MONOGRAPHIC SERIES

No. 1 — JUNE, 1940

Acta Medica Philippina

VISCERAL COMPLICATIONS IN INTESTINAL HETEROPHYIDIASIS OF MAN

By

Candido M. Africa, Walfrido de Leon

and

Eusebio Y. Garcia

(A Contribution from the Laboratories of the Institute of Hygiene)

MANILA
PHILIPPINES
1940

VISCERAL COMPLICATIONS IN INTESTINAL HETEROPHYIDIASIS OF MAN *

By

CANDIDO M. AFRICA, WALFRIDO DE LEON

AND

EUSEBIO Y. GARCIA

Institute of Hygiene, University of the Philippines

(with 23 plates and 4 tables)

CONTENTS

* Presented under the auspices of the National Research Council of the Philippines, at the Third International Congress of Microbiology, September 2 to 9, 1939, New York City.

VI. PATHOLOGICAL ANATOMY

A. *Small Intestine*

B. *Heart*

1. *Gross Lesions*
2. *Histopathology*
   (a) *Myocardium*
   (b) *Valves*

Central Nervous System

1. *Brain*
2. *Spinal Cord*

D. *Lesions in Other Viscera*

VII. VISCERAL LESIONS IN OTHER ANIMALS

VIII. EPIDEMIOLOGICAL CONSIDERATIONS

A. *Mechanism of Infection and Dissemination of Parasites in the Body.*

B. *Geographical Distribution*

1. *General*
2. *Local*

C. *Environmental and Human Factors*

1. *Piscine Intermediate Hosts*
2. *Resistance of the Metacercariae*
3. *Reservoir Hosts*
4. *Age*
5. *Sex*
6. *Occupation*
7. *Customs and Habits*

IX. SYMPTOMATOLOGY

A. *Intestinal Heterophyidiasis*
B. *Cardiac Heterophyidiasis*

X. DIAGNOSIS

XI. COURSE, DURATION AND PROGNOSIS

XII. TREATMENT

XIII. PROPHYLAXIS

XIV. COMMENTS

XV. GENERAL SUMMARY

I. INTRODUCTION

A. OBJECT AND SCOPE OF PRESENT WORK

Human infections with members of the family Heterophyidae Odhner, 1914, have been observed in various countries of the world such as Egypt, China, Japan (*Heterophyes heterophyes*); China, Japan, Korea, Formosa, Northern Siberia, and the Balkan states (*Metagonimus yokogawai*). Craig and Faust (21) quote Khalil who says that "the worms of the genus Heterophyes are attached to the mucosa, at times lodged deeply in the crypts of the small bowel, where they produce a mild irritation accompanied by colicky pains and mucous diarrhea, with production of excess mucous and a superficial necrosis of the mucous coat." Similar pathological findings and symptoms are observed in infections with *Metagonimus yokogawai* (21). On the basis of their observations in man, cats, and dogs experimentally infected with two members of the genus Haplorchis (*Haplorchis pumilio* Looss, 1899 [*Monorchotrema taihokui* Nishigori, 1924] and *Haplorchis taichui* [Nishigori, 1924] Chen, 1936) Faust and Nishigori (29) came to the conclusion that the position of these worms in the host tissues is similar to that of *Metagonimus yokogawai.* They thought that the pathological changes due to the presence of these flukes are so slight that their clinical importance is almost negligible. They further thought that these parasites are eventually spontaneously expelled, thus freeing the body from the worms, provided reinfection does not occur. On the whole, human infection with heterophyid trematodes was taken by them as a benign condition without much clinical significance, and believed to be confined exclusively in the small intestine of the host.

Our findings have not been so. Our discoveries in connection with human autopsies in the Philippines involving certain members of Heterophyidae including members of the genus Haplorchis, have been published in several installments (1 & 2a, b, c, d, and e) since 1935. It was then we first discovered that the eggs of these flukes can filter into the general circulation and

cause serious lesions in the heart, apparently ending in cardiac failure, and later found that they can cause lesions in the brain as well. These published facts seem to have altered some of the previous views held by other investigators concerning the pathogenicity of at least certain members of this trematode family. And since our findings, as has been noticed, have awakened new and greater interest in this group of trematodes, not only among the pure parasitologists but among pathologists and clinicians, as well, it has appeared to us advisable to collect all our observations, which at present are scattered in several separate publications, in to one single monographic volume, for the convenience of workers in other countries who may be interested in the subject, or who may want to amplify on whatever start has been made in the Philippines. Additional data which we have gathered from new cases that have come under our observation since the publication of our last report will be included in this work. We have also decided to add our observations in experimentally infected laboratory animals (6a & b) and in naturally infected birds (2f & g); because in these investigations we have accumulated interesting data that in our opinion would help us a great deal in elucidating our points and in presenting properly our findings as a whole in connection with the human host. This work, which has covered a period of nearly four years (1935-1938), has been done in the Institute of Hygiene, University of the Philippines, conjointly by the Departments of Parasitology and Sanitary Bacteriology and Immunology, and has had grants-in-aid from the Board of Regents of the university.

B. DEFINITION, NOMENCLATURE, AND SYNONYMY

Hitherto, infection of both birds and mammals with members of Heterophyidae was believed to be confined exclusively to the intestine. Hence, to designate infection with members of this group of trematodes, the term heterophyidiasis, either with or without the prefix "intestinal" has been universally used. With our findings of adult flukes in the liver (2g) and pancreas (2f) in birds, and of eggs and a few adult flukes in the heart (1, 2a & c), and of eggs alone in the cerebro-spinal system (2b & d), liver, spleen and lungs (2a & c) in man, this simple designation of the infection will no longer be satisfactory. It is, therefore,

proposed to use the term heterophyidiasis only whenever it is the intention to convey the meaning of the infection without reference to any particular organ infected, and to qualify the term with the prefix "intestinal," whenever it is meant that the infection is confined to the intestine alone (either in its wall or in its lumen); and with the prefix "visceral" whenever the infection referred to involves one or more visceral organs. Owing to the extensive distribution of the parasites in man, which may consequently give rise, logically, to great variations in symptomatology, the visceral infection may be further divided into several types named appropriately after the organ or combination of organs that receives the brunt of the infection with the corresponding symptoms or symptom-complex. Thus, infection of the heart may be called cardiac heterophyidiasis; of the brain, cerebral heterophyidiasis; of the brain and spinal cord, cerebro-spinal heterophyidiasis; of the liver, hepatic heterophyidiasis, etc. In one of the human cases of cardiac failure presumably due to this infection reported in this work, eggs were found in the liver, lungs, and spleen, besides in the myocardium and mitral valve; while in another heart-failure case, the same were found in the myocardium as well as in the spinal cord, and were found associated with lesions characteristic of heterophyidiasis. Thus, cases of visceral heterophyidiasis, involving a multiplicity of organs and giving a large variety of symptoms, may be recognized in the future in a large enough number to justify the use of such a term as "general heterophyidiasis," just as the term "general paragonimiasis" is now used to designate a general infection with the lung fluke.

