treatment was as follows: First attack, 4 injections of emetine hydrochloride and 3 days' carbarsone. First relapse (24/7/42), salts only; second relapse (12/8/42), salts only; third relapse (19/9/42), salts only; fourth relapse (12/10/42), 12 injections of emetine hydrochloride; 6 days' carbarsone. Fifth relapse (12/1/43), 12 injections of emetine hydrochloride; 10 days' E.B.I. Sixth relapse (12/3/43), 12 injections of emetine; 14 days' retention enemata (? type); 14 days' N.A.B. retention enemata. From this relapse until landing in England on Jan. 5, 1944, he had several further relapses and was under almost continuous treatment. Nothing brought about any great improvement with the possible exception of the first few emetine injections in each course; for after complete 26-day courses active entamoebae were still found in the stools. On arrival in the United Kingdom he felt better, and stools were negative. In Feb., 1944, he had diarrhoea, with blood and mucus. Treated with emetine hydrochloride, yatren, and E.B.I. at a Service hospital, stools were negative after 7 weeks. In June he relapsed again and active entamoebae were present. He was transferred to another Service hospital. The liver was then found to be enlarged 2 in. below the right costal margin. White cells, 11,600, with a normal differential. Treated with emetine hydrochloride 1 gr. for

3 days; followed by E.B.I. 3 gr. for 7 days, together with 2% stovarsol retention enemata; followed by carbarsone 1 tablet b.d. for 10 days. Stools were then negative, but in view of continued liver enlargement it was decided to give 10 further injections of emetine hydrochloride, followed by 7 days' E.B.I. and stovarsol enemata. At the end of these two courses active entamoebae were still present, and sigmoidoscopy showed typical amoebic ulceration on the posterior wall at 12 cm. A full course of didoquin was then started (3 tablets t.d.s. for 20 days). On Aug. 27 the course was concluded; 4 stools were negative for *E. histolytica* and macroscopically normal in every way. The liver was not palpable. White count normal. There were no ill effects from didoquin therapy. Further follow-ups two months later were negative.

Case 4.—Man aged 43. From 1919 to 1921 he was in India in the Army, and had had a few attacks of diarrhoea, in one of which he noticed blood and mucus. He was treated with castor oil and some white powder. He returned to England, was demobilized, and worked first of all for 10 years as a salesman and then for 10 years as a bus conductor in London. On Oct. 15, 1941, he enlisted in the R.A.F. He suffered all this time from recurrent bouts of diarrhoea, during which he sometimes noticed blood and mucus in the stools, and for 15 years was treated by his own doctor. He states that the attack started with a "terrific pain" in the abdomen, vomiting, and then diarrhoea, which relieved the pain. He was given castor oil and bismuth and placed on a milk diet; the symptoms would then subside in two to three days and he would be free from further attacks for three months, during which period he would pass one formed stool a day. He had never had a stool examined or been sigmoidoscoped, but got into the habit of treating his attacks himself without calling in his doctor. He served in Canada in the R.A.F. from 1943 to Oct., 1944. On his return the attacks became more severe and he reported sick to his Station M.O. who examined his stools and found numerous active *E. histolytica*; he was admitted to hospital. On examination he appeared to be prematurely aged. His abdomen was generally tender to palpation, especially over the sigmoid, which was thickened, and his liver was palpable and tender 2 in. below the costal margin. On rectal examination a fungating, soft, acutely tender mass could be felt some 4 in. from the anus; it was suggestive of an adenocarcinoma. A proctoscope revealed an intensely hyperaemic mucosa with typical raised crateriform ulcers and a protruding ulcerated mass at 4 in. suggestive of a neoplasm or amoeboma; numerous active entamoebae containing red blood corpuscles were easily obtained on gently scraping this mass. The patient was given six daily 1-gr. injections of emetine together with three tablets of didoquin daily for 20 days; in addition, he was given 200 c.cm. of 2½% yatren as a retention enema from the 6th to 20th days without a preliminary bowel wash-out, and stovarsol 4 gr. b.d. from the 20th to 30th days. On sigmoidoscopy on the 30th day a linear healing ulcer was seen at the site of the amoeboma; this was painful to the touch, but the sigmoidoscope was passed to 25 cm. and revealed no evidence of further ulceration although the mucosa was lax and rugose. He was sent on 14 days' sick leave, and on his return sigmoidoscopy showed that the ulcer was completely healed, but the mucosa was granular and hyperaemic at the site of the ulcer, although his stools were completely negative. His liver was no longer palpable or tender, and he said he felt a new man. In view of the long-standing history it was considered advisable to give him a 10-day course of E.B.I. and yatren. On examination three months later sigmoidoscopy revealed a normal mucosa, and six consecutive stools were negative.

