EXPERIMENTAL STUDIES ON THE ETIOLOGY OF HALZOUN

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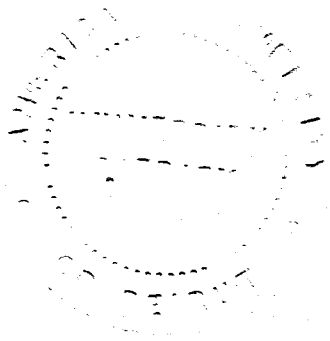

HALZOUN AND THE MARRARA SYNDROME

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ABSTRACT

Halzoun is a clinical condition epidemiologically associated with consumption of raw goat or sheep liver. Its etiology is obscure, having been in the past attributed to young Fasciola hepatica or Dicrocoelium dendriticum in ingested liver; other suggested etiologies have not gained recognition. Another condition, the "Marrara Syndrome" is felt by the writer and others to be etiologically identical with Halzoun.

In the present work, different agents and mechanisms underlying these two diseases are investigated:

(a) Mechanical attachment and irritation by adult or young liver flukes.

(b) Mechanical attachment and irritation by other parasites that may be present in liver.

(c) Localized hypersensitivity phenomena based on repeated ingestion alone or combined with infection by liver flukes.

(d) Attachment of nymphs of Linguatula serrata in uninfected or egg-infected persons.

Examination of livers, lymph nodes and gall-bladders of sheep, goats and cattle revealed only three parasites to be present: F. hepatica, and D. dendriticum adults and L. serrata nymphs.

Rabbits were given varying numbers of adult F. hepatica and D. dendriticum by mouth without any evident symptomatology. Attempts to complete the life cycles of F. hepatica and D. dendriticum for the purpose of obtaining immature specimens were unsuccessful.

Rabbits and guinea pigs were swabbed orally with powdered dried flukes for two weeks with no detection of antibodies at the end of this time. Necropsy

examination of re-swabbed animals one week later revealed no abnormalities. Two cats were fed exclusively for 15 days on liver containing D. dendriticum and for a like period on liver containing F. hepatica. One was necropsied after a meal of liver containing both flukes with no abnormalities noted.

Rabbits were sensitized by parenteral injection of Fasciola and Dicrocoelium antigens. Positive skin and precipitin tests were obtained. Animals were then orally swabbed either with homologous or with heterologous worm-powder. At necropsy, no abnormalities were noted.

Varying numbers of Linguatula nymphs were given orally to guinea pigs, white rats, cats and rabbits. Animals reacted by shaking their heads, vigorous coughing, sneezing and rubbing of the nose. At necropsy, nymphs were recovered alive from the nasal cavities, mouth, pharynx, larynx, trachea and bronchi, esophagus, stomach and small intestine. Maximal persistence of nymphs was: one month in rabbits, two weeks in cats and 8 hours in rats and guinea pigs. Some growth was attained in rabbits and cats.

Nymphs given by a stomach tube to rabbits and dogs migrated to the mouth and nose in from two to four hours.

Superimposition of nymphs in egg-infected rabbits resulted in congestion of the vessels of the nasal, pharyngeal, laryngeal and tracheal mucosa; tracheitis was evident histologically in some animals.

Nymphs given to three monkeys produced symptoms resembling those shown in the other experimental animals and those of halzoun. Congestion of the nasal mucosa and cellular infiltration of the pharyhgeal and laryngeal mucosa were noted following necropsy.

The incidence of natural infection in Beirut street dogs with L. serrata adults was found to be 43.3%. Nymphs of this parasite are more common in goat than in sheep liver and lymph nodes. Lymph nodes are probably as important

if not more so than liver as a source of infection in Lebanon.

The conclusion was reached that neither F. hepatica nor D. dendriticum are the etiology of halzoun, but that L. serrata nymphs are capable of producing symptoms of Halzoun-Marrara Syndrome in experimental animals and probably could do likewise in human beings. Differences in severity in human cases may vary according to the presence or absence of egg-initiated visceral infection and the degree of hypersensitivity of the infected person to the nymphs.

Skin testing may be useful for the detection of visceral infection in man. Local anesthetics and anti-histaminic drugs are suggested for the treatment of this condition when severe symptoms are present.

The host-parasite relationships of L. serrata nymphs and man are briefly discussed.

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INTRODUCTION

In Lebanon and nearby countries, Halzoun is a clinically well recognized but etiologically ill-defined disease-syndrome of man commencing shortly after the consumption of raw goat or sheep liver. Halzoun has various meanings in colloquial Arabic: as the common word denoting snails of any type, as a term used by butchers for any disease (except hydatid cyst) of animal liver, or as a common term for either Fasciola hepatica or Dicrocoelium dendriticum in the liver. Khouri (1905) explained that this name was applied to the condition because of the characteristic appearance of the hypertrophied cirrhotic bile ducts of liver infected with flukes, "La poche biliaire a alors, au dehors, l'aspect d'un Escargot, d'où le nom d'halzoun qui veut dire Escargot en Arabe." Textbooks of parasitology and tropical medicine also refer to this condition as "nasopharyngeal fascioliasis" or "parasitis pharyngitis".

The clinical picture was first described by Khouri (l.c.) and has been further defined by Watson and Abdel-Kerim (1956). The onset occurs a few minutes to half an hour after eating raw goat or less commonly sheep liver, when there is discomfortable itching "deep in the throat" that subsequently extends to the ears. Edematous congestion of the bucco-pharyngeal mucosa including soft palate, uvula and tonsils, and of the larynx, Eustachian tubes, nasal passages, conjunctiva and lips may be marked. Nasal and lachrymal discharges are common, submaxillary and cervical lymph glands are sometimes enlarged, and the neck may be swollen. Dyspnea, dysphagea and dysphony are common; frontal headache is frequent, the belief of Khouri being that it probably resulted from sinus congestion. Photophobia and exophthalmia are also recorded. Systemic symptoms, however, are absent. Khouri reported that vomiting is very common, giving much symptomatic relief, and that patients

could sometimes see in the vomitus "small living worms". In severe cases, the tonsils enlarge so as to produce asphyxiation and death. Complications in non-fatal cases include abscesses in the auditory canals and facial paralysis. Khouri summarized three clinical degrees of severity of the disease:

(a) A mild form with a gradual onset of one to two hours, with few symptoms, no dyspnoea, and a duration of usually not more than three days.

(b) A severe form with a sudden onset, pronounced symptoms, prominent dyspnoea and a duration of five to eight days.

(c) A fatal form resembling the severe form except that the symptoms become progressively more marked and asphyxiation leads to death.

Considered epidemiologically, Khouri (l.c.) stated that repeated attacks could occur in one individual while not all persons sharing the same liver contracted the disease.

Khouri (l.c.) claimed to have produced the disease in two rabbits by feeding them respectively six and eight immature F. hepatica of not more than 1 mm length, "... tout au début de l'état adulte et ne mesurant pas plus d'un millimètre....". The first animal developed acute symptoms and died with convulsions after 4½ hours; the second survived 8 hours. The cause of death was unstated. At necropsy, flukes were found attached to the center of an edematous area at the base of the tongue. They were said to be, "... augmentées de volume, gorgées de serum sanguin." He concluded that the disease was caused by ingestion of young F. hepatica contained in raw liver, those escaping mastication attaching to the bucco-pharyngeal mucus membrane. Edema and symptoms were thought to be probably due to injection of an irritant vaso-dilator at the site of attachment. The severity of the symptoms was felt to be directly proportional to the number of the attaching parasites.

Brumpt (1936) doubted the role of Fasciola hepatica in halzoun, concluding that the true etiology might be some other trematode. This was based on his failure either to produce symptoms or to show fixation of parasites in two dogs fed over one month on raw sheep liver heavily infected with young F. hepatica and D. dendriticum.

Witenberg (1944) suggested Clinostomum complanatum as the causative agent, but has not received acceptance for several reasons, primary of which is that this parasite of birds is acquired by ingestion of metacercariae in raw fresh water fish, something which is not done in Lebanon. Secondly, the disease is clearly tied on epidemiological grounds to the eating of raw visceral organs of sheep or goat.

Watson and Abdel-Kerim (1956) restudied halzoun in different villages and towns in Lebanon. Although they did not observe any cases at first hand, twenty one individuals who had previously contracted halzoun were interviewed and the clinical symptoms described by Khouri (l.c.) were confirmed. All but two cases ate raw goat or sheep liver a few minutes before the attack, the remaining two cases had no liver but had eaten only raw lymph nodes. They investigated the popular belief in the curative effects of "arak" (a local alcoholic drink) on halzoun, but thought it ineffective. They reported an effective remedy to be insufflation of citric acid powder.

Their experiments on the etiology consisted of introducing adult F. hepatica into the mouths of three rabbits and into the nostrils of one rabbit resulting in no symptoms suggestive of halzoun, while at necropsy, no trace of the introduced flukes could be seen. In discussion, they considered two theories of the etiology of halzoun:

(a) That it might be due to the injection of an irritant vasodilator secretion as suggested by Khouri (l.c.),

(b) That it might be a hypersensitivity phenomenon produced by repeated consumption of infected raw liver and absorption of toxins from crushed flukes by the mucosa. No definite conclusions were reached.

Investigating the first hypothesis, considering both F. hepatica and D. dentriticum, Azar (1964) was unable to produce symptoms in 92 human volunteers fed liver infected with either or both flukes.

