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Treatment of Intestinal Amebiasis and of Chronic Colitis with a New Bacterial Antibiotic («Colisan»).

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"Colisan" is a new antibiotic, isolated from a mutant (RB-103) of a bacterial strain which was isolated in 1945 by Reitler and Boxer from the mesenterial lymph glands of a patient who succumbed to paralytic ileus (1). The original strain showed antibacterial activity against various staphylococci and streptococci, but was inert towards enterobacteriaceae. It also possessed lytic properties against various protozoa. The mutant RB-103 is endowed with a much higher antiprotozoal activity (against Paramecium caudatum, Entamoeba histolytica and others) (2), but in addition exerts a pronounced antispasmodic effect on the smooth muscle of the intestine and other organs (3). The combination of these two properties, the parasitocidal and the organotropic effect, served as indication to try the bacterial extract for the treatment of intestinal amebiasis and of various forms of chronic colitis. Although information on the absorption, distribution and excretion of the active principle(s) in the body is still rudimentary, such a trial was justified in view of the present unsatisfactory situation regarding amebicides. All known drug treatments are unable to prevent relapses, although it must be conceded that in tropical and subtropical climates it is often difficult to distinguish between relapse and re-infection (4). Amebiasis is a serious problem in warm countries and exerts its effects far beyond the actual pathological changes, causing loss of working capacity, invalidity and sterility (4, 5, 6). The general physical and psychic changes in the patient, which accompany the disease and concentrate the patient's attention more and more on his condition, are the reason for the continued search of new and better drugs.

I. Classification of the cases of the present study.

The present studies were carried out with Colisan tablets, put at my disposal by Hillel Inc., Haifa. Each tablet contains 5 mg. of active material; the dosage is 3-6 tablets/day, for a period of 10-20 days. The cases under treatment can be grouped as follows:

- (1) Chronic amebiasis with clear laboratory results. These cases had previously undergone various unsuccessful or only temporarily effective treatments.
 - (2) Acute amebiasis with positive laboratory results.
- (3) Chronic colitis, without clear cut results of stool examination, but with clinical and rectoscopic symptoms of chronic inflammation of the colon.
- (4) Chronic ulcerative colitis, without specific laboratory results, but with mucus and blood in the feces and rectoscopic confirmation of the diagnosis.
- (5) Atypical cases with unspecific complaints, which had undergone various unsuccessful treatments.

II. Results.

- (1) In all cases, there was a pronounced improvement of intestinal symptoms (abdominal pain, nausea and flatulence).
 - (2) Progressive improvement of the form and quantity of the feces.

- (3) After a certain lag, rectoscopic controls showed a progressive change of the mucosa.
- (4) In a number of cases, side-effects such as increased nausea, diarrhoea or constipation, sharper abdominal pain and skin irritation were observed. One case developed a light oliguria during Colisan treatment.
- (5) Stool examination gave varying results: In practically all cases, in which amebae had been identified beyond doubt before the onset of treatment, they disappeared from the stools at the end of the Colisan cure. The number of leucocytes and erythrocytes was considerably decreased, sometimes to zero; the mucus showed a parallel reaction. If the urobilinogen content of the urine had been elevated before, it fell during the treatment to normal values. No significant changes in the blood status were observed.
- (6) Relapses: The number of relapses in the different groups of patients is shown in Table I. Discussion will be given separately for each group.

TABLE 1. Summary of all cases, undergoing treatment with Colisan.

Classification	Number of cases	Recovered after first treatment	Recovered after second treatment	Complete failure of treatment	Only clinical im- provement	Not followed up
Group 1: Chronic amebiasis	14	9 (+1) *	2		1	2
Group 2: Acute amebiasis	5	5				
Group 3: Chronic colitis, suspect of amebiasis	8	4	2	2		
Group 4: Chronic ulcerative colitis	1		1			
Group 5: Abdominal com- plaints with unclear diagnosis	6	4				
Total	34	22 (+1)	5	2	1	2

^{*} The case, indicated in brackets, No. 14, had—in addition to his amebiasis—also pancreatitis!

III. Detailed observations in each group.

A total of 34 cases has been studied.

Group 1. It comprises 14 cases, which for many years had been suffering from recurring attacks of amebiasis, accompanied by diarrhoeas with or without bloody stools; these patients all suffered from lack of appetite, loss of weight, fatigue and nervousness, frequent urge to urinate and in women irregular menstruation. All patients in this group had undergone previous treatments with a variety of drugs, and some had shown severe drug reactions. The application of Colisan began, when the patients started to complain again

about a return of their symptoms and when the stools showed trophozoites and cysts of *Entamoeba histolytica*.