Conclusions

The claims as to the efficacy of didoquin in amoebiasis advanced by the makers have not been fully substantiated so far as the treatment of chronic amoebiasis is concerned, as approximately one-third of the cases have relapsed. The drug, however, is very useful in cases in which, owing to inadequate treatment consisting of repeated courses of emetine hydrochloride by the needle, the entamoebae appear to have become temporarily emetine-fast. Here a course of didoquin has on many occasions effected a dramatic cure clinically, and in 77% of a small series of cases this cure appears to have been permanent. The administration of a new well-tolerated drug such as didoquin has a good moral effect on patients who have previously had repeated courses of a depressing drug such as E.B.I., especially when they notice rapid clinical improvement following its use. There is reason to believe that in these resistant cases a synergistic effect is produced by didoquin that renders their entamoebae once more sensitive to emetine. The greatest advantage of didoquin is that it can be taken concurrently with emetine injections in cases of amoebic hepatitis, thereby saving time, and I feel that this is its most useful role in the treatment of active amoebiasis over-seas. I would, however, suggest a course of 6 injections of emetine hydrochloride,

together with 3 tablets of diodoquin t.d.s. for 20 days, in a controlled series of primary acute amoebiasis over-seas, to be compared with a similar series treated with emetine, E.B.I., and yatren. In chronic established infections a cure will eventually be effected by a blunderbuss therapy of courses of E.B.I. orally and yatren enemata, followed by the 20-days standard course of diodoquin and ending with a 10-days course of stovarsol or carbarsone. The diet, a non-residue one, should be as nourishing as possible; it should contain a relatively high proportion of animal protein supplemented by vitamin preparations containing the B₂ complex. A course of sulphasuxidine, to eliminate secondary bacterial invaders, should be given, and recently penicillin has been successfully used in severe cases for the same purpose, although neither penicillin nor sulphasuxidine has any direct amoebicidal effect.

Summary

Diodoquin appears to be the best of the oxyquinoline group of drugs in the treatment of amoebiasis, and is a valuable addition to the therapeutic remedies available for the treatment of this insidious and intractable disease. It is non-toxic in therapeutic doses, and is well tolerated in all but a small minority of cases.

The practice of treating amoebiasis with emetine alone cannot be too strongly condemned; only a small percentage of cases are cured, and the vast majority are rendered more resistant to further treatment with emetine and less amenable to treatment with any other available drugs.

I wish to thank the Director-General of the R.A.F. Medical Services for his interest in these cases and for obtaining the supplies of diodoquin. I am indebted to Fl. Lieut. Daly, R.A.F.V.R., who was the medical officer in charge of the wards, for his careful recording and helpful criticism; to Miss Sage, senior laboratory technician, for her painstaking examination of countless specimens; and to Sgt. Greenfield, A.G., laboratory technician, for his technical assistance.

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RESTORATION OF DIPHTHERIA IMMUNITY WITHOUT INJECTIONS

TOXOID PASTILLES BY MOUTH

BY

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I have long sought a means of immunization whereby injections could be avoided entirely, but up to the present time I have not met with this degree of success. If, however, one could devise a method of *re-immunization* which could be applied to older children and adults without the production of functional disturbances of any kind a very considerable advance would have been made.

So far as can be seen at present, the future of diphtheria immunization will be concerned mainly with the treatment of infants aged 1 year, or slightly less. At this time of life the method of administration is likely to continue to be the injection. Considerable dosage of such antigens as A.P.T. can as a rule be given without causing constitutional disturbance of any kind, at the same time bestowing an effective basal immunity. It is usually considered desirable, at the beginning of school life, to boost this immunity by means of a further injection of A.P.T., and this can generally be administered to young subjects without fear of producing sore arms or other ill effects. Nevertheless, there are fairly numerous persons of more mature age—e.g., older school-children, hospital nurses, troops, etc.—who, owing to various circumstances, may require re-immunization. Then one is confronted with the possibility of sharp local or general reactions in some subjects, even when such a mild antigen as T.A.F. is employed, but more especially when injections of A.P.T. are given. Such results may occur when only Schick-positive reactors are inoculated, but when re-immunizing injections are given to all and sundry, without previous Schick-testing to establish the need, the incidence and severity of local reactions and constitutional disturbance rise sharply in adult age groups.

