NOTES ON A NEW ULCERATIVE DERMATO-MYCOSIS. (With Special Plate.)

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WITH REPORT ON THE CAUSATIVE FUNGUS

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SINCE 1907 I have come across in Ceylon a peculiar ulcerative condition which is clinically very characteristic. As to its hyphomycetic origin there cannot be any doubt, as from all the cases I have grown the same fungus. Cultures of this fungus have been given by me to Professor Pinoy, who has kindly investigated it botanically and classified it. The disease would appear to be present also in the Federated Malay States, as one of the patients stated that the ulcers had begun developing while he was employed on a Malaya plantation. This patient was seen by Dr. F. Grenier, who very kindly allowed me to investigate the case. I have recently observed a case of the same disease in the Balkans.

Etiology.

As a rule no hyphomycetic elements are seen microscopically in scrapings from the ulcers and contents of the nodules. If the material, however, is inoculated in glucose-agar tubes, small yellowish amber-coloured colonies appear four to eight days after inoculation; they enlarge fairly rapidly, become hemispheric, and often coalesce in a knotty mass. At times the colonies may not fuse together; each colony then remains separate, reaches a large size, and occasionally presents peculiar radiating furrows as seen in certain species of trichophytons. In many cases, when the material has been collected from ulcerated lesions, the fungus grows in symbiosis with a coccus, and it may be somewhat difficult to separate the two organisms. When the inoculations have been made from lesions not yet ulcerated, the fungus only is present. The disease has been easily reproduced in two coolies (who volunteered) by injecting cultures of the isolated fungus. Cultures used for such experiments must be recent, as old cultures apparently lose their pathogenicity. The experiments on this subject will be reported in detail later.

Botanical Description of the Fungus by Professor Pinoy.

Professor Pinoy of the Pasteur Institute has kindly investigated the fungus, a strain from a Ceylon case I supplied him with, and the following is his description:

"The fungus isolated by Professor Aldo Castellani belongs to the hyphomycetes or *Fungi imperfecti*, and is of somewhat difficult classification. I propose to include it in the genus *Accladium*, at least temporarily, and call it *Accladium castellanii*. The microscopic appearance on culture media (Sabouraud's agar, carrot) recalls somewhat the appearance of *Cladosporium herbarium*, with the difference that the colonies are whitish and amber yellow instead of being greenish-black. The growth consists of many small roundish masses which later on often coalesce, covered by spiculated formations consisting of erect, straight filaments parallel to each other or at times interlacing. These filaments are approximately 2 microns in diameter and carry laterally pseudoconidia of variable shape (Fig. 6, s), cylindric, pyriform, or spherical, attenuated in size at their points of insertion. Most of these pseudoconidia are 4 microns long with a breadth of 3 microns. This type of fructification recalls the type *Accladium* described by Bodin in some species of the genus *Trichophyton*. These pseudoconidia become detached and then develop by sprouting, and mycelial filaments are formed (Fig. 6, a, b, c). Certain filaments produce spherical chlamydospores (Fig. 6, ch) arranged in small strings as found in certain fungi of the genus *Fusarium*. These small chains of chlamydospores are very frequently terminal, the dimensions being variable—8 to 10 microns."

Symptoms.

In a well marked case ulcers are seen practically all over the body, though on the face, scalp, palms, and soles they are in small numbers or altogether absent. The

ulcers are generally sharply defined, roundish or oval, with red granulating fundus. Their appearance is well shown by the photograph of the arm reproduced in the accompanying plate. In certain cases there may be abundant purulent secretion, and the ulcers are often covered by thick yellow crusts. Gummata-like nodules and furuncle-like lesions may also be observed. Some of the superficial lymphatic glands are often enlarged. The lesions are not as a rule very painful, and there is little or no itching. The general condition of the patient is not seriously affected for a long time, but he often complains of weakness, general discomfort, and is unfit to attend to his work. Occasionally there is serotine temperature. In two cases in which the blood was investigated red blood corpuscles and haemoglobin were slightly below the normal, and in one case there was eosinophilia (5 per cent.). This feature of the blood may, however, have been due to intestinal parasites, the stools containing eggs of ascaris. The urine did not contain either albumin or sugar.