Some cases exhibited mixed infections, e.g. with Lamblia, Trichomonas, Enterobius, E. coli and E. minuta. In 2 cases, Oxyuris was present. Eight patients suffered from a more or less severe lack of gastric acid secretion; one of them showed complete absence of hydrochloric acid and a high level of blood diastase. Two patients of this group exhibited a chronic inflammation and enlargement of the gall bladder, with defect emptying, as shown by X-ray control. In 4 cases the liver was enlarged, palpable and sensitive. In this subgroup, one woman had undergone—2 years before the present attack—a period of jaundice, and at that time, amebae were found in the stools. Six cases suffered from severe hemorrhoids and one of them had undergone an operation, which, however, did not improve the complaints because of persisting amebiasis.

For Colisan treatment, the following schedule was observed: During the first 2-3 days, 3 times daily one tablet after meals. If this was well tolerated, the daily dosage was doubled and application continued for 10 to 15 days. In most cases, Vitamin B-complex and ascorbic acid were also given.

Ten cases showed rapid improvement of their symptoms already after a few (2-4) days. Diarrhoea and abdominal pain disappeared and the feces became compact. Stool examinations at the end of this period and again 3 months later gave negative results in 9 cases. One woman (case No. 10), however, returned after 2 months with her previous complaints, and numerous cysts of E. histolytica were formed upon microscopic examination. She received a second cure of 2 weeks, and from then on remained free of further relapses.

Case No. 11 was a woman who had suffered for 14 years from intestinal amebiasis; she showed excellent clinical improvement with Colisan. However, cysts were found in the feces at the end of the first cure. Therefore, in spite of her subjective well-being, a second cure was installed, but again without any change in stool examination. Case 12, who received Colisan and B-complex together, developed after a few days an allergic eczema, more severe diarrhoea and heavy abdominal pain. Colisan application was put off, but vitamin B was continued. Nevertheless, the symptoms became worse, so that pyribenzamine was considered necessary. Finally, as no improvement was achieved, all medicamentation was stopped and the patient now recovered within 3 days. After a pause of 2 weeks, Colisan treatment was started again, but this time without vitamin. The patient now was completely cured from his amebiasis and remained negative in all further checks.

Case 13 also reacted to Colisan with worsening of his symptoms (nausea, abdominal pain, skin irritation). Addition of pyribenzamine made it possible to continue the Colisan treatment for 10 days. He returned after some weeks with his old complaints, and stool examination was strongly positive. He now underwent a more systematic cure of 6 tablets of Colisan and 2 tablets of pyribenzamine for 16 days and remained from then on symptomless. No amebae were found in his feces upon repeated examination.

Discussion of case 14 see below.

Group 2. Five cases who had never before suffered from any disease which could have been suspected to be amebiasis. They all came for consultation a short time (3-10 days) after the first appearance of their symptoms. All suffered from severe abdominal pain and diarrhoea with mucus and/or blood and had 20 or more defecations per day. One showed subfebrile temperatures (37.6°C). In all five patients, stool examination showed trophozoites and/or

cysts of *E. histolytica*; in one also *E. coli* and oxyures were found. After 3 days on Colisan, these patients improved markedly, and after the application of 50 tablets, complete cure of their acute amebiasis was achieved. So far, no relapse has occurred in this group (during one and a half year).

Group 3. This group comprises 8 cases which were suspect for amebiasis because of their clinical symptoms, but gave only negative results in repeated stool examinations. However, much mucus and sometimes leucocytes and erythrocytes were present, and rectoscopic observations revealed marked inflammation of the colon. Some of these patients also showed incomplete digestion of fat and carbohydrate.

In 3 cases, which suffered from heartburn, gastric juice analysis gave the following results: 8/26; 14/46 and 12/20. In 3 other cases, liver function tests were performed with results near the border line. Cephalin \pm , Takata-Ara \pm , cholesterol 130-160, Weltman 5-6.

All cases had a moderate macrocytic anemia, slight leucocytemia with a light left shift, relative lymphocytosis (up to $48^{0}/_{0}$) and eosinophilia (up to $10^{0}/_{0}$). In 4 cases, blood sedimentation was normal, and in the other 4 above normal (up to 30/68).

These 8 cases had previously received various treatments, including amebicides, without satisfactory results. They were given a whole cure of 50-100 tablets of Colisan. Six of them showed rapid improvement and eventually regained full health. Their blood status was examined 3-4 months later with the following results: The leucocyte count and the blood sedimentation had returned to normal, but the relative lymphocytosis persisted. In two of these 6 patients, relapses occurred (after 3 weeks and 4 months resp.). After a second cure with 100 Colisan tablets, they remained symptomless throughout the whole period of follow-up (about 1 year).

The remaining two cases of group 3 did not improve under Colisan treatment and are to be considered as therapeutic failure.

Group 4. Only a single case of chronic ulcerative colitis falls into this category. The patient suffered from periodic attacks of severe abdominal pain, with bloody diarrhoea and serious loss of weight. Her weakness and fatigue sometimes led to fainting. Laboratory tests gave the following results:

Blood status: erythrocytes 3 millions, leucocytes 12,500, mononucleates 10, eosinophils 12, segments 30, monocytes 8, lymphocytes 36, myelocytes 2, plasma cells 2. Blood sedimentation 34/76. Gastric juice 4/42. Liver function tests normal, but Weltman 4.

