5. A large number of filarial cases have been studied with special reference to the presence of a toxin in this nematode, and the evidence for kataphylaxia. Though the presence of a toxin cannot be proved experimentally in the case of *Filaria bancrofti,* as has been done in the case of *Filaria medinensis,* circumstantial evidence, such as the onset of an eosinophile reaction, suggests the presence of a toxin. In persons with microfilariæ in their blood there is a higher percentage of eosinophile count than in those without them.

6. Additional proof of the existence of a toxin is obtained from the irritation and subsequent changes in the tissues brought about by the worm, similar to the effects produced by the guinea-worm.

7. It is suggested that these toxins produce allergic symptoms such as urticaria, periodic headaches, migraine, slight rises of temperature, etc.

8. The nature of the lesions caused by the filarial infection is discussed and it is shown that they are of two kinds—helminthic and bacterial. In the case of the former, the lesions are of a chronic type with a distinct eosinophile reaction, and in the latter an acute inflammatory type with a polymorphonuclear leucocyte exudate.

9. The action of the toxin on the lymphatics, leading to the formation of the different types of filarial diseases, is discussed in detail. Greater reaction of the lymphatic wall near the head (vulval) end of the worm points to a localisation of the toxin at this end. From a detailed study of a large number of glands and lymphatics from cases of filarial infection, it is concluded that this toxin sets up partial or complete obstruction by gradually bringing about desquamation and hypertrophy of the endothelal cells of the lining of the lymphatics, and thickening of the vessel walls. The progressive changes in the structure of the gland by the passage of the immature worms through it, or through the death of the immature worm during its passage, are reviewed.

10. The reason for the absence of microfilariæ in advanced cases of filarial disease, and aberrent migration of the adult worm leading to the aggravation of the pathological condition, are briefly indicated.

11. The changes taking place in the skin in cases of elephantiasis as a result of pathological changes in the tissue due to causes acting both from within and from without—in the latter case as a result of secondary infection—are described in detail.

12. The evidence of kataphylactic state is obtained from (*i*) a localised irritation of the reticulo-endothelial tissue of the lymphatic glands which lowers their defence and renders them more vulnerable to attack by the various pyogenic cocci: (*ii*) the production of œdema of the tissues with leucocytic migration of the polymorphonuclear cells and desquamation of the endothelial lining of the vessels: (*iii*) lymph stasis in the extremities and scrotum, lowering the cellular resistance and favouring the growth of pyogenic cocci: (*iv*) the gradual changes in the epidermis with the production of hypertrophy of the papillæ, papillomatous growths and lymphatic cysts of the skin, with secondary bacterial infection from external foci.

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A CASE OF HUMAN INFECTION WITH A GNATHOSTOME IN INDIA.

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Since "creeping eruption" was first described by Lee (1874) in England, it has been recorded from almost every country in the world, but although its manifestations in different countries are similar, it is now known to be caused by a variety of parasites.

Broadly speaking, creeping eruption of temperate climates is due to invasion of the subcutaneous tissue by larvæ of various species of the family *Œstridæ,* and creeping eruption of the tropics and sub-tropics is caused by immature nematodes.

The frequency of creeping eruption was first noted in Florida and the Southern United States

by Kirby-Smith (1925), and subsequently Kirby-Smith, Dove and White (1926), White and Dove (1927 and 1928), Shelmire (1928), and Kirby-Smith (1929) have clearly proved that in this locality the disease is due to larvæ of *Ancylostoma braziliense*. In Australia, Heydon (1929) found that the same species of larvæ is the causal factor, and he is also inclined to incriminate the larvæ of *A. caninum*. Cawston (1928) is of the opinion, on clinical and epidemiological grounds, that creeping eruption or "sandworm disease" as it is known in Natal, is due to the same cause. Thus in the course of about four years, since its first recognition, this form of creeping eruption has been identified in three widely separated countries, so it is probable that it will soon be found in other places as well. At the same time, frequency of infection of dogs and cats with *A. caninum*, and *A. braziliense* does not necessarily mean that creeping eruption will be common among human beings, for although practically all the dogs and cats of Calcutta harbour one or both of these parasites, the writer has been informed by Lieut.-Col. Acton, I.M.S., that no case of this condition has been seen at the skin clinic of the Calcutta School of Tropical Medicine, where many thousands of cases have been treated annually for the past seven years.

