

HUMAN STRONGYLOIDIASIS IN PANAMA.*

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Introduction.

In 1911 Darling published a report of his studies on *Strongyloides* infection in man and other animals in the Isthmian Canal Zone. By culturing the fecal material he was able to obtain a much higher record of incidence than had been previously secured by the simple film examination of the material. Among other data he found that patients in the Corozal Insane Hospital showed the following incidence of *Strongyloides* infection: average of all patients, 18 per cent; natives, 20 per cent; non-natives, 6.4 per cent; males, 21.3 per cent; females, 14.9 per cent; patients of particularly unclean habits, 28.5 per cent; and patients over fifty years of age, 31.7 per cent. In a culture of 23 strains of the organism from whites and blacks, both natives and immigrants, Darling (l.c.) found the following types to be present: 5, indirect only; 7, direct only (5 from Spanish whites of relatively recent immigration), and 11 strains exhibiting both indirect and direct types. Darling's discovery of the direct type alone and in combination with the indirect type, in long time residents of the tropics, was a direct refutation of Leichtenstern's hypothesis (1898, 1905), that the tropical strains utilized only indirect development, while temperate zone strains manifest only direct development. More recently, Sandground (1926) and Nishigori (1928) have confirmed Darling's data.

The present study was undertaken in order to reexamine the same population group which Darling had utilized and to make use of certain technic which was unknown to Darling at the time of his investigation. A series of 1662 individuals from the Santo Tomas Hospital of Panama City and from four Chagres river villages was utilized as the source of material. These individuals ranged in age from one to ninety years; they were either of Spanish-amerind-negroid blood or of pure negro blood (from the original strains introduced by

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the Spanish conquistors or of more recent Jamaican importation). A considerable proportion of these individuals was hospitalized for malaria; another large group consisted of women in the maternity service of the hospital, while about one third of the individuals consisted of native villagers who complained of no particular illness.

Presentation of data.

Altogether 348 individuals of the series examined (21 per cent) were found to harbor *Strongyloides*. Two hundred and seventy-six of these were examined three or more times. The age incidence of the positive group is shown in fig. 1. An examination of this chart

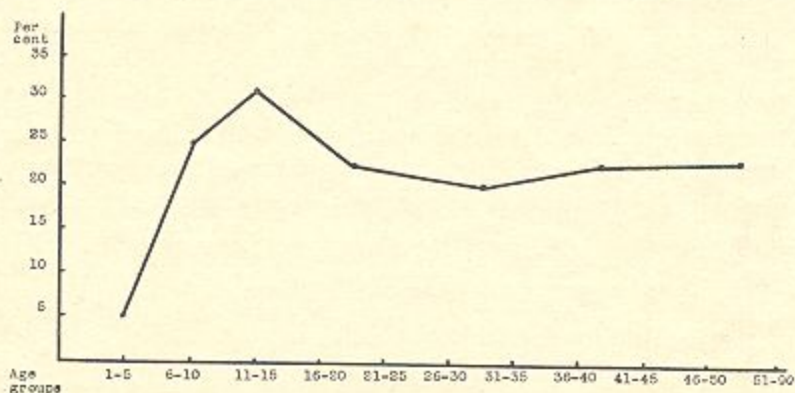


FIG. 1. Age incidence of *Strongyloides* in native Panama population groups.

shows that there is an appreciable infestation in the first year group (1-5 years); that the infestation increases rapidly in the second year group (11-15 years), after which it falls somewhat, but remains at an average high level of approximately 23 per cent throughout the remaining years of life. Of the group examined three or more times, 29, or 10.5 per cent, showed a heavy infestation, while 30 individuals (10.8 per cent) had active filariform larvae in the freshly passed stools. The degrees of infestation ranged from one in which only a few isolated larvae were obtained from centrifuged feces to one in which swarms of active larvae were seen in films of unconcentrated feces.

Culture studies.

Technic. Strains from 27 individuals positive for *Strongyloides* but negative for hookworm infection were selected for culture studies. Only those cases were utilized in which there were large numbers of actively motile larvae in a centrifuged specimen of freshly passed

feces. These precautions, therefore, ruled out the possibility of confusing hookworm larvae with those of *Strongyloides*, and also gave an opportunity for planting cultures almost as soon as they were passed by the patient. The larvae in the finely comminuted fecal centrifugate were cultured on moist animal charcoal in sterile petri dishes. These cultures were maintained at room temperature (26–35° C.) and were kept constantly moist. A representative sampling from each culture was examined daily to determine the type and stage of development and the relative numbers of the *Strongyloides* found. These data were recorded in tabular form, utilizing the following symbols. (1) Relative abundance of several stages of the organism was indicated by +, ++, +++, +++++, and in rare instances ++++++. (2) rh_1 , rhabditiform larvae of the parasitic generation, unfed; RH_1 rhabditiform larvae of the parasitic generation, fed (e.g., showing marked increase in size); (RH_1) , rhabditiform larvae of the parasitic generation, fed and ensheathed; f_1 , filariform larvae of parasitic generation, unfed; F_1 , filariform larvae of parasitic generation, fed; (F_1) , filariform larvae of parasitic generation, fed and ensheathed. Similarly rh_2 , RH_2 , (RH_2) , f_2 , F_2 , (F_2) indicate larvae of these respective stages derived from free-living worms. The symbols ♂ and ♀ are used to indicate the free-living unisexual adults.