The course of the disease is long, and if left untreated there is apparently not much tendency to spontaneous cure.

Diagnosis.

Most of the patients came to me with the diagnosis of syphilis, but in none of them except one was there a history pointing to that infection, and in two of the cases in which a Wassermann test was carried out the result was negative. Moreover, scrapings from the ulcers never showed spirochaetes, and salvarsan and mercury have no beneficial effect on the condition.

Prognosis.

As already stated, the course of the disease is very long, and there is little tendency to spontaneous cure; on the other hand, if properly treated, a complete cure can be obtained fairly rapidly.

Treatment.

Potassium iodide acts fairly well. It should be given in full doses, gr. xx, three or four times daily. The drug appears to act better if the patient is given a salt-free diet, as first suggested by Professor Pinoy in other dermatomycoses. If potassium iodide is not well borne, iodine and other similar preparations may be tried, but the result is not so satisfactory. Mercury and arsenic have no beneficial effect on the course of the malady. As regards local treatment, it is sufficient to keep the ulcers clean by dressing them with weak mercury perchloride lotion. Ointments are badly borne in most cases.

FURTHER EXPERIMENTS ON ASCARIS INFECTION.

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I WISH to record some experiments made since the paper published in the BRITISH MEDICAL JOURNAL of July 1st was written. These experiments may still not be conclusive but they appear to be highly significant.

The first two have already been published in *Parasitology* of August of this year.

1. The rat, F, to which reference was made in my previous paper, was killed twelve days after the first infection and nine days after the last. No nematodes were found in the nasal cavities, mouth, trachea, lungs, or oesophagus. One dead ascaris larva was found in the stomach, a second, also dead and partially digested, in the rectum. The former measured 1.3 mm. after mounting in Canada balsam. Both were more advanced than the larvae from the lungs of other animals. They had doubtless undergone this further development under the stimulus of the intestinal secretions before they succumbed to the unfavourable surroundings in an inappropriate host.

2. Mouse B, killed on eighth day after infection with a single dose of eggs of *A. suilla*. Larvae measuring 1 to 1.5 mm. (in normal salt solution) in the trachea and lungs. No larvae in nasal cavities, liver, or alimentary canal.

3. Mouse C, killed on the night of the seventh day after a single dose of eggs of *A. suilla*; 50 to 60 larvae measuring up to 1.8 mm. in the lungs and trachea.

4. Mouse D, killed on eighth day after a single dose of eggs of *A. suilla*; 12 larvae in lungs. Largest measures 1 mm.

5. Mouse E, killed on eighth day after a single dose of eggs of *A. lumbricoides*. Not less than 100 larvae in roots of lungs and trachea.

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FIG. 1.—Glucose-agar culture of the fungus.

FIG. 2.—Glucose-agar culture of the fungus (older).

FIG. 3.—Glucose-agar culture; rare type of colony.

FIG. 4.—Microscopical appearance of the fungus in hanging drop culture twenty-four hours old.

FIG. 5.—Microscopical appearance of the fungus in hanging drop culture three days old.

FIG. 6.—Microscopical appearance of the fungus in hanging drop culture five days old. *s* = Pseudoconidia. *a, b, c* = Development of mycelial filaments from pseudoconidia. *ch* = Chlamydospores.

FIG. 7.—Photograph of arm showing typical lesions.

6. Mouse F, died in the night of the fifth day after infection. Not examined.

7. Mouse G, killed on eighth day after infection with *A. suilla*. Numerous large larvae in lungs.

8. Mouse H, ditto. A few large larvae in lungs. Two larvae in mouth.

9. Mouse J, died on the third day after infection with *A. suilla*. Not examined.

10. Mouse K, killed on the eighth day after infection with *A. suilla*. Larvae in lungs.

Mice L, M, O, P, Q, R, S died from epizootic summer diarrhoea. Not examined.