A clinical condition similar to halzoun is that described by Salman and Mahdi (1955) and subsequently by Kirk (1958) from the Sudan. This condition is called the "Marrara syndrome" after a common Sudanese dish consisting of raw stomach, liver, lung and trachea of sheep or goats seasoned with bile, lemon, spices and sometimes onion. This syndrome occurs in the Abu Deleig-Gebel Geili area, Rajab near the Atbara river in the north of Butana, where it has long been known to the villagers. A few hours after consuming marrara, patients develop signs and symptoms resembling those of the common cold: running nose and eyes, sore throat, facial edema extending down the neck, and sometimes cutaneous wheals. Mild cases recover in about four days. Others develop complications such as impairment of hearing, discharge from the ears, dyspnoea, dysphagia, headache and vomiting. The same individual is reported to be repeatedly susceptible, while some persons eating from the same dish with affected ones escape the disease.

As summarized by Kirk (l.c.) there are several marked similarities between the marrara syndrome and halzoun:

(a) Constant association with the eating of raw sheep or goat liver.

(b) Escape of some individuals after eating the same dish as those contracting the syndrome.

(c) The possibility of repeated attacks in the same individual.

(d) The incubation period, the clinical features and the course of the disease.

(e) Restriction of the signs and symptoms to the head with the occasional death reported due to asphyxiation.

In preliminary investigations leading to the present work, four villagers with a recent history of halzoun were interviewed. On being asked what they ate prior to the onset of symptoms, all stated that they had consumed raw liver but volunteered that they had additionally eaten raw lymph nodes. All claimed to have seen "white worms" (doud abyad) which they had manually removed from the posterior pharyngeal region and the tonsils. One patient stated that a "white worm" was removed from his nares by a physician, but that this was not saved.

Two papers have been recently published in which the symptoms reported closely resemble those of the four cases above and those described by Khouri, (l.c.) and Watson and Abdel-Kerim, (l.c.) in the mild and severe forms of halzoun. Unat and Sahin (1950) reported from Turkey the case of a woman who had eaten improperly cooked lymph nodes about one to two hours before onset of symptoms, which lasted overnight: sneezing, coughing and severe itching in the throat. About twenty "worms" were seen by the patient in the nasal discharge following a paroxysm of sneezing. Medical examination showed nymphs of Linguatula serrata attached to and in the crypts of the tonsils and on the nasal mucosa. The nymphs, which were seen only with difficulty and could not be removed, disappeared on the fourth day, at which time the patient had completely recovered.

The second report (Papadakis and Hourmouziadis, 1958) described a human case in Greece. The patient suddenly developed an acute attack of cough and sneezing with increased rhino-pharyngeal secretion and allergic symptoms. After 8 hours, the symptoms subsided to reappear several hours later. Minor paroxysms interrupted by periods of amelioration continued for 15 days. During the attacks, a total of 20 nymphs of L. serrata were expelled with the

rhino-pharyngeal secretions. X-ray, blood and fecal tests were negative. The probable source of the nymphs was not stated.

Statement of Problem:

Halzoun and Marrara syndrome are two clinically similar conditions well recognized by physicians and the common people in Lebanon and the Sudan respectively. Both conditions are constantly associated with the consumption of raw liver and other visceral organs of goats and sheep such as lymph nodes, lungs and stomach.

In the present work, attempts are made to investigate the following agents and the mechanisms underlying these two syndromes:

(a) Mechanical attachment with injection of an irritant by adult or young liver flukes: Fasciola hepatica or Dicrocoelium dendriticum.

(b) Mechanical attachment with injection of an irritant by other small parasites that might be present in the liver.

(c) Localized hypersensitivity (Arthus reaction) developed as the result of repeated ingestion of crushed liver flukes.

(d) Localized hypersensitivity to the crushed flukes in persons infected with liver flukes.

(e) Attachment of nymphs of Linguatula serrata in uninfected and naturally infected persons harboring nymphal stages of L. serrata.

MATERIALS AND METHODS

Living F. hepatica adults were removed directly from bile ducts of fresh liver; adult D. dendriticum were obtained by soaking sliced fresh liver. Flukes were then kept in Hédon Fleig solution (Dawes, 1954) for not more than 30 minutes before use.

Immature flukes and any other organisms that might be present were looked for by soaking sliced liver as above and by sedimenting the washings from fresh sheep, goat and cattle gall bladders opened under water. Lymph nodes were examined by slicing and soaking following the suggestion of Watson and Abdel-Kerim (1956) that young flukes traversed the mesenteric nodes enroute to the liver.

Lymnaea species were collected from different habitats in Lebanon and were examined for natural Fasciola infection by inspection for shed cercariae and by crushing.

Ants collected from different pastures were examined for natural Dicrocoelium infection by dissection.

Flukes used in the preparation of crude worm-powder were washed in tap water, doubly rinsed in distilled water and homogenized in a high speed mechanical blendor. The resultant material was quick-frozen, lyophilized, pulverized and stored at $4^{\circ}C$.

F. hepatica and D. dendriticum sensitizing antigens were prepared by the method of Urquhart et al. (1954) except that one gram of dried powdered fluke material rather than one fresh fluke was extracted with one ml of saline solution. Kjeldahl analysis showed the Fasciola antigen to contain 0.84 mgm N/ml and the Dicrocoelium antigen to contain 0.11 mgm N/ml. The antigen was stored in 5 ml amounts in vials at $-20^{\circ}C$.

Antigen for the precipitin test was prepared by extracting one gram of powdered flukes in 100 ml of buffered saline at pH 7-7.2 for 24 hours at 20-22°C with occasional shaking. The extract was centrifuged 30 minutes in a high speed centrifuge and the supernate placed in vials. Sterilization was done by heating for 45 minutes at 56°C (Soulsby, 1954). The material was stored at -20°C. The precipitin test was performed using serial twofold dilutions of serum from 1:5 to 1:320 in three rows. An equal amount of antigen diluted 1:5, 1:10 or 1:20 was added to each tube and the mixture incubated at 37°C for 24 hours before reading. Skin tests were performed on the back of rabbits by injecting 0.1 ml of 1:100 saline extracted antigen; 1:100,000 merthiolated saline solution was injected as a control. Readings were made after 30 minutes and 24 hours.

Linguatula serrata nymphs were collected by soaking sliced fresh goat or sheep lymph nodes in water at 35-38°C for 10-20 minutes. Collected nymphs were kept in warm water for not more than one hour before use. Sheep, goat and cattle livers were examined for nymphs by slicing and soaking as above. L. serrata eggs were obtained from the uteri of gravid females recovered from the nasal cavities of dogs following sawing and splitting of the skull. Adults were removed manually or after overnight soaking in tap water. The number of eggs given to animals was determined by averaging the counts of three aliquot samples. Eggs were used within ten days of collection. Rabbits were infected orally by medicinal pipette, monkeys were infected by allowing them to eat previously inoculated apples.

Nymphs recovered from naturally and experimentally infected animals were measured after fixation in A.F.A. and clearing in glycerine or lactophenol. Adults were measured in 70% alcohol after fixation in A.F.A.

L. serrata antigen was prepared by homogenizing 25 nymphs per ml of 1:100,000 merthiolated saline solution using a Tenbroeck(R) tissue grinder. This homogenate was extracted at 4°C for 48 hours, centrifuged for 30 minutes at 3000 rpm, and the supernate was stored at -20°C until use in precipitin and skin tests. Skin and precipitin tests were performed as described above.

The experimental animals used were laboratory reared rats, guinea pigs and rabbits and stray mongrel cats and dogs. The Rhesus monkeys used originated in Malaya. Animals were killed by intraperitoneal injection of sodium pentothal. The nasal cavities were examined by splitting the skull, examining visually and then soaking for 24-48 hours in tap water. The larynx, trachea, bronchi and lungs were examined by eye under strong light and were then soaked in water overnight. Soakings were examined using a dissecting microscope. The digestive tract was opened and examined by eye, then the mucosa was scraped in water and the washed sediment was examined with a dissecting microscope.

Tissues for sectioning were fixed in Bouin's fluid, embedded in Tissumat(R) and sectioned at 7 micra.

PRESENTATION OF DATA

I. Attachment of Adult Flukes.

A. Fasciola hepatica

Two, four, four and five flukes respectively were introduced orally into four rabbits; two controls were fed minced flukes. One rabbit given four flukes was killed after 30 minutes, when one semi-digested parasite was found in its stomach. A second rabbit (given five flukes) was completely negative at four hours. The remaining two animals were observed for seven days; no reaction was seen.

B. Dicrocoelium dendriticum.

Six rabbits were fed 3, 4, 5, 6, 12 and 50 flukes respectively by pipette. Two control animals were fed minced flukes. The animals given 4 and 50 flukes were killed after 2 and 4 hours respectively. No trace of the introduced flukes was found in either the digestive or respiratory tracts. The remaining animals showed no outward signs during the one week they were observed.

II. Examination of Gall Bladders, Livers and Lymph Nodes For Potential Etiologic Agents and Rearing of Immature Fasciola hepatica and Dicrocoelium dendriticum.

A. Gall bladders, livers and lymph nodes were examined at various times during the year for the presence of immature liver flukes and other parasites:

(a) 38 sheep gall bladders in winter (December and January).
(b) 231 sheep gall bladders in spring and early summer (April and June).
(c) 10 cattle gall bladders in spring (April).
(d) 204 goat gall bladders in early summer (June).
(e) 20 Kg. of cattle liver in summer (May through September),
(f) 20 Kg. of sheep and goat liver in summer (July through September).
(g) 80 Kg. of sheep and goat (mixed) mesenteric lymph nodes in winter, spring and summer (November through July).

Many adult F. hepatica and D. dendriticum and numerous nymphs of Linguatula serrata were recovered, but neither immature flukes nor any other organism approximating the size (one millimeter) described by Khouri (l.c.) could be found in any of the material examined.

B. Attempts were made to complete the life cycle of F. hepatica in the laboratory with the intent to rear young stages in mice (Dawes, 1962), recover these from liver and feed them to rabbits. All attempts to infect locally collected Lymnaea spp. with Fasciola (Malek, 1962) failed due to refractoriness of the snails. Examination of eight hundred field-collected specimens of several species of Lymnaea from various habitats showed all to be negative.