Strains and combinations of strains found from the culture study. As pointed out in an earlier publication (Faust, 1930) the following types of strains have been found: indirect only, 2; direct only, 13; hyperinfective only, 7; and combinations of these types, 5. Representative culture strains are exemplified in the accompanying chart (fig. 2). It is interesting to note that the direct strains were viable for the entire period of the investigation, in some cases up to 9 weeks, showing no decrease in activity or in potential infectiveness. On the other hand, the indirect type had exhausted itself in 14 days or less (i.e. the free-living phase of the life cycle had been completed and the f_2 larvae had died for want of an infective host). Likewise, the hyperinfective strain (i.e. an abortive direct type in which the rh_1 larvae have metamorphosed into the f_1 larvae without feeding) died in 12 days or less under culture conditions. In five instances duplicate strains, representing all three types of the infection, were cultured as a check on the original. In each instance the duplicate strain paralleled the original (see fig. 2). Furthermore, the same conditions prevailed in a strain isolated from the red spider monkey (*Ateles geoffroyi*). This type (indirect) ran consistently indirect in successive cultures.

Effect of gentian violet on the strain types. Opportunity was provided for studying the effects on the culture strains after minimal doses of gentian violet had been administered therapeutically to the patients who harbored these infections. Whether the strain was originally direct, indirect or hyperinfective, the culture, following the oral administration of one grain of medicinal gentian violet, was consistently of the direct type only. This finding was true for the monkey *Strongyloides* as well as for the human species.

Pathological and therapeutic studies.

Autopsy findings. Necropsies were performed on two untreated *Strongyloides* cases who had died of chronic nephritis and myocarditis. The essential findings from these two cases are presented briefly in the accompanying protocols.

1. *Autopsy on Juan Felipes* (58 yrs. old). Antemortem exam. showed $rh_1 + +$ in feces on 3 successive days. Death 10 days later from chronic nephritis and myocarditis. Exam. of intestine (scrapings and sections) as follows:

Organ	Strongyloides	Lesions
1. Pylorus	—	Mucosa thickened
2. Duodenum	—	
3. Upper jejunum (40 cm. from pyloric valve)	$+++ rh_1$	Mucosa intensely injected
4. Middle jejunum	$++ rh_1$	Mucosa intensely injected
5. Lower jejunum	$++ rh_1$	Mucosa intensely injected
6. Upper and lower ileum	—	Mucosa not injected
7. Ileocecal valve	$+ rh_1$	Mucosa not injected
8. Cecum	$+ rh_1$	Mucosa not injected
9. Upper colon	$++ rh_1$	Mucosa moderately injected
10. Sigmoid colon	—	Mucosa not injected
11. Lower colon	—	Mucosa not injected
12. Rectum	—	Mucosa not injected

2. *Autopsy on Gregorio Aparicio* (ca. 30 yrs. old). Antemortem exam. showed intermittent appearance of $rh_1 +$ in feces on 2 out of 5 consecutive days. Death 9 days later of pulmonary congestion and edema, chronic nephritis and myocarditis. Examination of intestines as follows:

Organ	Strongyloides	Lesions
Stomach, duodenum, jejunum, ileum, cecum, upper and middle colon, appendix	—	None
Lower colon	$++ rh_1$	Many small basic ulcers
Rectum	—	Many small basic ulcers

The rationale of gentian violet therapeutics for Strongyloides infection. DeLangen (1928) was the first to show that gentian violet was effective for *Strongyloides* treatment. More recently the writer (Editorial,

International Medical Digest, 1930) has confirmed the efficacy of this treatment. A series of twenty-five patients covered in this study was given gentian violet treatment. The results of this therapeutic study will be covered in a separate paper. One case, however, deserves brief comment, because of its dramatic results.

Maria Cruz, age 28 years, patient on the Maternity Service of Santo Tomas Hospital, had been bedridden for some three months, during which period she was constantly passing a watery diarrheic stool. She was greatly emaciated and at the time when fecal examination was first undertaken, she was almost in a state of complete collapse. Examination of a freshly passed specimen showed myriads of rh_1 and f_1 *Strongyloides* larvae. Therapeusis was begun, giving enteric-coated gentian violet tablets, one grain three times a day. The accompanying protocol shows that the treatment was effective in

Case of Maria Cruz. History: watery diarrheic stool for 3 months. Emaciated. Examination and treatment as follows:

	Strongyloides	Feces	R	Clinical notes
6/24/30	+++++ rh_1, f_1	Watery	g.v. 1 gr. t.i.d.	Almost collapsed
6/25/30	+++++ rh_1, f_1	Much cellular exud.	g.v. 1 gr. t.i.d.	
6/26/30	++ rh_1	Cellular exud.	g.v. 1 gr. t.i.d.	
6/27/30	++ (2 ♀)	Cellular exud.	g.v. 1 gr. t.i.d.	Appetite improving
6/28/30	+ (2 $rh_1, 1 ♀$)	Cellular exud.	g.v. 1 gr. t.i.d.	
6/30/30	+ (1 rh_1 , several ♀'s)	Formed	g.v. 1 gr. t.i.d.	
7/1/30		Formed	g.v. 1 gr. t.i.d.	
7/3/30	+ (rh_1)	Formed	g.v. 1 gr. t.i.d.	
7/5/30	+ (3 rh_1)	Formed	Discont'd	Patient much improved
7/9/30	+ (rh_1)	Formed	Discont'd	Skin moist
7/10/30	+ (rh_1)	Formed	Discont'd	5 lb. gain in weight
7/11/30	++ (rh_1)	Formed	Discont'd	
7/17/30		Formed	Discont'd	Discharged with great improvement

Summary: A very severe (i.e. hyperinfective) uncomplicated case of Strongyloidiasis apparently cured by administration of 24 grains, gentian violet, over period of 10 days.

reducing the infection to an amount which was only a small fraction of the original; that the character of the feces changed from watery diarrheic to a normal formed type, and that the patient's condition improved remarkably within a period of three weeks, during which time the dye was administered.

Opportunity was also provided to study at autopsy the staining capacity of gentian violet on the tissues of the intestine in a case of advanced chronic dysentery in which *Strongyloides* was not found. The findings in this case are recorded in the accompanying protocol.

3. *Autopsy on Ernesto Frederickson* (65 yrs. old). *Clinical diagnosis*: advanced chronic dysentery. *Lab. diagnosis* (12 days *ante mortem*): *E. histolytica* +++ PC or inactive T. R. emetin and bismuth. Three days *ante mortem*, when it was apparent that death would ensue, the patient was given 1/3 grain tabs. gentian violet t.i.d. for 2 successive days, in order to have an autopsy determination of the staining capacity of this dye for the intestinal wall. Findings at autopsy as follows:

Organ	Stain	Lesions
1. Stomach	Wall stained; also partly digested pill	None
2. Duodenum	None (covered with mucus)	None
3. Jejunum	Diffuse stain	Practically all eroded
4. Ileum	Diffuse stain	Practically all eroded
5. Cecum, colon, rectum	Diffuse stain of mucus covering mucosa, which is little stained	Many discrete typical ulcers

Note: Where the mucosa is covered with a film of mucus, staining of the tissue is not effective.

Discussion.

The present study has indicated that in addition to the direct and indirect types of *Strongyloides* which have been previously recognized, there is a distinct hyperinfective type which has developed as a result of the rh_1 larvae metamorphosing before feeding. This provides an opportunity for the f_1 larvae to develop before they are evacuated from the rectum, and offers an explanation for the findings of Fülleborn (1926) and Nishigori (1928). The hyperinfective type is therefore the one which is responsible for the so-called "auto-infection" (i.e. "hyperinfection") of individuals who have once become parasitized.

The fact that minimal doses of gentian violet administered to the patient consistently alter both the hyperinfective and indirect strains to the direct type, while the direct type remains unaltered, suggests the possibility that both of these former types are fundamentally offshoots of the direct strain. This hypothesis is a consistent one, since the direct type is one offering the maximum security for the larvae outside of the body, whereas the indirect type is possibly an attempt to repeat the parasitic phase of the life cycle outside of the

body under conditions which more or less simulate those of the parasite in the body. These latter as well as the hyperinfective type are consistently short-lived and delicate individuals. Furthermore, if one may carry the hypothesis one stage further, it is possible to believe that the parasitic phase of the life cycle originally consisted of males as well as females, similar to the free-living generation.

The fundamental importance of the effect of minimal amounts of gentian violet on the host tissue, and therefore indirectly on the worms, should not be underemphasized. In heavy infestations, both in man and in monkeys, such minimal amounts of the dye are sufficient to kill the adult female worms *in situ* and to cause their evacuation in the feces, at the same time having no effect on the viability of the larvae which have already been hatched. However, the fact that these larvae, no matter from what strain they have come, always develop into the direct type, suggests that the differences in strains is not a matter of germ-plasm differentiation, but of the soma.

Conclusions.

1. This investigation has confirmed Darling's work (1911) in refutation of Leichtenstern's hypothesis that the tropical strain of *Strongyloides* is necessarily indirect and the temperate strain, direct.

2. A third strain, the *hyperinfective type*, has been differentiated in a considerable proportion of cases in this series. Most of these cases were heavily infected individuals showing clinical symptoms.

3. Symptoms may develop, due to heavy infestations, as a result (1) of the hyperinfective type, or (2) as a result of the gradual building up by the skin route of a heavy infestation over a long period of time.

4. The specificity of gentian violet as a strongyloidicide and the tissue-staining potency of this dye have been demonstrated.

5. The effect of gentian violet on altering the indirect and hyperinfective strains of *Strongyloides* to the direct type has a most important bearing on the fundamental biological conception of the life cycle of *Strongyloides* and its relatives.

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