The third type of creeping eruption is caused by an immature Gnathostome, and is much less common, and as far as is yet known it is much more limited in distribution. The first case of human Gnathostome infection was reported by Levinsen (1889) who identified a worm removed from an abscess of the breast of a Siamese woman by a Dr. Deuntzer. This observer said he had seen two similar cases but he did not find the parasite. Levinsen named the worm *Cheiracanthus siamense*.

The second case of this disease also came from Siam, the parasite being removed from the skin by a Dr. Kerr, who sent it to Prof. Leiper for identification. Leiper (1909) described this worm, and considered it to be identical with Levinsen's specimen, the name of which he corrected to *Gnathostoma siamense* (Levinsen, 1889). Following the examination of the type specimens of *Cheiracanthus robustus* Diesing, (1838) in Vienna, Leiper (1911) expressed the opinion that *C. robustus* Diesing, 1838, and *Gnathostoma spinigerum* Owen, 1836, were probably identical, and that *G. siamense* was also the same species. Therefore the correct name of the two Gnathostomes recovered from human beings was *Gnathostoma spinigerum* Owen, 1836.

The third case was reported from the Malay States by Samy (1918), who obtained his specimen from an abscess on the thenar eminence of a Chinaman, who had never been in Siam. This worm was identified as *G. spinigerum*.

The fourth case was that of a Japanese woman who had lived for a long time in China. She developed an abscess of the breast and the parasite was found on opening it. Tamura (1921) gave a full account of this case and a careful description of the parasite, which leaves little doubt that it was an immature male of *G. spinigerum*.

Robert (1922) reported three cases in Siam. The first patient was seized suddenly with a spasmodic cough, which lasted for about a day, and which resulted in the expulsion of a Gnathostome. The second began with swelling of the right hand which subsided and was followed by swelling of the right arm; a similar condition occurred later in the right foot, to be followed by patches of œdema on the abdomen, from the last of which the parasite was expressed. From the first onset to the expulsion of the parasite a period of eight months elapsed. The third case exhibited hæmaturia and hæmatemesis, which was succeeded by a localised œdema on the abdominal wall from which a worm was obtained. Robert does not say that the hæmorrhages were due to the parasite, they may have been merely coincident.

The eighth case, reported by Morishita (1923, 1924), was from the thenar eminence of an adult male Japanese who had lived for a long time in Tokyo. This case is consequently regarded as indigenous to Japan. Although it was somewhat damaged, Morishita was able to identify the worm with certainty as a specimen of *G. hispidum* Fedtschenko, 1872.

Two other cases, which have been reported, are those of Morishita and Faust (1924). Both of these worms were obtained from male Japanese who were resident in China; one specimen was from a serpiginous eruption on the left shoulder, the site of the other is not stated. Both worms were very immature and one of them had no body spines nor transverse striations, but in other respects it was so much like the second example, that they consider it justifiable to identify both specimens as specimens of Gnathostoma species, and possibly *G. spinigerum*.

The present case, which came to the writer's notice, is the first record of the condition in India. The patient was a Mahommedan male *aet.* twenty-six years, and a clerk by occupation. He has been resident in Jalpaiguri for many years, and he has never been out of Bengal. He first noticed a swelling between the thumb and first finger of the right hand, which gradually extended, involving first the dorsum and then the palm of the hand, in the course of three or four days. There was no pain nor tenderness, but the epitrochlear gland was enlarged. The swelling then spread to the right middle finger, which was somewhat red and painful, and in about two days time the patient noticed a small whitish point near the tip of the finger. He opened this with a needle, and the worm escaped from the puncture, accompanied by a serious discharge. All signs of inflammation rapidly subsided after the worm was removed. Previous to the present attack the patient had a

similar swelling of the right hand, which first appeared about seven years ago, and which lasted for about ten days. Ever since that time he has had attacks of the same nature at intervals of a year or more, this has been diagnosed as of filarial origin, but microfilariæ have never been found in the blood in spite of repeated examinations.

The Parasite.