An attempt was likewise made to collect ants naturally infected with D. dendriticum metacercariae (Krull and Mapes, 1952, 1953) to allow infection of laboratory animals with this parasite and recovery of young stages. About 400 ants collected from various sheep-pastures were dissected for metacercariae and found to be negative.

III. Repeated Ingestion of Fasciola hepatica or Dicrocoelium dendriticum.

Three rabbits and three guinea pigs were orally swabbed each day for two weeks with lyophilized F. hepatica powder using a cotton-tipped applicator-stick. Three rabbits and three guinea pigs were treated likewise with powdered D. dendriticum. Three control rabbits and three control guinea pigs were swabbed with lyophilized, powdered, uninfected sheep liver. After two weeks, the animals were bled and precipitin tests using the appropriate antigen-extracts in 1:100 dilution were performed. No antibodies could be detected by this method in any of the animals. One week later, all experimental and control animals were reswabbed with the appropriate powder. One rabbit and one guinea pig of each group swabbed with worm-material was

killed at 30 minutes, and another such animal from each group at one hour after swabbing. No gross changes were noted in either the digestive or the respiratory tracts of any of the eight animals. Neither experimental nor control animals showed any reaction during conduct of the experiment.

Two cats were fed exclusively liver grossly infected with D. dendriticum for 15 days. After an interval of three days, they were fed 15 days only liver infected with F. hepatica. After a rest period of 11 days, they were given liver heavily infected with both flukes. One animal was killed two hours after consuming the mixed diet. No reactions were seen in either the intestinal or respiratory tracts, and no living worms were recovered. The animals showed no symptoms during the course of the experiment.

IV. Localized Hypersensitivity in Sensitized Animals:

Two groups, comprising four rabbits each, were sensitized to either Fasciola or Dicrocoelium by intramuscular injection of 2 ml of alum-precipitated antigen (Urquhart et al., 1954) at 7-day intervals for five injections. After the fifth injection, immunization was continued at 14-day intervals. After 6 injections of Fasciola antigen and 8 injections of Dicrocoelium antigen, a precipitin titre of 1:160 was obtained in all animals of both groups using 1:100 antigen-extracts. Skin tests performed at the end of the immunization period were positive either after 30 minutes or at 24 hours or both. The criterion of a positive immediate reaction was formation of a red wheal at the site of antigen injection with lack of a response around the saline control injection. Positive animals at 24 hours showed an area of induration of variable size at the site of antigen injection.

The possibility of bucco-pharyngeal absorption of unde-graded antigenic substances (Drinker and Yoffey, 1941) with a resultant localized tissue-hypersensitivity reaction was then tested by orally swabbing two rabbits of each group above with powdered Fasciola and the remaining two with powdered Dicrocoelium. Swabbing with heterologous worm material in this way tested the possibility of cross reactions. No visible reaction to the concentrated powder was noted in any of the animals. One homologous and one heterologous test-animal from each group was killed after two hours. No abnormalities were noted in either digestive or respiratory tracts. The remaining animals were observed for one week, none had any notable untoward effects.

V. Attachment and Migration of Linguatula serrata Nymphs in Uninfected animals:

Nymphs of L. serrata from sheep and goat lymph nodes were given to several species of animals either by stomach tube or by oral introduction by medicinal pipette. Twenty such nymphs (Figs. 2, 4) were measured in glycerine following fixation with A.F.A. They ranged from 4.9 to 6 mm in length with an average of 5.6 mm.

A. Guinea Pigs:

In from 10 minutes to 2½ hours after the nymphs were introduced into the mouth by pipette, guinea pigs reacted by vigorously coughing, sneezing and shaking their heads. The animals attempted to induce coughing as if to eliminate a foreign body in their throats. Irritability and aggressiveness were recognized; the animals began to bite each other when disturbed. Normal activity was regained in from one to eight hours.

At necropsy at various times following inoculation, nymphs were recovered alive from the nasal cavities, attached to the trachea and from the stomach and intestine walls (Table 1). Maximal persistence of nymphs in this animal was 48 hours, although most appeared to be eliminated by 24 hours. No growth of the nymphs was observed.

TABLE 1

PERSISTENCE AND MIGRATION OF ORALLY ADMINISTERED *L. SERRATA* NYMPHS IN GUINEA PIGS KILLED AT VARIOUS TIMES FOLLOWING INFECTION

Time in hours	Number given	Number recovered and location			
		Nasal cavity	Trachea	Stomach	Intestine
1	50	0	4	21(4 dead)	1
	60	0	1	11(8 dead)	2
4	55	0	1	2(1 dead)	0
	70	1	0	6(1 dead)	2
8	85	0	1	22	4(1 dead)
24	55	0	0	(1 dead)	0
	75	0	0	0	0
48	45	0	0	(3 dead)	1
	62	0	0	0	0

B. White Rats:

In from 10 to 25 minutes after oral introduction of nymphs, rats began to sneeze, rub their noses and ears, and to show signs of distress in swallowing and breathing. Nymphs were recovered alive from the nasal cavities, attached to

the cheeks, on the soft palate, and on top of and beneath the tongue for as long as 8 hours (Table 2). Those found in the stomach and intestine were either attached to the wall or were found in sedimented washings. In those latter locations, nymphs were usually dead after 4 hours.

TABLE 2

PERSISTENCE AND MIGRATION OF ORALLY ADMINISTERED *L. SERRATA* NYMPHS IN RATS[1] KILLED AT VARIOUS TIMES AFTER INFECTION

Time in hours	Number given	Number of nymphs recovered and location							
		Nasal cavity	mouth	pharynx	larynx	trach. and bronchi	esop.	stom.	intes.
½	30	0	1	1	2	0	2	5(4 dead)	(12 dead)
	33	0	3	3	0	0	1	10(4 dead)	(3 dead)
1	80	0	3	3	5	0	3	32(30 dead)	8(7 dead)
	60	1	1	1	1	0	0	12(5 dead)	7(6 dead)
2	40	1	1	2	1	0	1	4(2 dead)	6(2 dead)
	70	0	1	5	0	2	0	(20 dead)	(2 dead)
4	50	0	0	1	0	1	0	2	(3 dead)
	50	1	2	1	1	0	1	12(9 dead)	2
8	27	1	0	0	0	1	0	(2 dead)	0
	60	3	0	0	0	0	0	5(4 dead)	(1 dead)

1. Two animals examined at 24 hours and two examined at 48 hours were completely negative.

C. Cats:

In from 5 minutes to 5 hours after receiving nymphs orally, cats began to sneeze, cough and shake their heads. Two, examined after 7 and 14 days, had discontinuous paroxysms of sneezing and coughing until necropsy. The cat

examined on the fifth day died prior to necropsy, when examination showed severe pneumonia with hemorrhagic areas in the lungs. Two nymphs were recovered alive from Baermannized lung material, but their role in the death of the cat could not be assessed.

Maximal persistence of nymphs in this host was two weeks (Table 3), and apparently some growth occurred. The one nymph recovered on the ninth day was 6.5 mm long, and one of the two recovered on the fourteenth day was 6.6 mm long (the other specimen recovered at this latter time was injured too much to be measured). These measurements exceed the maximal length (6.0 mm) of nymphs from sheep lymph nodes.

TABLE 3

PERSISTENCE AND MIGRATION OF ORALLY ADMINISTERED *L. SERRATA* NYMPHS IN CATS[1]

Time in days	Number given	Number recovered and location			
		nasal cavity	mouth	pharynx	lung
5	57	14	0	0	2
7	15	3	0	0	0
9	100	1	0	0	0
14	18	0	0	0	0
	60	2	0	0	0

1. Cats examined at 32, 45, 46, 60 and 60 days were completely negative.

D. Rabbits:

Nymphs were either given orally by pipette or by stomach tube. Within 2 to 4 hours after infection by either route, the animals began to sneeze

and to rub their noses and ears. Some were notably irritable and nervous and shook their heads vigorously.

At necropsy of orally infected animals, nymphs were found attached to the soft palate, on and under the tongue, clinging to the posterior and lateral pharyngeal walls, on the surface and in the folds of the tonsils, and in the nasal cavities (Table 4). Those in the tonsilar folds could only be expressed by squeezing. No gross congestion was seen in the pharynx, tonsils, trachea or nasal epithelium of any of these animals, however histological examination of tissues from one animal killed at 24 hours showed slight congestion, edema and fibrinous exudate in the submucosa of the trachea. The tonsils and pharynx were essentially normal histologically.

Two rabbits examined on the seventh post-infection day died prior to necropsy. Examination showed the lungs to be pneumonic and to contain small hemorrhagic patches. Two nymphs were recovered from the primary bronchi of one of these animals.

The length of nymphs recovered after two weeks was 5.9 to 7 mm (average 6.3 mm); two recovered after three weeks measured 7 and 8 mm. Those recovered after one month were from 7.4 to 10.0 mm long (average 8.6 mm).

The question of the tropisms and ability of swallowed nymphs to migrate from the stomach to the laryngo-pharyngeal and nasal cavities was tested by introducing nymphs by clear plastic stomach tube into rabbits (Table 5) and dogs (Table 6). The tube was in all cases flushed <u>in situ</u> with water to insure against nymphs either being deposited in the esophagus or being carried up with the tube.

At necropsy of rabbits infected 2-4 hours previously by stomach tube (Table 5), nymphs were found within two hours in the nasal cavities, mouth, pharynx, larynx and trachea.