Jensen's (1937) method of instilling drops of formol-toxoid into the nostrils might have solved the problem if the procedure had not been rather impracticable, and if the danger of producing rhinitis could have been overcome (*Lancet*, 1941). It has not been thought worth while to pursue that form of treatment to any extent in this country.

In a limited number of subjects I demonstrated (Bousfield and King-Brown, 1938) that deep inhalation of the air of a room which was impregnated with finely atomized formol-toxoid was capable of producing an excellent rise in the antitoxin titre of the blood: this method I could not follow up, as experience showed that most of the volunteers became highly sensitized and developed allergic symptoms. I then attempted to pass formol-toxoid through the skin, in a neutral glycerin medium, with inconclusive results (Bousfield, 1944).

The present series of experiments is concerned with attempts to apply stimuli to the upper portion of the alimentary tract. The idea was suggested by the fact that, during an attack of diphtheria, absorption of some toxin from the mouth, fauces, and oesophagus might be a factor in the production of any subsequently acquired active immunity. If toxin is thus absorbed during the disease it seemed logical to investigate whether formol-toxoid, given in sufficiently large dosage, would be absorbed by *healthy* membranes in amounts which would provide an adequate stimulus.

I conceived the idea of a fairly firm gelatin sweet or pastille, containing about 100 Lf units of formol-toxoid, suitably sweetened and flavoured with some fairly neutral agent such as peppermint. I am variously indebted to Sir Alexander Fleming, Mr. L. B. Holt, of the Inoculation Dept., St. Mary's Hospital, and to Dr. Stanley White and the chief chemist of Messrs. Parke, Davis and Co., for the final production of the pastille, which I required, in the form of a gelatin disk. In preparing the disks the toxoid was added to the melted gelatin at a low temperature—about 40° C.—and the pH was adjusted to 6.5. The formol-toxoid which Mr. Holt supplied for the purpose was highly concentrated (2,000 Lf per c.cm.) and was of great purity: it was no less than 75% pure, in terms of protein, having been prepared by a method developed by Mr. Holt at St. Mary's Hospital.

Serum-antitoxin Tests on Adult Volunteers

As I personally am highly allergic to diphtheria antigens, I tried the effect on myself of sucking the toxoid disks—four each day, for seven days—and experienced no inconvenience of any kind. I then obtained five volunteers, bled them for preliminary antitoxin titration, and gave each of them 28 toxoid-gelatin disks to suck slowly, at intervals, four a day, for seven days. Fourteen days after the conclusion of treatment they were bled again, to see whether any rise in circulating antitoxin could be demonstrated as a result of the treatment.

Sir Percival Hartley kindly undertook all serum-antitoxin titrations for me; at his request neither the main purpose of the inquiry nor the details of the individual experiments were communicated to him, in order that the antitoxin determinations should be done "blind." The importance of this fact in considering results will not escape notice. The changes in the blood serum titres in my first five cases will be found in Table I.

TABLE I.—*Dosage, Four 100-Lf Disks Daily for 7 Days*

Case	Sex and Age (Years)	Previous Immunization or History of Diphtheria	Original Serum Titre (Units)	Titre 14 Days After Treatment (Units)
1	F 19	Diphtheria at 5 years; Schick-neg. at age 17	> 0.1 < 0.2	> 0.2 < 0.4
2	F 40	3 inj. diph. prophylactic 15 years ago. No post-Schick test	> 1.5 < 2.0	> 4.0, nearly 8
3	M 17	2 inj. 2 years ago, probably A.P.T. No post-Schick test	> 0.05 < 0.1	> 8.0 < 16.0
4	M 33	Had diphtheria at age of 6 years	> 0.02 < 0.05	> 1.5 < 2.0
5	F 45	Naturally Schick-negative 10 years ago	> 1.5 < 2.0	> 4.0, nearly 8

At this point it may be stated that none of the subjects who took the disks by mouth, in this or in subsequent experiments, experienced any inconvenience whatever, with the exception of one adult female who complained of persistent repetition of the