11. Mouse T, killed on eighth day after infection with *A. suilla*. No larvae found in lungs. It is possible that this mouse did not actually swallow the eggs offered to it.

12. Two mice were examined without infection. No larvae found in lungs or liver.

The larvae of *Ascaris lumbricoides* and *A. suilla*, therefore, appear in the bronchi, trachea, and mouth of the mouse and rat on the night of the seventh day and during the eighth day after infection. I believe that they will be found to emigrate actively in the saliva on to the food which is being nibbled by the rodent.

13. *Experiment on the Quantity of Saliva Expelled by a Mouse in the Act of Biting.*—A mouse was held in the hand and irritated until it bit the finger of the observer. The skin was not broken, but two considerable drops of saliva remained corresponding with the upper and lower incisors. Larvae might readily be expelled in saliva in this manner.

14. Rat A had recovered from an attack of ascaris pneumonia one month previously. Killed on eighth day after a large dose of eggs of *A. suilla*. No larvae found in lungs.

It is possible that one attack of ascariasis in rats protects against subsequent attacks.

Experiments were made to test the power of survival of larvae in the outer world.

1. A portion of lung containing larvae was placed on a lump of hard earth which was standing in water. The lung was above the surface of the water. On the first day following the portion of lung was lifted and the surface of the earth scraped. No larvae were found in the scrapings. Active larvae were found in a small portion of the lung. On the second day following there were no larvae on the earth or in the water. The portion of lung was commencing to putrefy; the larvae present in it moved languidly.

2. Larvae placed in tap water were dead after three hours.

3. Larvae were placed in a 4 per cent. solution of hydrochloric acid, 0.8 per cent. salt. After fifteen minutes one larva was observed to be furiously excited. After twenty-four hours the larvae were dead.

4. Larvae placed in normal salt solution were alive and active after three hours.

5. Larvae placed in mouse's blood were alive and very active after three hours.

6. Larvae in mouse's blood with a little normal salt solution transferred to a small fragment of cooked meat. A number were alive after four hours.

7. Larvae in blood transferred to bread kept in a moist chamber. Larvae were alive after twenty-four hours.

The larvae, therefore, cannot live in tap water; they can survive for twenty-four hours on damp bread, and for forty-eight hours in fresh meat (rat's lung).

These experiments strongly suggest that man is infected by contaminated food.

Experiments on Infection of Pigs from Rodents.

Experiment 1, Pig B, was recorded in the previous paper. It was negative. It is possible that the pig was too old for ready infection.

2. Pig C. The faeces had been examined repeatedly, and no ascaris eggs found. On April 15th a portion of infected rat's lung was given to it. On May 13th infected mouse's lung. On May 24th the faeces did not contain ascaris eggs. On May 30th and 31st infected mouse's lung was given. On June 4th no eggs in faeces; June 6th, a few eggs in faeces (twenty-four days after May 13th). On June 11th, 12th, and 16th many eggs in faeces. On June 21st infected mouse's lung was given. On June 29th pig killed, and four male and two female ascaris, apparently of the same age, were found in the intestine.

3. Pig D. April 17th, no ascaris eggs in faeces. April 28th, infected rat's lung given (five days after infection of the rat with *A. lumbricoides* from man). May 24th, no eggs in faeces. June 11th, no eggs in faeces. June 15th (forty-eight days after April 17th) and 17th, unfertilized ascaris eggs in faeces. June 17th, infected mouse's lung (eight days after infection with human ascaris) given. June 24th, pig killed. One large female ascaris found.

This can hardly be considered a very satisfactory experiment. *A priori* it would appear doubtful whether fifth-day larvae would be infective. The long time (forty-eight days) elapsing between infection and the appearance of the eggs in the faeces is also somewhat against the

validity of this experiment. On the other hand, the delay may have been due to the absence of the stimulus of the male. If this experiment is valid, it is proved that the ascaris of man and of the pig are one species.