The worm is only slightly shrunken and is about 3.56 mm. in length, by 0.42 mm. in greatest diameter. The head bulb is 0.34 mm. in breadth and 0.20 mm. in length. There are two lateral crescentic lips each bearing two papillæ. The

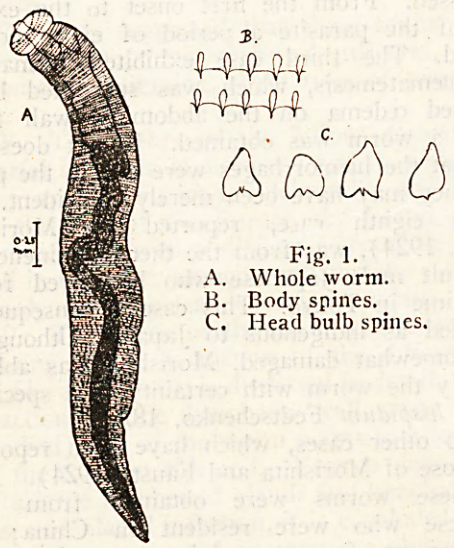

Fig. 1.
A. Whole worm.
B. Body spines.
C. Head bulb spines.

external surface of the lips is smooth, but internally three lobes are visible, indicating that when the worm is more fully developed the lips would probably be three-lobed structures, typical of the genus *Gnathostoma*. The head bulb is

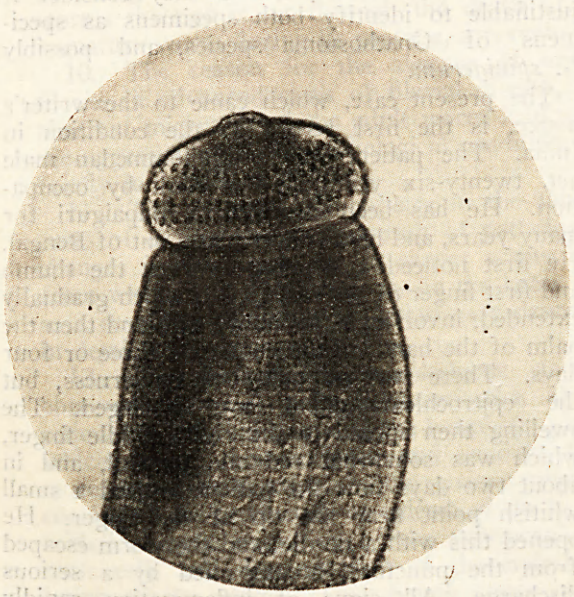

Fig. 2.—Photomicrograph of anterior portion of worm showing broad roots of spines on head bulb, and raised transverse striations.

armed with four rows of spines numbering about forty in each row. These spines have only a short sharp point projecting backwards through the cuticle, but beneath the cuticle they are seen to have broad roots of slightly varying shape. Usually there are two rounded or occasionally pointed processes running backwards beneath the skin, one on each side of the projecting spine; in some cases these lateral processes almost pierce the cuticle. The spines, including the roots, measure 12 to 16 μ in length, and 9 to 14 μ in breadth. The cuticle of the body is furnished with raised transverse ridges about 12 μ apart, and rows of spines project posteriorly from these ridges. They have simple sharp points, and beneath the skin the roots appear as simple oval structures. The length of these spines from root to tip is about 7 to 8 μ, and near the anterior end of the worm they are about 6 μ apart; they extend to the extreme posterior end of the worm, but they gradually become more widely separated in successive rows from before backwards, so that near the posterior end of the worm they are 15 to 20μ apart in each row. Very little internal structure could be made out, probably on account of imperfect fixation, but towards the anterior end there is a suggestion of ballonets, and behind these there is a broad clear œsophagus, which is followed by a dark intestine. The intestine follows a slightly wavy course to terminate in an anus near the tip of the tail. No genitalia are present, probably because the worm is too young.

Discussion.