Following the dictum established by the Committee on Terminology of the American Parasitologists (81) regarding this matter, the term "infection" instead of "infestation" and "infected" instead of "infested" we will consistently use throughout this work in connection with the invasion of the host by the parasite and the subsequent establishment of the parasite in the host body.

In a critical review of the various members of the subfamily Haplorchinae, Chen (16c) came to the conclusion that the sub-family Monorchotreminae and the genus Monorchotrema should fall into synonymy with the sub-family Haplorchinae and the genus Haplorchis, respectively, as priorly pointed out by

Witenberg (90a & b), since *Monorchotrema taihokui* Nishigori, 1924, was found to be identical with *Haplorchis pumilio* (Looss, 1899). In accordance with this view *Monorchotrema taichui* Nishigori, 1924, *Monorchotrema yokogawai* Katsuta, 1932, and *Monorchotrema calderoni* Africa and Garcia, 1935, should now, as the correct names of these species. stand as *Haplorchis taichui* (Nishigori, 1924) Chen, 1936; *Haplorchis yokogawai* (Katsuta, 1932) Chen, 1936; and *Haplorchis calderoni* (Africa and Garcia, 1935) Africa 1938 (6c), respectively.

Prior to the appearance of Chen's paper (16c), there was no available description of *Haplorchis yokogawai* (*Monorchotrema yokogawai*) except in Japanese. Upon reading Chen's clear description of this trematode in English, one of us (6c) realized that the fluke we had assigned to *Monorchotrema taihokui* (*Haplorchis pumilio*) and erroneously given this name in all our previous publications in heterophyidiasis should have been assigned to the former species, instead. This view was confirmed when our material was compared with paratypes of *Haplorchis yokogawai* kindly furnished by Professor Chen, from Canton, China. The Philippine specimens have been found identical in all essentials with the Chinese material. Comparison was also made with the one specimen labeled *Monorchotrema yokogawai* furnished by Professor Yokogawa from Formosa; and this specimen was likewise found identical in essentials with the Philippine material. Chen (16c) previously had declared that the Chinese and Formosan specimens are identifiable as of the same species. When furnished with several mounted specimens of our local material, he declared in a personal communication to us that they clearly belong to *Haplorchis yokogawai.*

With regard to *Haplorchis taichui,* a careful comparison of the Philippine specimens assigned to this species with paratypes kindly furnished by Professor S. Yokogawa from Formosa and Professor Chen from Canton, has disclosed no significant differences between the Philippine and foreign specimens. Professor Chen who has examined several mounted Philippine specimens of this species stated in a personal communication that the Philippine and Chinese materials are identical. Several specimens of *Haplorchis taichui* were received from Palestine, through the courtesy of Professor G. Witenberg of the Hebrew University, Jerusalem, and upon comparison of this material with the

local specimens, again no difference between the materials compared could be elicited. On the basis of this observation, it is believed that this Philippine trematode can be correctly assigned to *Haplorchis taichui* (Nishigori, 1924) Chen, 1936.

Heterophyes brevicaeca Africa and Garcia, 1935, has been determined by Tubangui and Africa (83) to be a Microphallidae instead of a heterophyid, and hence redescribed and renamed by these authors *Spelotrema brevicaeca.* The position of Spelotrema and related genera in the scheme of classification of the trematodes has been a matter of uncertainty. Some writers have classified them together with Microphallus, Maritrema and Monocaecum under the sub-family Microphallinae of the Heterophyidae; while others have removed these different genera from the heterophyids and placed them in a separate family, the Microphallidae. According to Mueller and Van Cleave (62), however, "until the detailed morphology of Livenseniella, Spelotrema, Spellophalus, Monocaecum and Maritrema has been determined as compatible with that of Microphallus, these genera should be excluded from Microphallidae, though Poche (1926: 151) has attempted to relate them to the sub-family Microphallinae".

Diorchitrema pseudocirrata Witenberg, 1929, is, according to Alicata and Chattenburg (8), synonymous with *Stellantchasmus falcatus* Onji and Nishio (1924). We have not had the opportunity to compare the specimens we have assigned to *Diorchitrema pseudocirrata* with any of Onji and Nishio's original specimens but comparison of our typical specimens with Katsuta's (46b) text figure of *Stellantchasmus amplicaecalis* seems to bear out Alicata's contention. Dr. Alicata saw our material and compared it with his specimens of *Stellantchasmus falcatus* which he recovered from a Japanese in Hawaii, and he declared that the two materials are identical. Dr. E. W. Price saw our specimens of *Diorchitrema pseudocirrata,* and he likewise declared that our material is identical with *Stellantchasmus falcatus.* By right of priority, therefore, *Diorchitrema pseudocirrata* should fall into synonymy with *Stellantchasmus falcatus.*

C. HISTORY OF THE DISCOVERY

In the early months of 1935, two of us (C.M.A. and E.Y.G.) decided to find out what percentage of our dogs were infected

with *Echinococcus granulosus*, because about ten years previously de Leon and Leiva (50) reported the occurrence of a unilocular hydatid cyst in the lung of a native Filipino. In accordance with this program the small intestines of a large number of street dogs caught in Manila and environs were examined for the presence of this tapeworm. As this tapeworm is rather minute in size it was thought that in order to facilitate its finding the intestinal mucosa should be scraped, comminuted thoroughly in water, and the mixture passed through a series of sieves with from 20 to 100 meshes per linear inch, and the sieved material examined minutely for its presence. Instead of encountering this tapeworm, a large number of minute trematodes of various forms, which were easily recognized as members of the family Heterophyidae, were found one after another in rapid succession in the mucosal scrapings. Since no member of this family was hitherto reported in mammalian vertebrates in the Philippines, this finding excited considerable local zoologic interest. The search for Echinococcus was naturally abandoned and the whole interest focussed on this interesting group of trematodes.