The presence in Experiments 2 and 3 of worms of one age only, after repeated doses of infected lung, raises the question whether the adult worms found originated from the larvae administered or from other and accidental infection. On the other hand, it is possible that one infection prevents subsequent infections. In collections of worms removed by anthelmintics or *post mortem* I have never seen worms of obviously different ages associated together.

4. Pig E. June 20th, no ascaris eggs in faeces. June 21st, infected mouse's lung (eight days after infection with ascaris from the pig) given. June 25th, no eggs in faeces. July 24th (thirty-three days after June 21st), many eggs in faeces. July 25th, pig killed, three male, twelve female ascaris in intestine.

5. Pig F. June 25th, no ascaris eggs in faeces. June 28th, infected mouse's lung (eight days after infection with ascaris of the pig) given. July 4th, no eggs in faeces, infected lungs of two mice given. July 7th, 8th, 10th, and 22nd, no eggs in faeces. July 27th (twenty-nine days after first infection), pig killed, no ascaris in intestine.

Out of five experiments, therefore, three gave positive results, two negative. In estimating the value of the negative experiments the very high mortality among the parasites employed under somewhat unnatural conditions must be kept in mind. To obtain an estimate of this mortality I compared the number of ripe eggs given to a mouse with the number of larvae found in the lung. An average dose of eggs consisted of about 5,000, the average number of larvae found in the lungs has certainly not exceeded 50—that is, only 1 in 100 survives. It must also be remembered that the transfer from the rodent to the pig must be the most vulnerable part of the life-cycle, since the larva is a very delicate organism.

Conclusions.

If ripe eggs of *Ascaris lumbricoides* are swallowed by rats or mice they hatch. The larvae enter the bodies of the rodents either by boring into venules of the portal system or by ascending the bile duct. They are found in the dilated blood capillaries of the liver between the second and fifth days. The larva is in diameter three times the diameter of a red blood corpuscle of the mouse. It cannot therefore pass through a normal capillary. The liver cells in the neighbourhood of the larvae undergo rapid degeneration. The larvae are thus enabled to work their way into the hepatic venules and pass by the hepatic vein and vena cava to the heart and by the pulmonary artery to the lungs. In the lungs they are filtered off at the entrance to the capillary field. Embolism of the arterioles takes place, and the larvae pass with the effused blood into the air vesicles. They are found in the air vesicles on the sixth day, in the bronchi on the seventh day, and in the trachea and mouth on the eighth day after infection. It is probable that they emigrate in the saliva of the rodent on to food substances, such as bread. It has been shown that they can live for twenty-four hours on damp bread. The experiments which have been conducted so far tend to prove that the larvae from the lungs of rodents can infect the pig, and it is probable that in nature infection of man and the pig takes place by food contaminated by rats or mice.

Controls on Experiments with the Pig.

Pigs A and B were kept in the same outhouse in which Pigs C, D, E, and F were afterwards kept. They were, however, fed in a different manner. Pig A, after three months, was found to harbour one ascaris; accidental infection was therefore proved to be possible. Rats and mice doubtless had access to this outhouse. That accidental infection was not frequent is proved by the case of B, which was kept here for seven and a half months without being infected.

Pig G was obtained at the same time as Pig E, on June 20th. On arrival its faeces were found to contain unfertilized ascaris eggs. On July 2nd 0.7 gram of areca nut was administered, which must have caused the expulsion of the worm, since on July 24th and 27th and August 4th and 10th no eggs were present in the faeces. On August 16th again no eggs were found. This animal was kept in the same compartment as Pig E and fed out of the same bucket, but had not become infected in one month and fourteen days.

Pig H was bought on June 26th with Pig F. It was kept in the same outhouse as the other pigs and fed in the same manner. Its faeces were found to be free of ascaris eggs; 0.7 gram of areca nut was administered to it on July 2nd. On July 3rd,

7th, 8th, 9th, and 10th the faeces were free of ascaris eggs. On July 16th very large doses of eggs of *Ascaris mystax* 10 days old and of *A. marginata* 7 days old were given to it. These eggs contained active vermiform embryos. On July 17th a second dose of the eggs of *Ascaris marginata* was given from the same culture now 14 days old. On July 22nd, 26th, 27th, and 31st, and on August 4th, 10th, and 16th the faeces were found to be free of ascaris eggs.