Urine: Traces of protein; urobilinogen ++. In the sediment only phosphates.

Feces: Incomplete digestion of fats, proteins and carbohydrates; much mucus and epithelial cells; many erythrocytes and leucocytes. Many bacterial strains were present, but no amebae were detected. X-ray pictures of the colon showed spasms, irregular emptying and were suspect of ulcers and polyps. Rectoscopy: Severe inflammation, small and medium-sized ulcers, blood, cell detritus.

The patient had received over the years many different treatments, including prednison, which at the first application led to a remission over a period of 4 months. But later repetitions were much less effective and accompanied by disagreeable symptoms, so that the patient refused to accept this drug again.

Treatment with Colisan gave the patient rapid alleviation of her symptoms. After 2 weeks, the stools had improved and rectoscopy showed marked repair of the mucosa. The patient gained 3 kg. in weight. After 100 tablets, the cure

was interrupted, but after an interval of 4 weeks the patient had a relapse, although her suffering now was much less severe than before. After a second cure with 100 tablets Colisan together with vitamin B complex, ascorbic acid and calcium-desterol, no new relapse occurred during the following 6 months. The patient had gained in the meantime another 3 kg. in weight. Rectoscopy did not reveal any ulcers.

Group 5. It comprises 6 cases, with complaints about abdominal symptoms, but without any objective findings (rectoscopy, X-rays) and with no pathological change in the feces. These cases may be considered as "psychosomatic". They had received various therapeutic trials, but always came back with their old complaints.

They were given 50 tablets of Colisan each. Four cases responded rapidly and remained symptom-free for an observation period of 8 months. The other two (female) patients returned after one month with their previous symptoms. A second Colisan cure was installed. One woman left this country in the middle of the treatment. The other one completed the second series of 100 tablets, but did not appear again for a check-up.

The favourable results in the first 4 cases may be taken as indication that they suffered from an undiagnosed amebiasis or chronic colitis. But since no placebos were tried, psychological effects can not be excluded.

I would like now to describe case 14 of group 1.

A woman, aged 39, suffered for many years from severe abdominal pain, frequent diarrhoeas with light-colored stools, flatulence and nausea. She lost 10 kg. of weight and also had various allergic symptoms.

Blood status: Moderate anemia; 8000 leucocytes. Differential count: 5 mononucleates, 30 segments, 9 cosinophils, 2 monocytes, 54 lymphocytes. Blood sedimentation 44/86.

Gastric juice 0/12.

Feces: Much mucus, undigested proteins, fats and carbohydrates, various cocci; numerous trophozoites and cysts of *E. histolytica*.

Urine: Traces of protein; urobilinogen ++.

X-ray examination: Inflammation of the stomach, with increased gastric secretion; rapid passage of the barium brei through the digestive tract; spastic signs all along the intestines.

All previous therapeutic trials gave this patient only short-lasting relief. When she received Colisan with vitamins, her status worsened rapidly and after a few days she reacted with urticaria, itching and increased diarrhoea. Pyribenzamine alleviated somewhat the allergic symptoms, but not her other complaints.

All medicamentation was stopped for 2 weeks. Then Colisan with pyribenzamine and vitamins was again started. But again there was no clinical improvement. Laboratory tests showed the following:

Blood diastase increased (292). Liver function tests: Tekta-Ara \pm , cephalin \pm , Weltman 4.

Rectoscopy: Chronic colitis.

Feces: Erythrocytes and leucocytes, meat fibers, fat droplets.

No amebae!

When the patient was now treated with pancreatin and HCl, she recovered rapidly.

Discussion.

34 patients, of whom 19 suffered from intestinal amebiasis, 8 from chronic colitis, 1 from chronic ulcerative colitis, and 6 of whom had no clear diagnosis,

received Colisan treatment per os with the following results (Table I):

23 cases (= $68^{0}/_{0}$) were healed by a single cure.

The other 11 cases received a second treatment.

Five $(=15^{0}/_{0})$ then recovered completely.

In one more case (=30/0), the amebae disappeared, but for other reasons a third application was necessary.

In two cases $(=60/_0)$, a systematic follow-up was not possible.

In one case (=30/0), clinical improvement was achieved, but the stools remained positive.

In two cases (=60/0), the treatment did not effect any change.

Therefore, in $83^{0}/_{0}$ of these patients, Colisan treatment gave satisfactory results; in $12^{0}/_{0}$, the results were doubtful and in $6^{0}/_{0}$ negative.

Side-effects occurred in 2 cases (= $6^{0/0}$).

This short summary justifies the conclusion that Colisan is an important new addition to our antiamebic armatory; that it is effective in chronic colitis and that it causes relatively little side-effects.

The new drug compares favorably with other known anti-amebic drugs, but excels them because of its additional effect on the smooth muscle. It is therefore worth further clinical trials. At present, it is too early to give a final evaluation of this drug. Many problems still await further investigation, e.g. its effect on extra-intestinal amebiasis, its metabolic fate in the body, and others.

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