Besides several new forms, two species of Monorchotrema thought to be identical with *Monorchotrema taichui* and *Monorchotrema taihokui* which Nishigori (66) described from dogs and birds (*Nycticorax nycticorax* and *Milvus migrans*) in Formosa, and *Diorchitrema pseudocirrata* which Witenberg (90a) described from dogs in Palestine, were recovered from the small intestines of a large percentage of the dogs examined. Knowing that infections with this group of trematodes are contracted by eating fish in the raw or semi-cooked state, we suspected at once the presence of these flukes in the small intestine of our human population in view of the prevalence of raw fish-eating in many sections of the country. Through the courtesy and kindness of the Head of the Department of Pathology and Bacteriology, College of Medicine, U. P., we were able to examine the small intestine of persons autopsied in the Manila City Morgue, which serves mainly the Philippine General Hospital. The latter institution, which in fact is the government's insular hospital, admits patients not only from Manila but from all over the Philippines. Our curiosity was amply rewarded in a short time by finding not only *Monorchotrema taichui* and *Diorchitrema pseudocirrata*, which we previously recovered from dogs, but

also an apparently new trematode parasite of the human intestine even before our tenth autopsy. The first two flukes were recovered from the small intestine of an adult Filipino, native of Leyte Island, but residing in Manila at the time of his death, due to acute cardiac dilatation; the last from the small intestine of an adult male Filipino, native of La Union, Northern Luzon, but residing in Manila at the time of his death, due to the same cause. A short time later *Monorchotrema taihokui** was recovered from an old man from the Visayas.

After 108 nearly consecutive autopsies had been made, we were able to show, besides members of other groups of trematodes (Plagiorchis and Echinostoma), heterophyids of one form or another, or in combination of two or three species, as recovered from 9 of the cases.

Although we were interested only in a zoologic way, nevertheless our curiosity was aroused when we noted that out of the 9 cases from which heterophyids had been recovered, 6 had died, according to the morgue protocols, of either cardiac beriberi or acute cardiac dilatation. Besides this interesting observation, we had noted previously in our dog autopsies that the flukes could still be recovered from the intestinal wall even after several scrapings had been made, a fact which indicated to us a deep-seated parasitism of these flukes in this organ; we were impressed by the minute size of the eggs of these flukes (some eggs being only about two times as large as the erythrocytes), a fact which suggested to us the possibility of these eggs' filtering into the lymphatic and blood streams; we failed to demonstrate eggs in the fecal contents of the cadavers by the ordinary smear method, and had had the same experience in our previous dog autopsies, no matter how large the size of infection. Moreover, we had found in sections of dog intestine dead flukes undergoing disintigration, leaving all the egg contents *in situ* in the submucosa. We noted further that only one of these nine human cases did not come from sections of the Philippines where the eating of raw fish is extensively practised as an established habit.

Although deeply impressed by these observations, we entertained only a faint suspicion of a casual relationship between the presence of these flukes in the intestine of these six cases and

* This fluke was later identified as *Haplorchis* (*Monorchotrema*) *yokogawai*.

the heart condition observed in them, because to us these facts then seemed totally unrelated. There was a deep rooted belief in us that the heterophyid trematodes were more or less inoffensive parasites of the small intestine, and to connect their presence in this organ with heart failure seemed fantastic. But the idea persistently challenged our attention; the clues literally danced before our thought, demanding attention, until we could not well ignore them. Pressed by the idea that since the eggs of these flukes could not be demonstrated in the fecal contents of the cadavers, they must be present elsewhere in the body, we decided at least to make further investigations; and since of all the organs the heart seemed to be the seat of trouble, we concentrated our attention to this locality for the possible presence of ova, or to find out at best what was wrong with it.

The autopsies had been performed some months before we came to our decision to do something more. Fortunately we were able to retrieve, one after another, five of the six suspected hearts from the pickling jars in the Museum of the Department of Pathology and Bacteriology, through the courtesy and kindness of its staff. Our next move was to ascertain the presence of eggs in these hearts. A large number of histological sections were made from cuts obtained from different parts of the first of the five hearts that were retrieved. After a prolonged search, no eggs were found. However, we knew that we were not dealing with a bacterial infection, or a toxic condition in which the effects are expected to be registered generally in the entire organ. We were aware that in helminthic infections the parasites or the effects of their presence are usually localized. Our problem then was to strike the particular locality infected. The problem, in fact, was to explore the whole organ.

Working under the information that the shell of trematode ova is believed to be made up of chitin material, and as such, indigestible, large strips of muscles from suspected spots of the heart were carved out, ground to pieces and artificially digested with artificial gastric juice at 40°C. When the fluid from the mixture was centrifugalized after sieving, heterophyid eggs, some still intact, others crinkled and still adhering to undigested muscle fibers, and still others broken to pieces, were found in the sediment. As at that time we were handling specimens of these flukes in our laboratory the possibility that those eggs we

found in the sediment were extraneous ones and did not come from the digested heart muscles was entertained. New centrifuge tubes and glass containers were, therefore, ordered direct from the store room and great care was taken to forestall any possibility of contamination. Eggs were again found in the sediment.

The presence of eggs having been determined in the first of the suspected hearts, histological sections were prepared from it and examined. After prolonged search, eggs were found in the histological sections this time, and what was most encouraging and interesting, these eggs were found to be associated with serious injuries in the form of embolism, capillary hemorrhages, and infarctions, not only in the myocardium but also in the subepicardial tissue. Identical findings resulted from the examination of the rest of the suspected hearts, except the sixth. The sixth heart, we were unable to deal with since it could not be produced.

Upon submitting those five hearts to further exploration we discovered in different parts of the myocardium more chronic lesions apparently specific in character or peculiar to this infection. Heterophyid eggs could almost invariably be found to be associated with these lesions. Degenerative changes with eggs fossilized in the calcified areas were also discovered. Two hearts labeled "beriberic", donated to us by the Department of Pathology and Bacteriology from its museum, were revealed to be positive also for heterophyid eggs under identical conditions. In both these hearts, the mitral valves were sclerosed, and eggs in large numbers were seen fossilized in the calcified matter in the interior of the valvular leaflets, changes which had been observed also in one of our first five cases. Cases with similar revelations have, since then, been noted from time to time in subsequent autopsies, up to this writing.

D. ACKNOWLEDGEMENTS

We desire to express our appreciation and thanks to Dr. Jorge C. Bocobo, then President of the University of the Philippines, for the moral support he extended to us at all times in the course of this investigation; also we wish to thank the Honorable Members of the Board of Regents of the university for their financial support in the form of liberal grants-in-aid, without

which this work would have remained unfinished; and to Dr. Fernando Calderon and Dr. Antonio G. Sison, former and incumbent Deans of the College of Medicine and Directors of the Institute of Hygiene (previously the School of Hygiene and Public Health), respectively, for the deep interest they have shown in our work; likewise to Dr. Hilario H. Lara, Assistant Director and Secretary of this institute, for valuable cooperation.