These cases of Pigs B, G, and H prove that accidental infection was not common under the conditions of the experiments and therefore greatly enhance the value of the positive experiments with Pigs C, D, and E.

The experiment on Pig H of administering ripe eggs of *A. marginata* and *mystax* was performed to exclude a somewhat remote possibility—namely, that the life-history of *Ascaris lumbricoides* (suilla) was highly extended and that *Ascaris mystax* (or *marginata*) was only a stage in the life-history of *Ascaris lumbricoides*.

Corrections.

1. In the summary of results in the paper published in this JOURNAL on July 1st the following sentence occurs: "Between four and six days after infection they (the larvae) are found in the blood vessels of the lungs, liver, and spleen." I have never found larvae in the spleen. The statement is due to a clerical error in the manuscript.

2. The following sentences also require correction: "On the tenth day they are found only in the air vesicles of the lung and in the bronchi." "On the sixteenth day the host is free from parasites." Further experiments proved that the larvae appeared in the bronchi on the seventh day and that no larvae were found in the respiratory tract later than the eighth day after infection. The inaccuracies were due to the use of repeated infection in the earlier experiments.

Experiments on Infection of Mice with *Ascaris marginata* of the Dog.

Mouse N. July 9th: Given eggs of *A. marginata* six days old, containing embryos. July 12th: Eggs nine days old. July 13th: Eggs ten days old. July 14th: Mouse killed; no larvae in liver or lung.

Mouse P. Died on the first day after infection with eggs of *A. marginata* eleven days old. Larvae present in the liver.

Mouse U. Killed on the first day after infection. Larvae in liver, none in lung.

Mouse V. Killed on the fourth day after infection. One larva found in liver, none in lungs or trachea.

The mouse is therefore the intermediate host of *Ascaris marginata* as well as of *A. lumbricoides*.

VACCINE IN MEDIASTINAL ACTINOMYCOSIS.

BY

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DUNDEE.

ONE cannot fail to be impressed by the increasing frequency with which one or other of the protean forms of actinomycosis is being recorded. This increased recognition is due not wholly to habitual examination of discharge or tissue, but largely to greater familiarity with the forms the ray fungus may assume in its life cycle.¹ The increase in the number of diagnosed cases gives an ampler field for improving treatment. Mr. Telford's article² on actinomycosis of the parotid, in which treatment by salvarsan met with success, illustrates what is meant, and adds another to the list of cases similarly treated. Certainly we are confronted at times by advanced or inaccessible actinomycosis where iodine locally cannot be employed, where massive dosage by potassium iodide³ has met with limited success, where the disease is beyond the limit of surgical procedure. At such a time the only recourse is to a method by which we rely on the vascularity of the part ensuring the presence of the remedy at the seat of disease by introduction of a substance such as salvarsan, or by use of a vaccine. The employment of vaccine in the treatment of actinomycosis has been so rarely mentioned as to form an excuse for recording even a single case. The patient had actinomycosis at one of its less usual sites. It came to the body surface in the precordial region from the anterior mediastinum. Presumably the infection was air-borne, and inspired directly or indirectly from the mouth after chewing infected straw or grain. The fungus has been recognized at all the stages from the epithelium of the air vesicle through the visceral pleura adherent to its parietal layer or to the pericardium in the areolar tissue subjacent to the chest wall and to the subcutaneous tissue through intercostal spaces. This case presented a boggy swelling in the region stated. A shorter route for infection would have been through the skin, but there was no evidence in its favour. Languor, and pain on

coughing were present before any swelling was observed, and the latter appeared from within outwards. The burden of *post-mortem* evidence and of the clinical history of similar cases favour the pulmonary route. There may be no initial cough, and no sputum⁴ to attract notice in such cases, yet the oldest lesions are pulmonary.⁵ Fortunately, one cannot confirm or refute one's conceptions of this case by *post-mortem* findings.