Most of the worms described by other workers have been much more fully developed than is the writer's specimen, and consequently they have been specifically identified, but the two specimens from Morishita and Faust's cases are of approximately the same size as the writer's, and it is interesting to note that all three of these specimens have only four rows of spines on the head bulb. But the similarity ends here, for in Morishita and Faust's specimens the spines are only 10μ in length by 5μ in breadth, and they are described as simple structures, whereas the writer's specimen bears head spines which are much larger and which have broad complex roots. It is conceivable, that on fuller development these head spines might have three points projecting from the cuticle, as there is already an indication of these extra points beneath the skin. Another interesting fact is the presence of rows of simple spines throughout the length of the worm; these of course might give place to multi-pointed spines on fuller development, but it is not likely that the spines on the posterior part of the body would disappear completely. Therefore it seems unlikely that the writer's specimen is an immature example of *G. spinigerum* because the spines do not extend to the posterior extremity in this species; nor is it likely to be an immature

example of *G. hispidum,* because, although the body spines of this species extend throughout the length of the worm, the head spines of *G. hispidum* are simple structures. It therefore seems possible that this specimen may be a young worm of a species not yet recognised.

The finding of this immature worm with a suggestion of three-pointed spines on the head bulb raises the question whether *G. spinigerum* Owen, 1836, and *G. robustum* (Diesing, 1838) are really identical, for Owen (1836) in his original description stated that the spines on the head bulb had three points, similar to those on the body of the worm. As far as can be ascertained, Owen's original material has not been re-examined, but Leiper (1909) says that *G. robustum* of Diesing is most probably a synonym of *G. spinigerum* Owen. Leiper (1911) examined Diesing's original material of *G. robustum* in Vienna and he says it ".....is acceptedly the same as *Gnathostoma spiningerum* Owen, of the tiger." This view is now generally accepted, for Baylis and Lane (1920) in their exhaustive revision of the family *Gnathostomidæ* go even further and define the genus *Gnathostoma* as having simple spines on the head bulb. The fact that Owen described triple-pointed spines on the head bulb seems to have been ignored without comment, and his species has been made to include specimens which have single spines on the head bulb. Under the circumstances it would seem preferable to leave Owen's species intact until it is definitely known whether Gnathostome species do or do not exist with complex head spines, and at the same time to re-erect *G. robustum* (Diesing, 1838), as a distinct species, and to place in it all those specimens which Leiper's researches have shown to be identical with Diesing's type material.

Although a search of the literature has only produced ten cases of human infection with a Gnathostome, in which the parasite has been recovered, it is obvious, from the excellent paper of Robert (1922), that this condition is a common and definitely recognised clinical entity in Siam, which is the most important endemic centre of the disease. Robert says the disease is always characterised by transient and migrating œdema, and apparently the serpiginous raised line regarded as characteristic is only exceptionally present, when the worm is burrowing just beneath the skin. More often the parasite is situated deeper in the tissues, when all that is manifest on the skin is an œdema which moves from place to place as the parasite proceeds through the tissues. Many cases in Siam undergo spontaneous cure without the parasite being found; Robert considers this may occur in one of two ways. Either the worm dies *in situ,* or else it may be spontaneously evacuated through an internal mucous surface. In support of the latter method of cure being common there is Robert's first case in which the worm was coughed up, and the same author quotes the case of an intelligent and reliable Siamese lady who described to him the escape of a worm from the side of her tongue.

Nothing is yet known of the etiology of the disease, for the life history of the causative parasite is only most imperfectly understood. Robert says that after most careful inquiries lasting over a period of twenty-five years he has only been able to hear of one case in a male; he is therefore inclined to consider that infection is probably acquired during some typically female domestic work such as the preparation of food. Against this observation of Robert, that it is essentially a disease of females, is the fact that out of the six cases reported in this paper, which have come from outside Siam, only one was in a female. It has been suggested that infection may occur by the accidental ingestion of an insect intermediate host of the worm, or that the young worms have a free-living stage during which they have the power of penetrating the skin. In support of the latter view is the fact that of the eleven cases reported above at least four have occurred in the hand.