We also wish to thank particularly the following gentlemen for numerous courtesies and assistance in facilitating and making possible our investigations in the Manila City Morgue: Professor Liborio Gomez, Head of the Department of Pathology and Bacteriology, College of Medicine, University of the Philippines and Professors Regino Navarro, Juan Z. Sta. Cruz, Benjamin Barrera and Carlos Monserrat of the same department.

We also wish to acknowledge our gratefulness to Professor S. Yokogawa of the Government Medical College of Formosa, Taihoku; Professor H. T. Chen of the Department of Biology, Lingnan University, Canton, China; Professor G. Witenberg of the University of Jerusalem, for their kindness in lending and, in certain instances giving to us specimens of various members of Heterophyidae for comparison with local materials. We also wish to express our thanks to Dr. Deogracias Villadolid, ichthyologist of the Bureau of Science, Manila, for identifying the fishes involved in this investigation.

To Professors W. W. Cort, Robert Hegner, and Justin Andrews of the School of Hygiene and Public Health, Johns Hopkins University; to Professors Richard P. Strong, Jack H. Sandground and Donald L. Agustin of Harvard Medical School; to Professor Hans Vogel of the Tropen Institute, Hamburg; to Dr. E. D. W. Greig of the University of Edinburgh, Scotland; to Dr. Paul Bartsch, of the Smithsonian Institution, Washington, D. C.; to Professor R. Wetzel of the University of Berlin; to Professor Horace H. Stunkard of New York University; to Dr. Benjamin Schwartz of the Bureau of Animal Industry, Washington, D. C.; to Professor William S. Carter, formerly of the International Health Board, Rockefeller Foundation and now Dean of the Medical School, University of Texas; to Professor E. C. Faust of Tulane University, New Orleans; to Professor Asa S. Chandler of Rice Institute, Texas; and to Professor W. G. MacCallum of Baltimore, and to others, the authors wish to express their

grateful appreciation for kind words of encouragement. Special thanks are due to Dr. E. W. Price of the Bureau of Animal Industry, Washington, D. C. for many helpful suggestions in connection with the zoological aspect of this work.

Finally, we wish to thank our colleagues in the Department of Parasitology, Institute of Hygiene, University of the Philippines, Drs. Ana Vasquez-Colet and Pedro G. Refuerzo for valuable technical assistance; and also Messrs. Florentino Makabuhay and Alejandro Arenas, artists in the same institution, for some of the illustrations that appear in this work.

II. REVIEW OF THE LITERATURE

A. SURVEY OF LOCAL TREMATODES

1. NON-HETEROPHYID TREMATODES

According to Musgrave (64) trematode infections, next to protozoan diseases, are the most important parasitic conditions to be met with by medical men in the Philippines. This statement was evidently inspired by the discovery of the endemicity of schistosomiasis japonica in the Islands by Woolley (91) in the previous year and the subsequent finding by himself of a large number of cases of this disease both at the clinic and autopsy table; and by his own (Musgrave's) discovery of 17 authoctonous cases with 8 autopsies of *Paragonimus westermanni* infection. In addition to these two important trematode infections, Musgrave mentioned 18 cases of *Opistorchis sinensis* (probably referring to *Clonorchis sinensis*) infection, one infection with *Opistorchis noverca* (?) Braun in a Chinese, and one autopsy case, each of what he suspected were *Fasciola hepatica* and *F. gigantica* infections.

That schistosomiasis, as predicted by Woolley (91) would be proved endemic in the Philippines and that it would be found in increasing number among the native population as the years go by has been amply demonstrated by the reports of Garrison (36a), Strong (78), Crowell and Hammack (22), Willets (89), Mendoza-Guazon (59) and Africa and Garcia (4a). Further confirmation of its endemicity followed Tubangui's work (82a), which incriminated *Blanfordia quadrasi* Mollendorf as the molluscan host of *S. japonicum* in the Philippines. It is

generally believed that in this country this trematode disease is largely confined to the islands of Leyte and Samar, at present, although there are indications of its spread to other areas.*

To judge from Musgrave's report (64), in which 17 cases of paragonimiasis were collected in less than one year from widely different points in the country, this disease must be fairly common among the natives. In fact, he said that the discovery of this number of cases in less than one year by one observer did not, in his opinion, indicate any exacerbation of the infection nor any change in the class of available material, but, in his belief, was due to a closer observation and study of that which was at hand. Musgrave was at the time dean of the Government Medical School. However, it is interesting to note that in spite of the tremendous growth of hospital facilities and more extensive practice of autopsy that have developed in the country since Musgrave's administration, not to mention the increase in the number of workers on tropical diseases, no one later seems to have had the same experience that Musgrave had. Cases of this infection are from time to time noted in hospitals and in private clinics, but they are few and far between. In a little less than two decades of microscopical work in an institution connected with the Philippine General Hospital, the largest in the Philippines and serving the whole archipelago, one of us (C. M. A.) came across only four cases of clinical paragonimiasis, which were referred to him by private physicians. Our colleagues in the Manila City Morgue, which also serves this hospital, claim a similar experience. There is no doubt, however, that paragonimiasis is endemic in this country, although the foci of endemicity, unlike in the case of schistosomiasis, have not been determined nor the molluscan and crustacean intermediate hosts of the fluke worked out.

Although Musgrave expressed intention in his paper referred to above to publish something on his human material involving *Opistorchis sinensis* (*Clonorchis sinensis*), *Opistorchis noverca, Fasciola gigantica* and *F. hepatica,* there seems to be no publication by him on these subjects available either in local or foreign literature. It is to be regretted that he also failed to

* Recent unpublished findings of Dr. Marcos Tubangui of the Bureau of Science, Manila indicate that schistosomiasis japonica is also endemic in Agusan and Surigao, Mindanao, and in Mindoro.

mention, except in the case of *Opistorchis noverca*, whether his subjects were indigenous natives or foreign orientals who established their residences in the Philippines. The endemicity of clonorchiasis in the Philippines is still questionable since so far as is known this infection is limited to the members of the Chinese community. Although a large number of the Philippine Chinese population are native born, many of them make periodic visits to the land of their forebears. One of us (C. M. A.) has on quite a number of occasions during the last nineteen years come across eggs of Clonorchis in the feces of patients referred to him by private physicians in Manila, but in all cases the subjects were Chinese who had resided in China. With regard to Opistorchis infection there is no doubt that it is endemic in the Philippines since Wharton (88) reported a species of this genus which he described as a new form (*Opistorchis wardi*) occurring in the bile ducts of 50 per cent of cats dissected in the College of Medicine, U. P., in Manila. Musgrave was probably dealing with this species when he referred to *Opistorchis noverca*. The same is true with *Fasciola hepatica* and *Fasciola gigantica* infections, since both flukes are common in the bile ducts of native cattle slaughtered in the public abbatoir in the same city. The endemicity of fascioliasis has been further confirmed by de Jesus (44) who has implicated *Lymnea philippinensis* as the molluscan host of *Fasciola hepatica* in this country. So far as known, however, not a single case of fascioliasis in man has been reported in the Philippines.