TABLE 4

PERSISTENCE AND MIGRATION OF ORALLY ADMINISTERED
L. SERRATA NYMPHS IN UNINFECTED RABBITS

Time	Number given	Number of nymphs recovered and location							
		nasal cavity	mouth	pharynx	larynx	trach. and bronchi	lung	stomach	intes.
2 hrs	34	0	8	6	0	2	0	5(3 dead)	0
	70	6	17	9	2	2	1	16(4 dead)	0
8 hrs	75	1	2	1	0	2	0	1	2(1 dead)
	85	4	0	3	3	3	0	5	0
	85	5	0	3	0	0	1	(5 dead)	(1 dead)
24 hrs	10	0	1	0	0	0	0	0	0
	90	0	0	0	0	1	0	(1 dead)	0
	230	22	0	0	0	1	2	0	3
7 days	17	1	0	1	1	2	0	0	0
	10	2	0	0	0	0	0	0	0
	25	1	0	0	0	0	0	0	0
14 days	10	2	0	0	0	0	0	0	0
	230	16	0	0	0	0	0	0	0
21 days	10	0	0	0	0	0	0	0	0
	57	2	0	0	0	0	0	0	0
30 days	110	4	0	0	0	0	0	0	0
	63	7	0	0	0	0	0	0	0
	35	0	0	0	0	0	0	0	0

D. Dogs:

The only apparent sign in four dogs given nymphs by stomach tube was sneezing. At necropsy (Table 6), nymphs were recovered from the nasal cavities of one of two dogs killed at 4 hours. Many were found in the course of migration to this area in all the dogs examined both at 2 and at 4 hours. All of the nymphs recovered at

these times from dogs were alive in contrast to findings in other animals at like time intervals following infection.

TABLE 5

MIGRATION IN RABBITS OF L. SERRATA NYMPHS GIVEN BY STOMACH TUBE

Time in hours	Number given	Number of nymphs recovered and location						
		Nasal cavity	mouth	pharynx	larynx	trach. and bronchi	esoph.	stomach
2	100	2	4	10	3	0	0	57(38 dead)
	100	1	9	10	0	1	0	30(8 dead)
4	100	1	19	6	1	5	1	12(8 dead)
	100	0	10	10	0	5	2	16(1 dead)

TABLE 6

MIGRATION IN DOGS OF L. SERRATA NYMPHS GIVEN BY STOMACH TUBE

Time in hours	Number given	Number of nymphs recovered and location							
		nasal cavity	mouth	pharynx	larynx	trach. and bronchi.	esoph.	stom.	intes.
2	100	0	9	17	10	12	3	14	6
	33	0	1	7	15	0	4	2	0
4	75	3	7	20	3	9	2	4	3
	80	0	8	5	2	3	1	8	4

VI. Attachment and Migration of Linguatula serrata Orally Superimposed on Animals Previously Infected by Eggs.

A. Rabbits.

Animals were orally inoculated with varying numbers of L. serrata eggs 42-62 days before oral superimposition of nymphs. Before the experiment, animals were precipitin-and skin-tested using saline-extract antigen. Precipitin tests gave inconsistant results, with no apparent correlation between positivity and either length of inoculation or egg-dosage. Strongly positive immediate skin test reactions were, however, obtained in all cases. These persisted, increasing in intensity up to 24 hours. Criteria of skin-test positivity were the same as those previously described. Control rabbits (laboratory reared) were negative to both the injected antigen and saline.

Nymphs were given orally by pipette. The reactions observed in those animals were similar to those of uninfected rabbits, but compared with other (uninfected) rabbits in the same cage, the experimental animals looked very quiet and seemed "unhappy" before and between paroxysms.

At necropsy, nymphs were found attached to the larynx, the upper trachea and to the pharyngeal walls (Table 7). Slight patchy congestion was observed at the base of the tongue; there was a patchy erythema of the pharyngeal walls and a moderate to severe congestion of the blood vessels of the larynx and especially the trachea. In most cases, the trachea contained much tenacious mucus. Moderate to severe congestion of the blood vessels of the nasal mucosa covering the turbinates was also observed. These findings were seen in all rabbits except that killed at 14 days when congestion was observed only in the nasal mucosa.

Microscopic examination of sections from pharynx, tonsils, larynx and trachea showed moderate to extremely marked congestion, with some cellular infiltrate in the submucosa of the trachea and larynx (Figs. 13, 14) in all rabbits killed prior to 14 days. Partial desquamation of the tracheal mucosa was sometimes seen (Fig. 17) and mucus, occasionally containing clumps of tracheal or bronchial cells, covered the ciliated epithelium (Fig. 16). These findings would, in short, be consistant with an acute tracheitis. Pharyngeal blood vessels were dilated more markedly in the nasal area, where the epithelium was covered with mucus. The tonsils showed an inconsistant and non-specific slight or moderate hyperplasia of the secondary follicles, but sometimes were normal.

TABLE 7

PERSISTANCE AND MIGRATION OF ORALLY ADMINISTERED
L. SERRATA NYMPHS IN PREVIOUSLY
INFECTED RABBITS

Number of eggs given	Time[1]	Number of nymphs given	Number of nymphs recovered and locations					
			nasal cavities	pharynx	larynx	trachea	stomach	intes.
200	4 hrs	40	2	2	0	0	8(7 dead)	1
500	8 hrs	52	3	0	0	0	(1 dead)	0
1000	14 hrs	100	5	0	0	3	(7 dead)	(1 dead)
1000	24 hrs	100	10	0	1	0	(3 dead)	1
500	2 days	82	11	0	0	0	0	0
200	4 days	108	6	0	0	0	0	0
500	7 days	82	15	0	0	0	0	0
500	14 days	82	11	0	0	0	0	0

1. Time after oral superimposition of nymphs

B. Monkeys.

Two monkeys were given infective eggs of L. serrata 60 and 63 days respectively before oral superimposition of nymphs by pipette. A third animal was not given eggs but received nymphs orally only, while a further monkey was infected by eggs but was not given nymphs so as to serve as a tissue section and infectivity control.

All three animals reacted to the introduced nymphs within two hours, but the reactions of those previously infected by egg developed more rapidly than in the uninfected control. The animals' reactions were quite striking: extreme extention of the tongue, continuous grinding of the teeth, near-retching actions, repeated yawning, shaking of the head, and rubbing and picking at nose and mouth with the paws. Coughing and sneezing paroxysms were severe between 2-4 hours after infection, with clear or blood-stained mucus containing nymphs being discharged from the nose. (In these experiments, monkeys were confined in clear plastic boxes so that expelled nymphs could be clearly seen). One animal sneezed so vigorously as to produce a mild nose-bleed. Some animals inflated their cheek-pouches repeatedly so that the cheek and upper neck region became explosively enlarged. Sneezing and coughing continued irregularly until necropsy in both monkeys killed at 24 hours and for 48 hours in that killed after 6 days, but acute naso- or glosso-pharyngeal signs were rare after the fourth hour. Nymphs were seen attached to the soft palate of one monkey examined visually 8 hours after infection. Unless these are in motion, they are very difficult to see. Their clear bodies do not contrast markedly with the wall of the pharynx, hence they appear much like a small mucus fleck on the mucosa.

At necropsy, nymphs were found embedded in the tonsilar crypt (Fig. 10) attached to the median septum or in the bottom meatus of the turbinates, and attached to the stomach wall. Gross congestion was noted only in the nasal mucosa.

TABLE 8

PERSISTENCE AND MIGRATION OF ORALLY ADMINISTERED
L. SERRATA NYMPHS IN MONKEYS

Number of eggs given	Time[1]	Number of nymphs given	Number of nymphs recovered and location		
			nasal cavities	tonsils	stomach
0	24 hrs	164	7	1	0
1000	24 hrs	100	2	1	2
5000	6 days	425	0	0	0

1. Time after oral superimposition of nymphs

Microscopic examination of tissue sections from tonsils, pharynx, larynx, trachea and nasal epithelium showed slight hyperplasia of lymphoid elements in the tonsils and small cellular infiltrates in the submucosa of the pharynx, larynx and trachea. In some area of the larynx small mucus deposits were found attached to the mucosa. This mucus contained many eosinophils (Fig. 15). The blood vessels of the nasal epithelium were markedly dilated and the submucosa was heavily infiltrated with leukocytes (Figs. 11,12).

VII Incidence in Dogs of Natural Infection with L. serrata

The nasal cavities of 30 street-dogs were examined for adult L. serrata (Fig.1). Thirteen (43.3%) were found to be infected, with the parasite burden per animal ranging from 1-14; the male:female ratio was 25:15. Adult males were from 15 to 27 mm long (average 22 mm). Adult females were from 64 to 113 mm long (average 90 mm).

The point of attachment of adult females was generally in the middle meatus of the turbinates, with the body extended in the posterior half of the nasal cavity. The attachment of males did not appear to follow a regular pattern but this cannot be said with certainty, for because of their smaller size and clear body, they were often missed visually and were recovered only after soaking. The position of the females might tend to show that eggs would regularly pass back with nasal secretions into the pharynx. It is however also possible that eggs would be sneezed out by dogs as regularly as they would be swallowed and passed in faeces.

VIII Incidence of Natural Infection with L. serrata Nymphs in Sheep and Goat Livers

200 gm. from each of 10 livers from sheep and a like amount from 10 goat livers were examined by slicing and soaking. Out of 10 sheep livers, nymphs were found in the hepatic lymph nodes of only one with a living nymph found attached in the general area of the hepatic lymph nodes of another liver. The hepatic lymph nodes were infected in four of the 10 goat livers examined. One of these livers showed surficial white spots about one mm in diameter. Microscopic examination of these spots disclosed nymphs (Fig. 5) near to granulomatous areas containing what appeared to be molted cuticle of previous growth stages (Fig. 6).

DISCUSSION

Halzoun is associated epidemiologically and in the popular mind in Lebanon with a cultural food habit: the eating of raw goat or sheep liver (Khouri, 1905; Watson and Abdel-Kerim, 1956; Azar, 1964; present work.) Lymph nodes have been mentioned as a source of infection (Watson and Abdel-Kerim, l.c.; present study), but their relationship to the disease has been less emphasized.