The behaviour of the worm in the human being probably represents the wanderings of a parasite in an unsuitable host, in which it is not able to reach full development, but it should be borne in mind that although the larvæ of *A. braziliense* behave in a similar manner in certain individuals, in others they are able to reach the small intestine and to undergo full development. It is therefore possible that in the course of time, exceptional cases of Gnathostome infection in human beings will be encountered in which the worm has reached the stomach and undergone full development, as it does in its normal hosts. Fulleborn (1927) has produced a similar condition to the eruption caused by *A. braziliense,* by the application of the larvæ of *Uncinaria stenocephala* to his own skin, so it seems probable that many other larval nematodes eventually will be found to produce allied skin lesions when they gain entrance to man, he not being the suitable host.

The discovery of the worm described above, in a man who has never been out of Bengal extends the distribution of human *Gnathostomiasis* to the Westward of its hitherto known distribution, because, since its first recognition in Siam the only other countries in which it has been found are once in the Malay States, once in Japan, twice in China, and once in a Japanese recently returned from China.

The writer is indebted to Captain K. M. Basu, I.M.S., of Jalpaiguri, first for sending the specimen, and later for supplying notes of the case.

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*Original papers not consulted.

(*Note.*—It would probably add greatly to our knowledge of the rarer parasitic worms if readers of the *Indian Medical Gazette* were to forward parasites, either from men or animals, which they do not recognise. The writer of the above article would always be pleased to receive and identify such material and to render due acknowledgment for it. If parasites are first washed by shaking in normal saline and then dropped into hot 70 per cent. alcohol, and forwarded in the latter fluid, they would almost certainly arrive in a state fit for identification.—EDITOR, *I. M. G.*)

NOTES ON THE DETECTION IN THE URINE OF SOME DRUGS USED FOR THE TREATMENT OF MALARIA.

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A. THE DETECTION OF SOME OF THE ALKALOIDS OF CINCHONA IN THE URINE.

SOME little time ago an enquiry was received by this Institute concerning the absorption from the bowel and the excretion in the urine of quinine-ethyl-carbonate (euquinine). On this occasion a child had been given treatment for malaria; "tasteless" euquinine had been employed and in view of its comparative insolubility the medical adviser wished to know whether the drug was being absorbed. In reply it was suggested that the child's urine be tested with Mayer's reagent, but it was not known how soon after administration the euquinine could be demonstrated in the urine by the reagent, the period of maximum excretion, or when the drug would cease to be demonstrable; nor was it possible to indicate the degree of variation to be expected among individuals in absorbing and excreting euquinine or any of the other derivatives of cinchona used for the treatment of malaria.

An endeavour was made, therefore, to gain some information on the points mentioned above, the conditions of the enquiry being briefly as follows:—

(*i*) The drugs chosen for investigation were quinine alkaloid, quinine sulphate, quinine hydrochloride, quinine-ethyl-carbonate (euquinine) and cinchonine; all of which have been shown by Fletcher (1923) to be effective against malarial plasmodia. These various cinchona derivatives were obtained from the British Drug Houses, London.

(*ii*) Where possible the drugs were given on each occasion to the same three cases; healthy persons of different nationalities. Case 1 was a European weighing 150 lbs., Case 2 a Chinese (128 lbs.), and Case 3 a Tamil (105 lbs.). On one occasion when quinine sulphate was investigated, Case 1-A, a Malay weighing 113 lbs., was substituted for Case 1.

(*iii*) The drugs on each occasion were given in powder form to the cases already mentioned and their administration was followed by drinking about half a pint of water. The drugs were swallowed between 8.30 and 9 a.m.; from one hour to one-and-a-half after the morning meal.

(*iv*) Following the administration of the drugs, urine was passed at intervals of twenty minutes during the first hour and subsequently every hour until retirement to sleep. The urine passed the following morning was also obtained for testing.

(*v*) It is well known that when Mayer's reagent* is added to urine containing alkaloids, a whitish opalescent cloud forms (which if due to alkaloids, disappears on heating and reappears on cooling) the density of which is generally in proportion to the amount of alkaloid present in solution. Accordingly, each specimen of urine obtained was filtered, 10 c.c. was reserved as a control and to another 10 c.c. was added fifteen drops of Mayer's reagent. If a precipitate was observed this was tabulated in accordance with its quality as dense, medium or faint, the standard of this tabulation remaining the same throughout the experiments.

* Mayer's reagent = Mercuric Chloride 6.8 grm.
Potassium Iodide 24.9 grm.
Water 500 c.c.