That Opistorchis infection is also present among the human population seems to be indicated by the results of Garrison's (36a) fecal examination of 4,106 prisoners in Bilibid Prison, among whom he found 11 infections of this trematode. Five of these eleven prisoners with Opistorchis were native Filipinos, five were Chinese, and one was a Japanese. However, in the light of present development which indicates that heterophyid infections occur among the human population in this country with relative frequency, the possibility that Garrison was dealing with eggs of the latter group instead of opistorchid ova in at least a proportion of his cases cannot be ruled out, because the ova of these two groups of trematodes are very similar both in size and in shape, although our experience seems to indicate that the eggs of heterophyids are harder to detect in the stool of infected persons than are those of the opistorchids.

About three decades ago Garrison (36b) discovered a new trematode from the intestine of an Ilocano prisoner in Bilibid Prison, Manila which he named *Fascioletta ilocana*, now called *Euparyphium ilocanum*. Subsequent examination of the stools of over 5,000 native inmates of this prison representing all parts of the islands showed only five infections with this fluke. Significantly, all five of the infected persons came from the northwestern provinces of Luzon, and two of them including the one from whom the worms were obtained, had lived all their life in the province of Ilocos Sur. Accordingly, Garrison opined that the parasite may not be equally distributed throughout the Islands. Subsequent unpublished observations by us and other observers seem to bear out Garrison's opinion, and now this infection is generally believed to be confined to the Ilocanos. We have on various occasions met with this infection both in autopsy cases and in routine examination of feces of patients in the Philippine General Hospital; but in all cases the subjects were from the Ilocano provinces except one, who was from Zambales, a province closely adjacent to the south of the former with a large number of Ilocano elements. Primarily a rat parasite, "its life cycle, elucidated by Tubangui and Pasco, explained its occurrence only in the Ilocano, for the cercariae after escaping from the first intermediate host, *Gyraulus prashadi*, penetrate into and encyst in various kinds of snails, including *Pila luzonica*, which is habitually eaten raw by the Ilocano but not by other Filipinos" (15). The pathogenicity of this trematode is considered *nil* at least for the present. Chen (16a & b) states that this fluke is present in 13.5 per cent of native dogs and cats in Fukien and Canton, China, so that its distribution is apparently not strictly confined to the Philippines.

A lone case of Plagiorchis sp. infection was recorded in the Philippines by Africa and Garcia (4d). Several specimens of this fluke together with *Heterophyes brevicaeca* (*Spelotrema brevicaeca*) were recovered at autopsy from the intestinal scrapings of an Ilocano subject, who, as far as could be determined, had never been out of the country. This infection is the first in this genus ever reported in man. In this connection, McMullen (58) working in the United States apparently succeeded in establishing a human infection with *Plagiorchis muris* by feeding the latter with metacercariae found in *Stagnicola emargina-*

ta. This author observed precocious development of the cercariae into metacercariae without leaving the sporocyst in *Plagiorchis muris* and *P. proximus,* although the usual second intermediate hosts of these flukes are aquatic insects. Because raw snails are habitually eaten by the Ilocanos, as pointed out above, and the grub* of an unidentified aquatic insect is considered a delicacy in certain parts of Central Luzon (4d) more infections with this trematode are likely to occur in these sections of Philippine population.

Human infection with *Fasciolopsis buski* has been, although rarely, encountered in the Philippines, but in every instance so far as we could gather from private physicians who handled these cases, the patient has been a Chinese, who probably contracted his infection abroad. At least there is no authentic record yet of this infection among native Filipinos. Schwartz (74) reported eggs of this fluke in the stool of several Chinese in the town of Jolo, Sulu Archipelago, P. I.; but it is not definitely known whether the infection was contracted locally or in China. Extensive search for this fluke in native pigs slaughtered in Manila has so far failed. Most likely this trematode infection like clonorchiasis, is not endemic in the Philippines. However, the possibility of the eventual spread of these two trematode infections to the Philippines should be considered because this country has perhaps one of the richest and most varied fish and molluscan fauna in the world. Since a variety of Eliocharis, an edible equatic plant in which the metacercariae of Fasciolopsis encysts, is present in this country, the possibility of the introduction of fasciolopsiasis here should always be kept in mind; and even if such a plant is lacking here, the lack cannot be taken as a safeguard against the introduction, since the metacercaria of this fluke encysts in other aquatic plants as well.

Refuerzo and Garcia (73b) described a new species of Neodiplostomum (*N. Larai*) from the cattle egret. That the parasitic fauna of the Philippines is exceptionally rich in trematodes may be appreciated from the work of Tubangui (82b), in which he listed 65 species of flukes belonging to the sub-class Digenea

* The grub of an unidentified insect called by the natives of Central Luzon "Kamamaro" which lives in rice paddies is considered by the natives a delicacy in this region.

distributed among 57 genera and representing 24 families. Of these 66 species, 37 were either new or just recently described by this author.