The close similarity between the sources and method of infection and the clinical picture and course of the marrara syndrome (Salman and Mahdi, 1955; Kirk, 1958) and halzoun is striking. In the writer's opinion, the conclusion of Kirk (l.c.) that they probably have a common etiology is a very valid one.

The etiology of halzoun is not as clearly defined as the source(s) of infection. In his original description, Khouri (l.c.) claimed to have produced the disease in two rabbits by feeding immature Fasciola hepatica removed from dilated, cirrhotic bile ducts. According to Dawes (1962), although F. hepatica may enter the bile ducts of mice from the hepatic parenchyma when they are from 2.37 to 5.60 mm long (by 0.95 to 2.88 mm wide), most young flukes do not migrate to the ducts until they are 5.90 to 6.78 mm long (by 2.35 to 2.52 mm wide). If a similar development and migration pattern obtains in sheep, Khouri's experiments must be interpreted with caution. In the present study, repeated examination of livers and lymph nodes at various times during the year disclosed nothing approximating to the size of "... pas plus d'un millimètre ..." given by Khouri, and the organism he described must be considered as undefinable.

The animal experiments of Brumpt (1936), Watson and Abdel-Kerim (l.c.),

and the present work; and the study of Azar (1964) using human volunteers, all tend to eliminate any potential role by adult (or sub-adult; Brumpt, l.c.) Fasciola hepatica or Dicrocoelium dendriticum in the causation of this condition by their mechanical attachment.

The theory that the symptoms described in halzoun and the marrara syndrome might be due to localized tissue-hypersensitivity reactions initiated either by mucosal absorption of undegraded antigens from repeated ingestion of crushed flukes or to undiagnosed fluke-infection is of interest in its possible relation to localized Arthus reactions previously reported (Walzer, 1927; Walzer et al., 1935; Gray and Walzer, 1936, 1938; Gray et al., 1938, Sherman et al., 1938; Drinker and Yoffey, 1941; Pollard and Stuart, 1942; Seegal, 1949; Goldgraber and Kirsner, 1958, 1959 and Kirsner et al., 1959). Despite the rarity of reported cases of autochthonous human liver fluke infection in Lebanon (Yenikomshian and Berberian, 1934), the absence of infection in locally raised goats (most sheep and cattle eaten in Lebanon are imported from Syria or Turkey), and the writer's failure to find naturally infected snails or ants, the possibility of sporadic human infections with either of the liver flukes in Lebanon cannot be completely ruled out. In a survey of Fasciola infections seen at the American University Hospital, Uthman et al. (1964) found 14 cases in the period from 1940 to present. Four of these cases were members of the same family. All these cases are presumed to have been acquired in Lebanon.

Hepatic infection could reasonably be expected to produce sensitivity, and the chance of the occurrence of localized reaction to ingested material cannot be entirely eliminated. However, the failure to elicit reactions in artificially sensitized rabbits (with high precipitin titres and positive skin tests) by orally swabbing with concentrated antigen tends to indicate that halzoun is not an Arthus phenomenon localized in the glosso-pharyngeal or

upper respiratory region initiated by hypersensitivity to liver flukes. Continuous feeding experiments using dogs (Brumpt, 1936) and cats (present study) also tend to support this conclusion. The human volunteer study of Azar (l.c.) might be similarly interpreted, as most of the volunteers were people who probably ate raw liver customarily.

The livers and lymph nodes of goats and sheep examined in the present study disclosed only three genera of parasites, any of which might be described as "white worms" by patients: Fasciola hepatica and Dicrocoelium adults and Linguatula serrata nymphs. This latter, however, was the only parasite found in (locally raised) goat livers and in either sheep or goat lymph nodes (Fig. 9)

Liver was the first reported source of infection for halzoun and remains, in the popular view, the only source. But, closer examination of the epidemiological study of Watson and Abdel-Kerim (l.c.) shows 2/21 persons to have consumed only lymph nodes. Rabbits experimentally or naturally infected with L. serrata eggs in the present study (and in one case naturally infected prior to use), were found to harbor nymphs in their livers, lungs (Figs.7,8),visceral lymph nodes and mesenteries. All these organs are included in the Sudanese dish of "marrara" prepared from sheep, goats, cattle or camels. The four cases interviewed in the present study likewise admitted eating lymph nodes, and these organs were definitely incriminated in the case report of Unat and Sahin (1950).

The exact animal-source of the liver eaten by persons contracting halzoun is worth consideration. Of the 21 cases (excluding two leech infections) described by Watson and Abdel-Kerim (l.c.), 15 had eaten raw goat liver. Examinations of goat and sheep livers for L. serrata in the present study showed 10% of the goat livers to have parenchymal infections, 40% to have

nymphs in the hepatic lymph nodes. Twenty per cent. of the ovine hepatic lymph nodes were found infected, but no infections of the parenchyma were seen. It is doubtful whether this difference in infection rate reflects a differential susceptibility between sheep and goats. It may be due to differences in animal husbandry practices or grazing habits of the animals, but until a comparative study can be done using sheep and goats known to have been raised in the same area the question cannot be definitely settled. The important point is that nymphs could be acquired by eating either sheep or goat liver, but that the latter entails greater risk.

A similar but more marked differential infection-pattern obtains with regard to mesenteric lymph node infection. Midway in the present study, it was recognized (and finally confirmed by abattoir workers and butchers) that the mesenteric lymph nodes of goats are dark, almost black in color, and that they are more commonly and more heavily infected than those of sheep (which are lighter in color). When this color difference was noted, comparison of the rate and intensity of infection could be done. As many as 150 nymphs have been recovered from a single mesenteric node of goats, while in repeated trials examining one kilogram of nodes per time, sheep-nodes yielded very few nymphs and were often negative in contrast to the large number obtained from the same quantity of caprine nodes.

This finding may be of some epidemiological significance, helping to explain the predominantly rural distribution of halzoun and why it appears to be less common than might be expected. Although lymphs nodes (Ma'ash) are commonly eaten in Lebanon (raw or, more commonly, very slightly broiled), sheep nodes are preferred for their better appearance and taste. (The reverse is true, however, in the case of liver to be consumed raw -- here goat is preferred). Most of the sheep slaughtered in Lebanon are imported, and are consumed

principally in the cities and larger towns and villages. Goats are locally raised in large numbers, and are probably eaten more commonly in smaller villages than are sheep. Although the statement can be made that halzoun is not commonly seen by physicians, this may not indicate that it is rare. The rural Lebanese is halzoun-conscious. He believes he knows the source of infection, and feels he can treat the condition if it is contracted. Thus he rarely consults a physician for treatment, and continues his ethnic food pattern, eating the animals he raises.

L. serrata nymphs possess both the tropisms and the ability to migrate to and within the area usually affected in cases of halzoun. Considerable symptomatology is evoked by their presence both in man (Unat and Sahin, 1950; Papadakis and Hourmouziadis, 1958) and in experimental animals (present study), and the picture produced is similar to that described for halzoun and for the marrara syndrome. In halzoun, the commonest symptoms (15/21 cases of Watson and Abdel-Kerim, l.c.) were irritation, itching and discomfort or pain in the throat beginning from a few minutes to a few hours after eating suspect food. These symptoms were prominent in both cases of confirmed L. serrara infection in man and were clearly evident in experimental animals. Variations in the length of time between eating and the onset of symptoms can be attributed to difference in the release-point of nymphs, those freed in the mouth attaching directly and provoking more rapid evolution of symptoms. It might be expected that if nymphs are swallowed in food, a variable time would be required for upward migration as shown in rabbits and dogs infected by stomach tube. This upward migration of swallowed nymphs appears to be the usual pattern in infections of the natural host, the dog, in agreement with Sinclair (1954), but contrary to the findings of Hobmaier and Hobmaier (1940).

Most (15/21) cases of halzoun recovered from acute symptoms in from half an hour to two days with nearly half (9/21) recovering in less than one day (Watson and Abdel-Kerim, l.c.). In the cases of human L. serrata infection, major symptoms lasted for 8 hours and one day respectively. In monkeys, symptoms began to be evidenced in from 10 minutes to two hours, but were severe for only about 4 hours or less and completely vanished within two days. Other symptoms such as lachrymation, coryza and cough are recorded in common for halzoun, the marrara syndrome and the human cases of nymphal L. serrata infection. They were likewise seen in animals given nymphs in the present study.

The symptomatology and pathogenesis of halzoun and the marrara syndrome can be explained reasonably well if L. serrata nymphs ingested in raw liver or lymph nodes are accepted as the etiology and the possibility of co-existing prior infection by egg is not excluded.

Mild to severe symptoms (depending on degree of infection) could, and probably would, be caused by the nymphs mechanically attaching to the pharyngeal and nasal mucosa. As the patient rids himself of the organisms by coughing or sneezing, symptoms would subside gradually and then disappear.

The high incidence of mature infection in street-dogs (43.3%) supports the possibility that man may commonly have visceral infection with this parasite in Lebanon. Such egg-initiated infections, chiefly of lymph-nodes, but of other organs as well, have been reported from man in various regions of the world for over a century (Zenker, 1854; Sagredo, 1924; Faust, 1927; Sonobe, 1927; Symmers and Valteris, 1950; Tobie et al., 1957; Gast-Galvis, 1960; Hunter and Higgins, 1960; Rendtorff et al., 1962). The prevalence of hydatid disease in this area is high (Pipkin et al., 1951; Schwabe and Abou Daoud, 1961), with the epidemiologic pattern of dog-sheep-dog. The normal cycle of

L. serrata is likewise probably dog-sheep-dog or dog-goat-dog. As with Echinococcus granulosus, man is probably interposed accidentally into the life cycle of Linguatula serrata by ingesting eggs from the dog. It is, however, possible that foxes (Vulpes v. palestina are very common on the barren hillsides where goats graze) are the principal definitive hosts, with rodents of one type or another as the major intermediate host in nature. Foxes have been reported as hosts in North Ireland (Griffiths and Sinclair, 1953). Goats would probably be more exposed while grazing to fox excreta than that of dogs, but dogs would have more ready access to goat material than foxes.