Though a radical operation involving rib resection had been successfully performed two years before this treatment was initiated, and iodide in maximum doses swallowed month after month and pound after pound, two sinuses continued to discharge, one of which was connected with a nodule on the pericardial surface. Collie's case⁶ attracted attention to the potentialities of a vaccine, although Wynn⁷ first of all, and others^{8, 1} since have employed it.

Treatment was started by weekly subcutaneous injections of 2½ million actino-fragments. The dose was gradually increased up to 10 million. The latter was an overdose. The temperature gave no indication of this. No opsonic indexes were done. The patient's sensations proved a rough and ready index. Overdosage made him feel wretched and caused anorexia, and if one failed to recognize the importance of these symptoms and continued the overdose, a local reaction was set up, the nodule standing out in higher relief from the pericardial surface. This observation was verified, and on reverting to smaller doses the nodule receded, becoming flatter on each occasion. Ultimately 4 or 5 million was found to be an effective dose without bad effects, and this quantity was continued till about fifty doses had been given. The discharge soon lessened, the sinuses healed, the nodule in time could not be made out, and a "fullness" present in the parts disappeared.

Considerably fewer doses might have sufficed, but in view of the serious nature of the illness and the wish of the patient to "make sure of it" they were carried on. If records of other cases treated by vaccine were available they would prove of certain value. When confronted with the duty of applying this treatment one felt the lack of records to be a severe handicap. References to some of the other instances of pericardial involvement by direct spread are given.⁹

REFERENCES.

- ¹ Foulerton, *Lancet*, 1913, i, p. 361.
- ² Telford, *BRITISH MEDICAL JOURNAL*, 1915, vol. ii, p. 534.
- ³ Wild, *Ibid.*, 1910, ii.
- ⁴ Godlee, *Lancet*, 1901, i; Bridge, *Journ. Amer. Med. Assoc.*, 1911, November 4th; Israel, *Actinomykose des Menschen*; Knox, *Lancet*, 1904, ii, 1204.
- ⁵ Martin, *Journ. Path. and Bact.*, 1896, iii, 78; Israel, *Virchow's Archiv*, 1878, Bd. 74, S. 15.
- ⁶ Collie, *BRITISH MEDICAL JOURNAL*, 1913, May 10.
- ⁷ Wynn, *Ibid.*, 1908, i, 554.
- ⁸ Mousarrat, *Ibid.*, 1909, i; Whittier, American Association of Pathology and Bacteriology, 1909; Harbitz and Grondahl, *Amer. Journ. Med. Sci.*, 1911, September; Kinnicutt and Mixer, *Boston Med. and Surg. Journ.*, 1912, July 18th; Haynes Lovell, *Royal Society of Medicine*, 1913, January 14th.
- ⁹ Weigert, *Virchow's Archiv*, Bd. 84, S. 303; Rubrah, *Annals of Surgery*, vol. xxx, p. 435; Konigund Israel, *Bert. Klin. Woch.*, 1884, No. 23.

POST-MORTEM FINDINGS IN A CASE OF EXOPHTHALMOS OF LONG STANDING ORIGINALLY DUE TO GRAVES'S DISEASE.

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THE condition which produces exophthalmos in cases of exophthalmic goitre has never been clearly understood. It seems to me desirable that the following notes on a case in which all the other symptoms of Graves's disease had disappeared, but the exophthalmos remained to a marked degree, should be put on record:

J. B., aged 35 years, was admitted with acute lobar pneumonia (double) and died on the sixth day of the disease. There was nothing unusual about the illness during life or in the condition of the lungs after death. He had very marked exophthalmos of both eyes, together with external squint and cataract of the left eye. The eyeballs were sluggish in movement and the eyelids followed them without lagging. Winking was normal.

History.

Later in 1901, while he was in the Boer war, the graver signs and symptoms of exophthalmic goitre began to show themselves. He returned to England and was treated for three years, but made no progress. In 1904 he attended a clinic at Vienna. There he began to improve, and he continued his treatment till 1906, when all the graver signs and symptoms