2. Heteropyid Trematodes

Although the Philippine Islands lie in the bosom of the Orient where a large number of heterophyid trematodes have been known for a long time to occur as natural parasites of man and other fish-eating mammals, as well as of birds, yet knowledge of this group of parasites infecting mammals is new in this country. Prior to 1935 when Africa and Garcia (4b & c) began to find members of this group in the intestines of dogs and later of man (1b) at autopsy, the only members of the family Heterophyidae known to occur in the Islands were *Phagicola pithecophagicola* described by Faust (28b) from the intestine of monkey-eating eagle (*Pithecophaga jefferyi*), *Haplorchis anguillarum* described by Tubangui (82b) from the intestine *Anguilla mauritiana,* and *Scaphanocephalus adamsi* (82b) represented by some immature forms encysted in the fins and under the scales of *Lepidaplois mesothorax.* After a restudy of the original material, Tubangui and Africa (83) have agreed with Chen (16c) that *Haplorchis anguillarum* does not belong to the genus Haplorchis Looss, 1899, and should be assigned to the genus Galactosomum Looss, 1899, to which this parasite has closer affinity. Africa and Garcia (4b & c) described five new members of the family Heterophyidae: (1) *Heterophyes expectans* (2) *Stictodora manilensis,* (3) *Apophallus eccentricus* and (4) *Monorchotrema calderoni* from the small intestine of dogs, and (5) *Heterophyes brevicaeca* from the small intestine of man, all as natural infections. On account of a number of morphological features which separate *Heterophyes expectans* from the established members of the genus Heterophyes, as pointed out by the authors in their original descriptions of this fluke, which Tubangui and Africa (83) consider to be of more than specific importance, the latter authors have proposed the new genus Heterophyopsis * for this trematode. More recently Yamaguti

*The creation of genus Heterophyopsis by Tubangui and Africa (1938) for the reception of Heterophyes expectans Africa and Garcia, 1935, brings to two the number of genera of the family Heterophyidae which have a ventral sucker independent of the genital sac, the other being the genus Heterophyes which heretofore was the only genus having the genital sac independent of the acetabulum.

(92) erected the genus Pseudoheterophyes for the reception of *Heterophyes continuus* Onji and Nishio, 1924, which he rightly believes does not belong to the genus to which it was assigned, just as Tubangui and Africa believe *Heterophyes expectans* should be given a generic status. Since *Heterophyes continuus* and *Heterophyopsis expectans* appear to be morphologically identical, and since the creation of the genus Heterephyopsis antedated that of Pseudoheterophyes, Heterophyopsis should stand as the accepted name of the genus. In this connection we should like to point out that when *Heterophyes expectans* was described from dogs in Manila its authors were unaware of the existence of *Heterophyes continuus* of Onji and Nishio. It is interesting to note that both materials were assigned to the same genus quite independently. In the same paper as has been pointed out previously, Tubangui and Africa have decided that *Heterophyes brevicaeca* is not a Heterophyidae but a Microphallidae, and consequently assigned it to the genus Spelotrema, to which, they think, it is more closely affiliated.

Besides these new heterophyids, three more members of this family which could not be differentiated from *Monorchotrema taichui* Nishigori, 1924 (*Haplorchis taichui*), *M. taihokui* Nishigori, 1924 (*Haplorchis pumilio*, 1899) and *Diorchitrema pseudocirrata*, respectively, were encountered in the Philippines as natural infection in both man and dog. (4b). Lately, as pointed out previously, it was realized that the species we assigned to *Monorchotrema taihokui* (*Haplorchis pumilio*) should have been assigned to *Monorchotrema yokogawai* (*Haplorchis yokogawai*) instead. However *Haplorchis pumilio* is also present in the Philippines, as shown by the finding of this heterophyid in experimental kittens and pups fed with certain species of both fresh-water and marine fishes such as *Ophicephalus striatus, Glossogobius giurus* and *Ambassis buruensis* and others (85b).

Garcia and Refuerzo (34) further enriched the Philippine heterophyid parasitic fauna by finding two more species of Stictodora. One was described as a new species (*Stictodora guerreroi*) from the small intestine of both dogs and sea-gulls (*Larus ridibundus*) as natural infection, and the other, which was recovered from the intestine of dogs alone, is believed to be identical with *Stictodora sawakinensis* Looss, 1899. Refuerzo and Garcia (73c) also described a new species of the genus *Pygi-*

diopsis from the small intestine of a white-breasted sea eagle, *Haliaetres leucogaster* (Gmelin), which they named *Pygidiopsis marivillai.*

Africa, de Leon, and Garcia (2f) reported the occurrence of huge collections of eggs in the pancreas of *Larus ridibundus* presumably those of Stictodora spp. found parasitising the small intestine of this bird. Similar findings, although involving another organ (liver), were made by the same authors (2g) in cattle egret (*Bubulcus ibis coromandus* Boddaert). Dissection of a considerable number of this bird showed that more than fifty per cent of them harbored intestinal infection of Monorchotrema (Haplorchis) spp. either *Monorchotrema* (*Haplorchis*) *yokogawai,* or *Monorchotrema* (*Haplorchis*) *taichui* or both. A small proportion of the dissected birds showed extention of the infection by the adult worms in the bile ducts but none in other organs. These findings are specially interesting because according to Witenberg (90a) one of the main differences between the family Heterophyidae and the family Opistorchidae is that the former parasitise the intestine, while the latter are found in the bile ducts of the final host.

Two more members of the family Heterophyidae were added to the growing list of Philippine trematodes when Africa (6c) described two new species of the genus Haplorchis; namely, (1) *Haplorchis vanissima* recovered from the intestinal scrapings of an adult male Filipino, native of Bohol island, who was autopsied in the Manila City Morgue, and (2) *Haplorchis sisoni* recovered from the small intestine of various laboratory animals fed with metacercariae obtained from *Therapon plumbeus* (Kner). In the same paper, the author recorded the finding of *Haplorchis calderoni* (*Monorchotrema calderoni*), previously described as from the dog, as a natural parasite of man also, thus rounding a total of five heterophyids naturally infecting man in the Philippines; that is, if *Heterophyes brevicaeca* is really not a heterophyid but a microphallid as posited by Tubangui and Africa (83).

The metacercariae, particularly those of the heterophyids, of our fishes—fresh-water, brackish water, and marine—were likewise practically unknown. Preliminary examination of only half a dozen of our common fishes has shown that they are heavily infected with various forms of metacercaria, of the

family Heterophyidae, judging from the results of feeding experiments in which animals fed with a single species of fish were found to yield as many as eight different species of heterophyids (85a). Further work by the same authors (85b) incriminated ten more Philippine fishes as second intermediate hosts of heterophyid trematodes, bringing the total number of our fishes so far known to contain heterophyid metacercariae to sixteen.

Members of other trematode families have also been recovered from experimental animals fed with metacercariae from several species of Philippine fish; namely, one echinostomatid and one strigeid, represented by *Echinochasmus novalichesensis* Tubangui, and an unidentified Neodiplostomum, respectively.