Animals harboring visceral nymph-infection are more reactive to orally superimposed nymphs than non-sensitized hosts. This is shown by the extensive and marked congestion of vessels, desquamation of the epithelium and the cellular response in the tissues of the upper respiratory tract in previously infected animals. In addition to its strong hooks and body-spines, (Figs. 3, 4), nymphs possess well developed salivary glands (Sambon, 1922) the secretions of which might be antigenic. The mode and place of attachment and mechanisms of feeding may thus explain the more severe symptoms and the pathogenesis of halzoun: congestive and edematous changes in the naso- and bucco-pharyngeal and laryngeal areas, in the trachea, and in the lungs. Eustachian tube and inner-ear involvement can be explained either on a basis of edematous closure of the orfice or by direct migration of nymphs into the Eustachian canal. Erratic migration of parasites in this way in hosts whose anatomical peculiarities are ill adapted to the parasite's normal route of travel (but which may be physiologically able to support it) have previously been reported (Schwabe, 1951).

In this connection, it is interesting to note that Eustachian tube involvement has been reported in dogs (Lapage, 1956). Dyspnoea in patients may be caused by reactions in the respiratory tract due to erratic nymphal migrations or perhaps may be based on hypersensitivity phenomena centered in the lungs. Although it has not been reported, superimposition of pneumonia could be easily postulated.

Patients rarely seek medical advice for treatment of halzoun unless complications such as dyspnoea, facial edema or Eustachian tube involvement are present. The traditional remedy, drinking or gargling with arak, was thought to be ineffective by Watson and Abdel-Kerim (l.c.) who advocated insufflation of lemon powder (citric acid) into the throat. In their paper, other (ineffective) folk remedies were listed such as hot tea, olive oil, strong tobacco infusions, raw onions and smoke from cigarettes or the arghileh (water pipe).

If nymphs of L. serrata are the causal agents of this condition, treatment of two types might be advocated. The first would be directed towards elimination of the nymphs from the affected area, the second toward symptomologic relief.

Local anesthetic sprays might have some effect on nymphs, relaxing their hold so as to facilitate coughing or sneezing them out. Topical application of anesthetic agents might likewise diminish the symptoms of irritation. More severe symptoms such as dyspnoea, dysphagia, edema of the fauces and involvement of the auditory canal may be based on hypersensitivity phenomena, so the use of antihistaminic drugs such as adrenalin or ephedrin might be recommended. In this regard it is of interest to note that one of four cases showing dyspnoea in the series of Watson and Abdel-Kerim (l.c.) was given adrenalin. In this patient, symptoms disappeared within 36 hours. In the other three cases, symptoms persisted for 3 to 7 days.

The host-parasite relationships in naso-pharyngeal linguatulosis may be considered in some regards as parasitologically unique. The adult has been reported once from man (Laudon, 1878), but is commonly capable of developing to maturity only in canid carnivores. However, infective-stage nymphs are capable of remaining alive in the nasal cavities of man (Unat and Sahin, 1950; Papadakis and Hourmouziadis, 1958) and some animals (present study) for limited or more prolonged periods. Man must be considered an abnormal and unsatisfactory definitive host. On the other hand, egg-initiated visceral infection in which man is an intermediate host to exactly the same stage as that ingested may be more common than generally recognised (Zenker, 1854; Sagredo, 1924; Faust, 1927; Sonobe, 1927; Symmers and Valteris, 1950; Tobie et al., 1957; Gast-Galvis, 1960; Hunter and Higgins, 1960; Rendtorff et al., 1962).

The host-parasite relationship is thus closely aligned but not identical with that seen in Trichinella spiralis and Taenia solium-Cysticercus cellulosea infections where in man can synchronously be host to two stages of the same parasite. In the case of L. serrata, man may at least temporarily be host to the same stage but in different organs simultaneously, with the resultant host response being chiefly determined by the organ-location of the agent.

Figure Legends

Fig. 1. Adult male (smaller) and female Linguatula serrata removed from the nasal cavity of naturally infected dogs. (Natural size.)

Fig. 2. L. serrata nymph, whole mount cleared in methyl salicylate, lateral view (43X).

Fig. 3. Head of L. serrata nymph to show hooks and supporting elements from lateral aspect; cleared in methyl salicylate (125X).

Fig. 4. Anterior end of L. serrata nymph from ventral aspect. To show cephalic papillae, median stoma and four lateral hooks with supporting bars. Note also the numerous rows of backward-directed spines covering the body. (Glycerin-mount; 125X).


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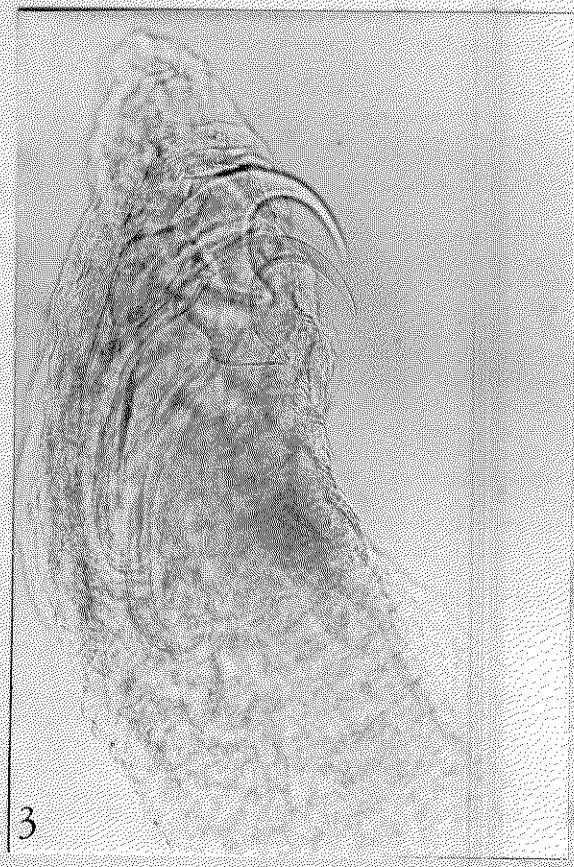
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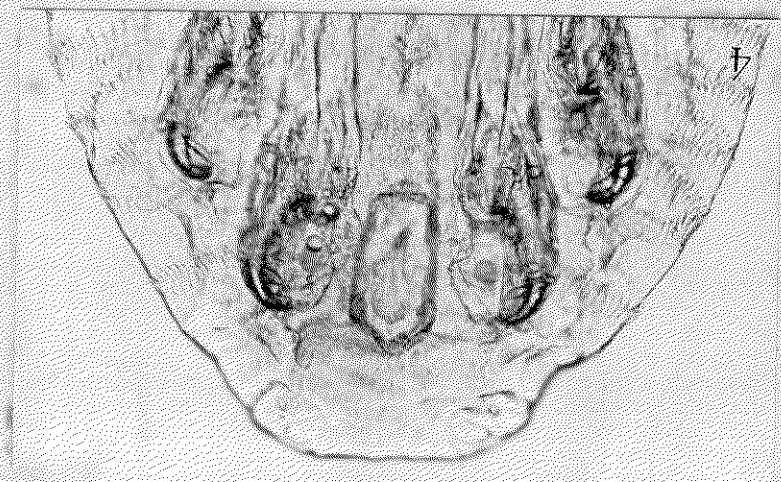
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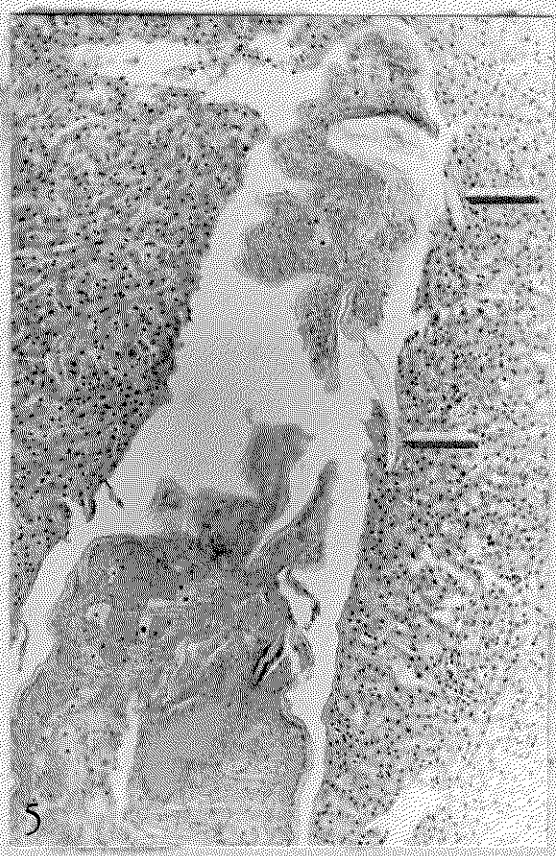
Figure Legends

Fig. 5. Tangential section through anterior end of a nymph in goat liver to show teeth (arrows). Note that the host response is minimal. (H&E, 125X).

Fig. 6. Granulomatous reaction in goat liver to molted cuticle of L. serrata nymph. Note the foreign-body giant cells. The central areas comprised mainly macrophages and lymphocytes with the peripheral zone made up of eosinophils and neutrophils. (H&E, 247X).

Fig. 7. Encysted L. serrata nymph in rabbit lung (natural infection). Note the thin wall of the capsule and the minimal host response. (H&E, 43X).

Fig. 8. Higher magnification of Fig. 7 to show capsule wall.



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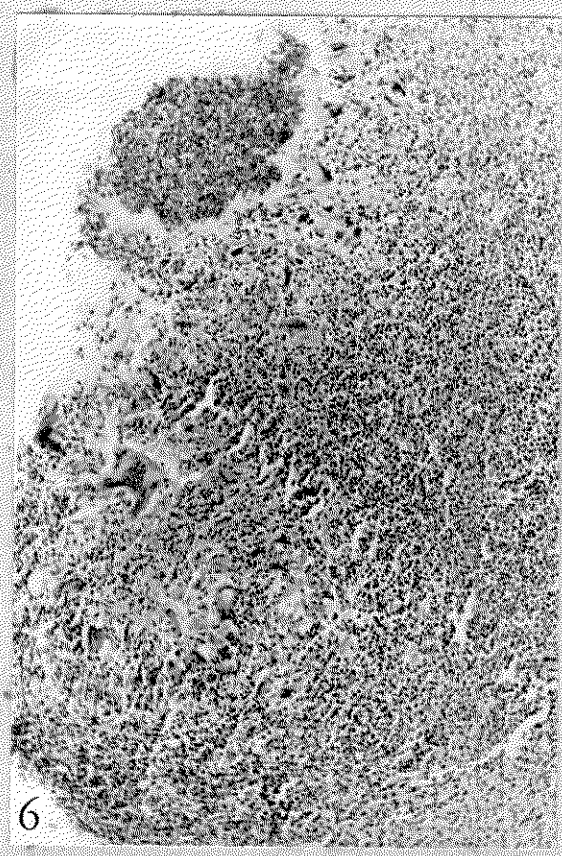

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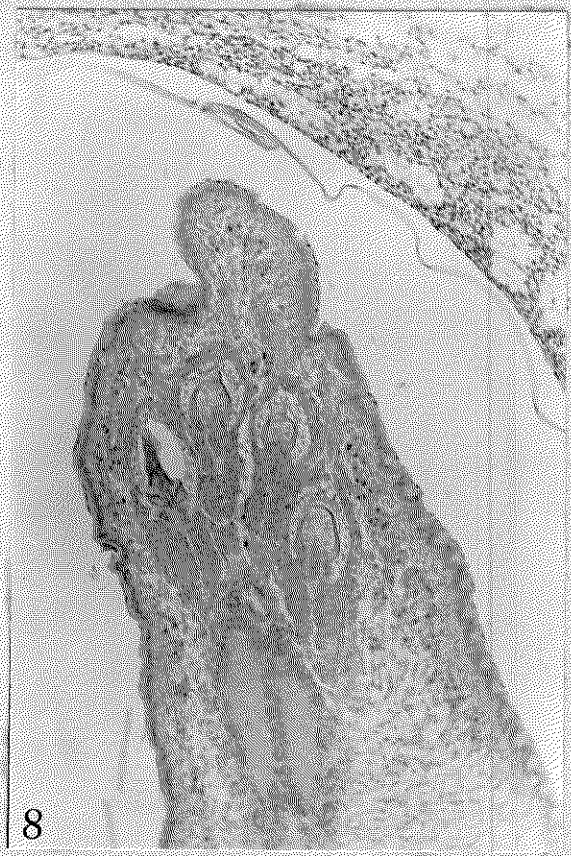

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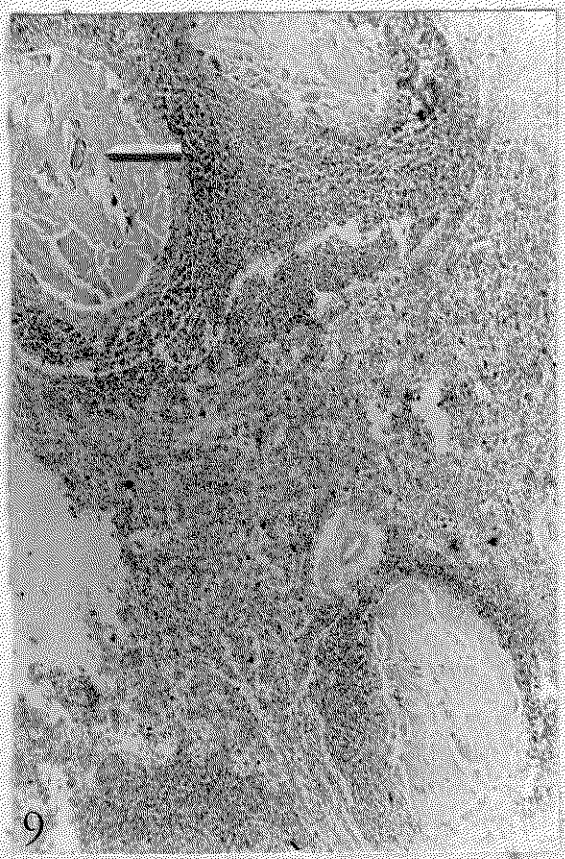
Figure Legends

Fig. 9. Calcifying remains of dead nymphs in goat lymph nodes. Note the surrounding cuff of lymphocytes and the remains of the nymphal hooks (arrow) (H&E, 43X).

Fig. 10. Off-median sagittal section of a L. serrata nymph in monkey tonsilar crypt killed 24 hours after oral administration of nymphs. Note the depth of penetration of the tooth (arrow) into the tissue. (H&E, 125X).

Fig. 11. Nasal epithelium of a monkey given nymphs 24 hours before sacrifice. Note the dilated lymphatics and infiltration of the submucosa by leukocytes. (H&E, 43X).

Fig. 12. Higher magnification of Fig. 11 to show the surface covered with P.M.N.-containing mucus. Eosinophils were numerous. (H&E, 125X).



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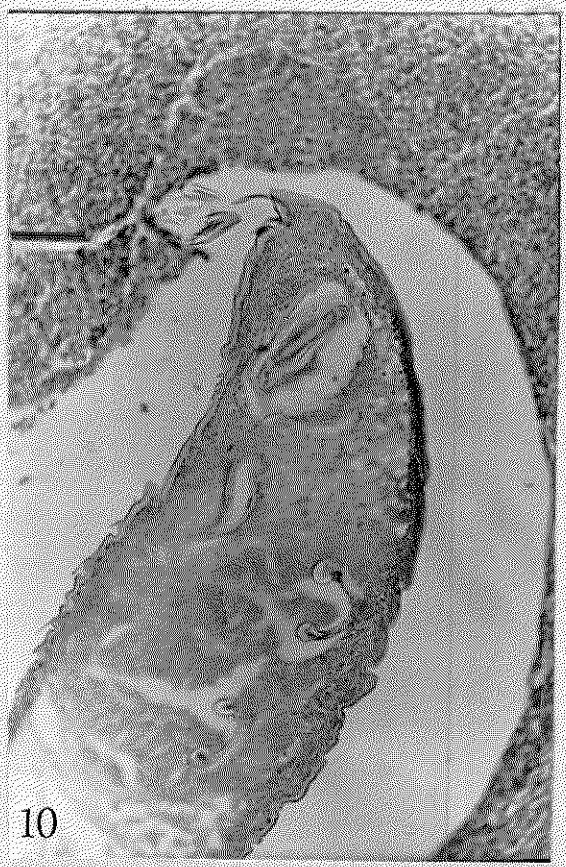

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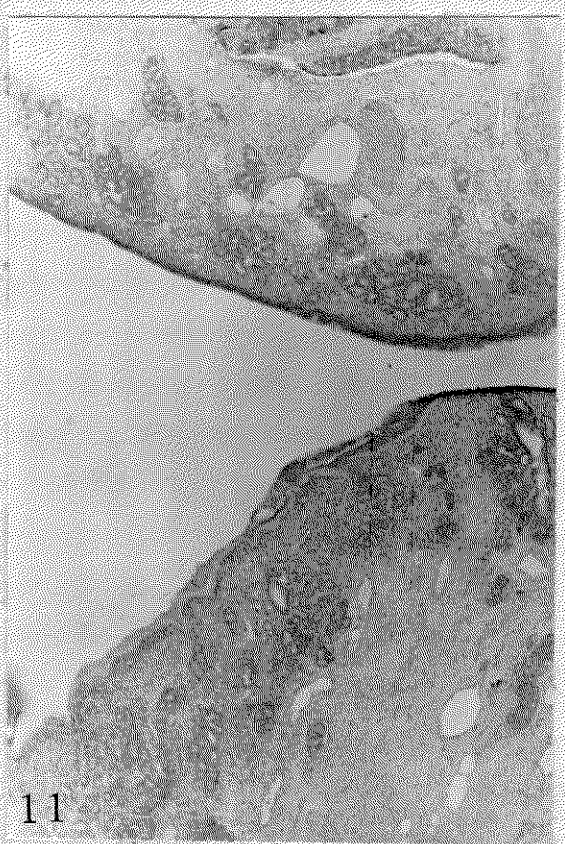

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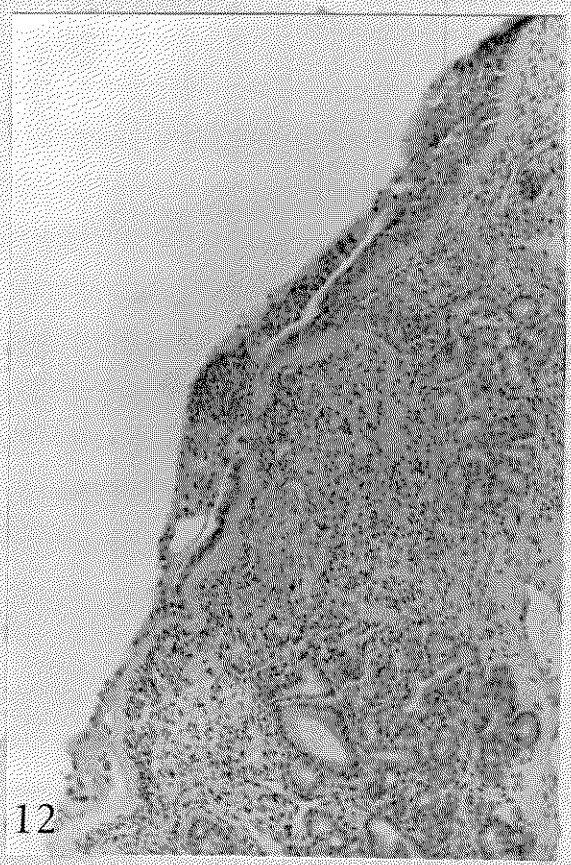