Judging from these preliminary findings, the Philippines bids fair to be designated in the future as the paradise of heterophyid trematodes, and consequently of students of this group of flukes. And it may well be that this country should bear such a designation; because the Philippines has, perhaps, the richest and most varied fish (41a & b) and molluscan (27) fauna in the world. In the preface of his book (Catalogo de la Fauna de Filipinas-Moluscos y Radiados) Fray Elera (27), referring to the molluscan fauna of the Philippines, says: "La malacologia de estas Islas ha sido siempre tenida como una de las mas abundantes y variadas del universo, y sus especies, muchas peculiares y exclusivas, notables por su forma, tamaño y coloracion. La situacion geografica del Archipélago, su clima con una temparatura elevada y bastante uniforme, sus extensas y variadas costas y la abundancia de la vegetacion y de lluvias son circumstancias que en gran manera favorecen el desarrollo de estos animales. La simple lectura del presente volumen justifica perfectamente la frase del sabio naturalista Fischer, que en su Manual de Conchyliologie llama a estas Islas el paraiso de los moluscos." Herre (41a) writing about fishes, in his paper appraising the Philippines as an ideal site for a biological station, says: "In the Philippine waters is perhaps the richest and most varied fish fauna in the world, probably a tenth of the existing species occurring in the seas, lakes, and rivers of the archipelago. Not only do we find there the otherwise unrivalled littoral fish life of the East Indies, as well as the wide-roving or cosmopolitan pelagic fishes, but to these are added

forms which stray over from the coast of China or wander southward from Japan. So little known are the fishes of the Philippines that we never make a collecting trip without bringing in a new species, or something Ruppel discovered in the Red Sea nearly a century ago and which has not been collected since, or some fish hitherto known only from the South Sea Islands."

According to Dickerson (24) the Philippine bird fauna includes about seven hundred fifty species in two hundred ninety-three genera with a high percentage of endemism. A large number of these birds are fish-eaters. Considering these facts and the added fact that the habit of eating raw fish, both fresh-water and marine, is prevalent among a very extensive portion of the population, the reader may have a pretty fair idea of the Philippine possibility of becoming one of the richest fields in the world for hunters not only of heterophyid flukes but of other groups of trematodes as well.

B. OTHER HELMINTHS THAT HAVE LODGED

1. In the Heart

Musgrave (64) included in his report on paragonimiasis in the Philippines a case in which adult flukes and eggs were found in the pericardium; but, unfortunately, he failed to give an account of any associated lesion. Ferguson (30) made mention of the finding of a lone calcified egg presumed to be of *Schistosoma hematobium* in a cancerous infiltration of the pericardium. Africa and Sta. Cruz (5b) reported the occurrence of *S. japonicum* ova associated with typical pseudotubercles in sections of the myocardium obtained from the interventricular septum of the heart of an adult Filipino, in whom eggs of the same worm were also found in the intestinal wall, liver, kidneys, lungs and brain.

Many cases of hydatid cyst occurring in the heart and causing cardiac symptoms and eventual failure of function of this organ have been reported in the literature. Martin and Crespigny (57) have reported a case of a 49-year old Australian farmer who complained of shortness of breath and edema of the lower extremities. Fluoroscopy showed the heart pushed to the right of the sternum and a large non-pulsatile, rounded opacity in the left thoracic cavity as large as a foetal head at term. Autopsy confirmed the diagnosis of hydatid cyst, which

was found to be multiple in the right and left sides of the heart. One of the cysts invaded the myocardium to such a degree that in several places a layer of fibrous tissue, only one millimeter in thickness, separated the two cavities.

Hynd (43) has reported a case of a young apparently healthy man, 24 years old, suddenly rushed to the hospital in a moribund condition. Before he died he was markedly dyspneic and comatous. Autopsy showed a large infarction of the right lung. The right ventricle was full of cysts varying in size from a pear to a marble. Closer examination showed a cavity as big as a hen's egg containing cysts in the wall of the right ventricle just under the endocardium near the apex. The wall of the cavity had ruptured, the cysts passed out of the right ventricle and carried to the branches of the pulmonary artery, where several cysts were found. A similar case has been reported by Finney (31) in India.

Another remarkable case of hydatid cyst in the heart was reported by Goldsworthy (37), again from Australia. The case involved a 40-year old female, who for a year before her death had fainting spells and complained of swelling of the right side of the neck, sensation of pressure of the wind-pipe and prominence of the veins of the thorax and upper abdomen. Autopsy showed a chronically collapsed lung. The right pulmonary bronchus and artery were pressed between mediastinal cysts anteriorly and the vertebrae posteriorly. More recently Khalil (47c) has reported a case of a 30-year old Egyptian who was found dead and upon autopsy revealed a large hydatid cyst (10 cm. $\times$ 11 cm.) in the wall of the left ventricle obliterating the apex. Rupture of the cyst into the left ventricular cavity, where daughter cysts were found, was believed to have caused the death of the patient, who had a previous history of fits of unconsciousness lasting for a long time. A case similar to Khalil's was reported by Anderson and Patterson (9). As early as 1878 Bobwiez wrote a thesis: "Hydatid Cysts in the Human Heart" in which he stated, "The observations of pathologic anatomists have taught us that echinococci, cysticerci, and a great variety of tumors may occur in the heart muscle. In some cases parasites or tumors may produce a clinical picture of heart disease. Even in such cases, however, the disease during the patient's life will often be comfounded with more common and frequent morbid conditions". Other authors who have reported on hydatid cysts

in the heart are Bacaloglu, Balan, Ballif and Vasilescu (11), Agote and Bianchi (7), Gonzales and Mosto (38), and Morquino (60), and Pico Duni (70).

We expected to find much reference in the literature concerning the occurrences of Trichinella larvae in the heart. On the contrary, however, we found very few reports of their occurrence in this organ. Jurgensen and Schotter (45) in their treatise "Diseases of the Heart" made mention of trichinae, cysticerci and echinococci among others as pathologic curiosities which may occur in the pericardium but which they thought were not of great clinical interest. Buck* (1902) refuting the allegation of many writers during his time that *Trichinella spiralis* never occurred in the heart muscle stated in his "A Reference Handbook of the Medical Sciences" that cases of such occurrence were observed by Leuckart, Zenker and Virchow. Incidentally, this author also mentioned *Pentastoma denticulatum* (a species of Porocephalus, an arthropod) as one of the parasites that lodge in the heart. Van Cott and Lintz (86) cited encysted larvae, discovered during examinations of tissue sections from the heart of a case that died of trichiniasis.