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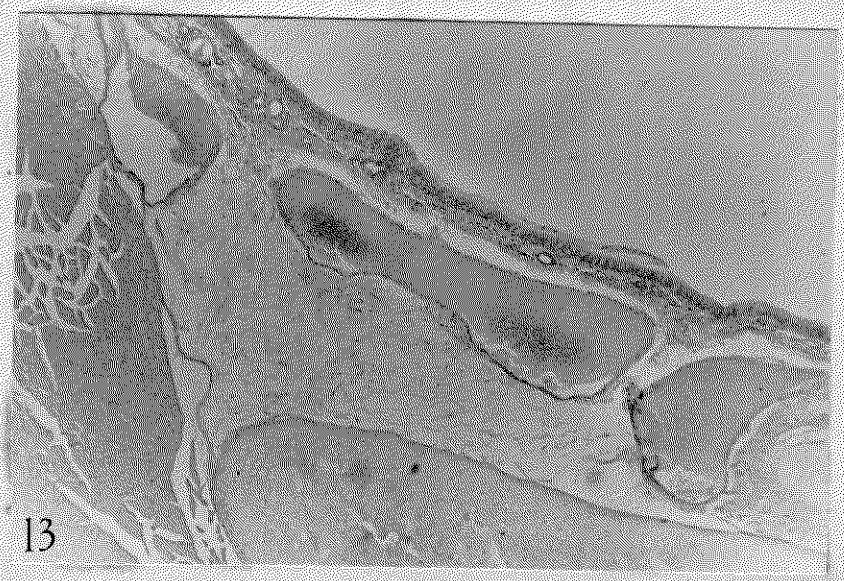
Figure Legends

Fig. 13. Nasopharynx of sensitized rabbit killed 4 hours after giving nymphs orally. Note the congestion of the blood vessels. (H&E, 43X).

Fig. 14. Higher magnification of Fig. 13 to show the adherent mucus covering the epithelium; congestion, slight edema and leukocytic infiltration of the submucosa. (H&E, 125X).



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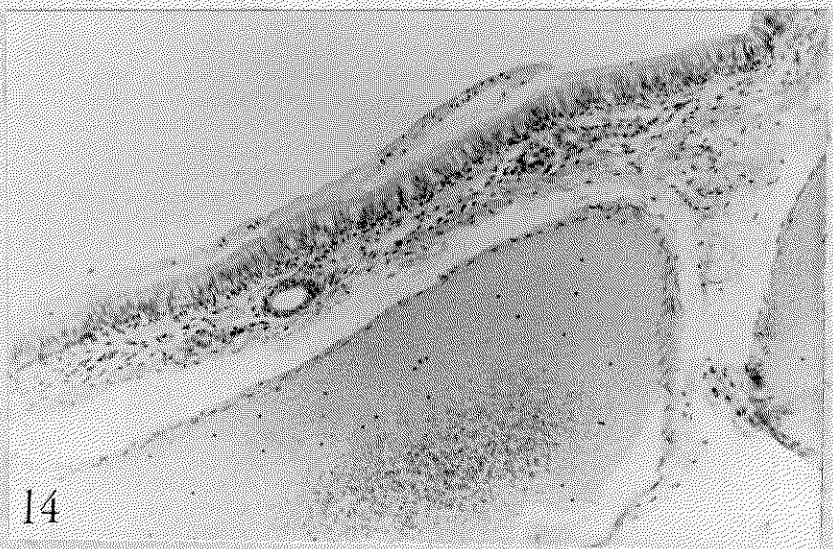

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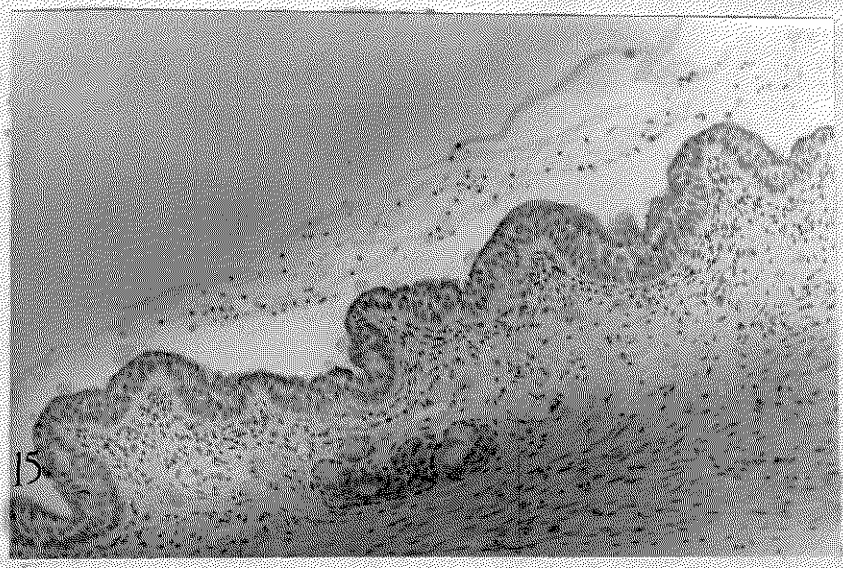
Figure Legends

Fig. 15. Larynx of a monkey given nymphs orally 24 hours before sacrifice. Note the cellular infiltration in the submucosa and the cells in the surface layer of mucus. Many of the cells in this mucus layer were eosinophils. (H&E, 125X).

Fig. 16. Trachea of sensitized rabbit killed 14 hours after oral administration of nymphs. Note the clumps of desquamated cells and leukocytes in the mucus film covering the ciliated epithelium. (H&E, 247X).

Fig. 17. Trachea of sensitized rabbit killed 24 hours after giving nymphs. Note the sloughing of the mucosa, cellular infiltration of the submucosa, congestion of the blood vessels and edema. (H&E, 125X).



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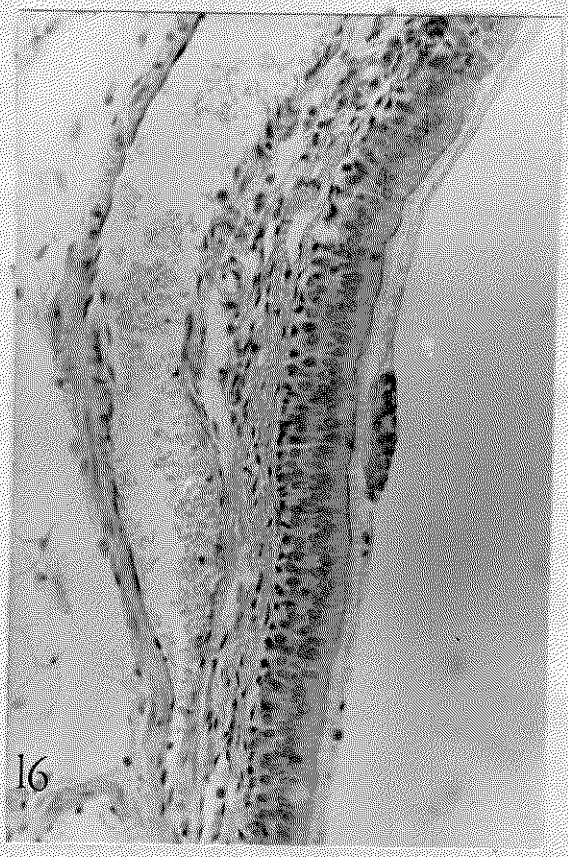

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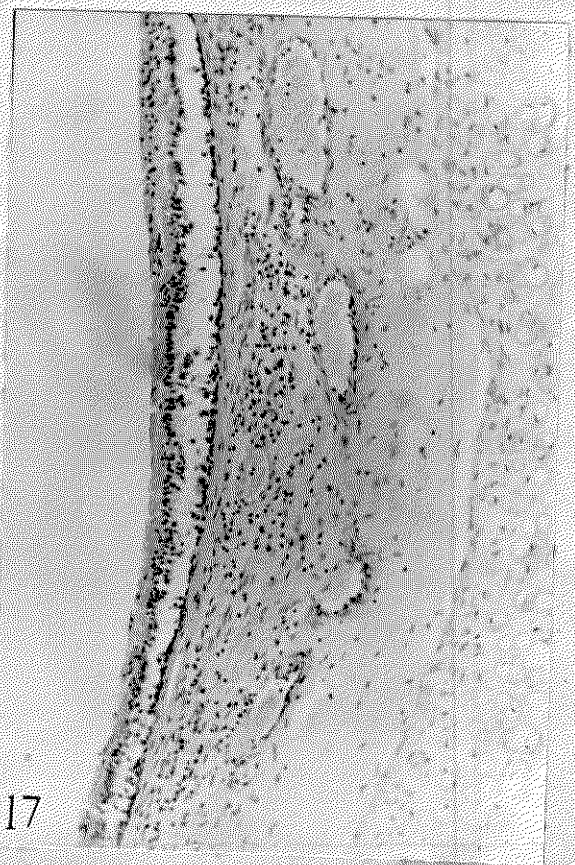

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