Although as far as we are aware, the larvae of Ascaris have not been actually demonstrated yet in the heart of man, *a priori* their passage through the coronary circulation may be conceded; since it has been demonstrated in laboratory animals by Ransom and Foster (72) that a proportion of the migrating larvae fail to leave the lung capillaries and are swept to the left side of the systemic circulation and become lodged in the different visceral organs. The same may be conceded in the case of other round worms such as the strongyloides and hookworms, and of the blood flukes (schistosomes) whose larvae also migrate through the lungs as part of their natural life cycles. The possibility that these larvae filter out from the circulation and cause lesions in the various visceral organs is entertained by many parasitologists.

Of interest also in this connection is the finding of an adult Ascaris in the right ventricle of a man at autopsy by Boettiger and Verney (12). Dr. Musgrave, is said to have found an adult Trichocephalus in the coronary artery at an autopsy in the Philippines (6d).

---

* Buck, Albert H. "A Reference Handbook of Medical Science," v. 4, p. 583 (1902).

2. In the Central Nervous System

Notable among the parasites that have been found to lodge in the brain and spinal cord are the eggs of blood flukes (*Schistosoma hematobium, S. mansoni* and *S. japonicum*), and of *Paragonimus westermanni*, and hydatid cyst and *Cysticercus cellulosae.*

Thirty years ago Shimamura and Tsunod (75) described the presence of *S. japonicum* eggs in the brain associated with Jacksonian epilepsy and cerebral embolism. Since then, many cases of this type of epilepsy that have been observed in Japan from time to time have been attributed to the presence of eggs of this fluke in the brain. Ferguson (30) found eggs of *Schistosoma hematobium* in the brain and spinal cord of a case that died of urinary schistosomiasis. A remarkable case of transverse myelitis presumably due to eggs of *S. mansoni* was reported in Brazil by Mueller and Stender (63). The patient, who had had urinary trouble diagnosed as gonorrhea, developed six months later and in a single night a hemiplegia, from which he died. Autopsy revealed lesions about the second and third dorsal vertebrae, and microscopic examination of the cord at this level showed plentiful pseudotubercles centered on the eggs, which Prof. Fulleborn recognized as those of *S. mansoni.* A similar case has been reported by Day and Kenway (23). A boy of ten died with complete paralysis and anesthesia of both legs spreading to the trunk, and incontinence of urine and feces. Autopsy showed small necrotic areas in the lumber enlargement of the spinal cord. Under the microscope in the grey matter and just behind the anterior horns were ova of *S. hematobium.* Nerve cells near the ova were more or less degenerating with disappearing dendrons and dissolution of Nissl's granules. Edgar (26) has reported a case of epilepsy due to *Schistosoma japonicum.* "Epiliptiform convulsions, preceded by closing in one eye of the right side of the field of vision, some worsening of sight, and an occasional fumbling for the correct word, a paracentral scotoma in the right inferior temporal quadrant, and some aching on the left parietal bone led to operations, which displayed, under this bone, a sharply-outlined spherical yellowish tumor an inch in diameter, which was pronounced to consist of the ova of *S. japonicum.*"

Musgrave (64) discovered cystic abscesses containing eggs of *Paragonimus westermanni* in the brain of one of nine cases of paragonomiasis he observed in the Philippines. On the basis of the results of their experimental studies on intracranial infection with *Paragonimus westermanni*, Yokogawa and Suyemori (94) have concluded that the cranial cavity is an unfavorable location for the development of the worms. This, they state, is also suggested by the relative infrequency of cerebral paragonomiasis in man. They believe that in the great majority of cerebral paragonomiasis the pathological changes are produced by the entrance of partly grown or adult worms through the foramina of the base of the skull, and their subsequent invasion of the brain tissue, and not by emboli composed of eggs. There are other references in the literature concerning cerebral paragonomiasis which have not been accessible to us because they are written in Japanese. In fact, according to Craig and Faust (21) "in endemic foci in Japan, brain symptoms in children under fifteen years have frequently been attributed to infantile paralysis, cerebral hemorrhage and encephalitis or meningitis, whereas the causative agent was this fluke."

The occurrence of hydatid cyst has been not infrequently reported in the literature. Fleming and Bury (32) have reported an interesting case of hydatid cyst in the brain. The patient was a soldier who complained of weakness of the right arm and leg, poor sight, loss of memory, inability to read and write, and occipital headaches. Physical examination revealed acute optic neuritis of both eyes, ptosis on the right eye, left vestibular nystagmus and loss of sensation over the whole right side. X-ray showed two to three small opaque bodies in the right frontal lobe. Operated on for cerebral tumor, the patient died during the operation. Autopsy revealed a unilocular hydatid cyst, the size of a large orange, in the left brain from which were obtained hooklets and scolices. The opaque bodies showed by the X-ray on the right brain turned out to be "amorphous calcified material" which the authors thought were remnants of cysticerci.

Another remarkable case of hydatid cyst in the brain has been reported by Shuman (76). The patient, a soldier, had a history of chancre and for four years had been complaining of occipital headache. Treated for syphilis he developed bilateral optic neuritis two weeks later. During the next seven days the

patient complained of inability to awaken in the morning and trouble at the beginning of micturation. He staggered slightly to the left. He departed from the hospital but soon returned in a condition of collapse and died immediately afterwards. Autopsy revealed a hydatid cyst in the right cerebrum. Death was believed to be due to intracranial pressure. A similar cyst (coenurus), the larval stage of *Multiceps serialis* of the dog was found in the lateral ventricle of a Paris locksmith with a history of aphasia and epilepsy (cited by Faust, 1929), and in the brain by Turner and Leiper (84) in a man in West Africa.

There are scores of reports on the occurrence of hydatid cyst in the brain and spinal cord, but the original papers were not available to us at this writing.

Cysticercosis is by far the most frequently encountered helminthic infection of the central nervous system. In reviewing 807 cases of cysticercosis, Vosgien (87) found that the nervous system was involved 330 times, or in 40 per cent. Hare (39) quotes Dressel, who found the brain affected 72 times in 87 cases, or in 82 per cent. This author also cites Sato who collected 128 cases of cysticercosis of the brain and found the ventricles involved in forty-eight instances, and Hanneberg who collected the reports of fifty-six cases of cysticerci in the fourth ventricle.

MacArthur (55) called attention to the frequent occurrence of cysticercosis in the British Army. He thinks that a large number of cases of epilepsy among the soldiers at Millbank are due to cysticercosis of the central nervous system. He mentioned that during 1933 twenty cases of cysticercosis were identified at this barrack, and that in a single trooping season 8 cases of cysticercosis were again found among the soldiers, 6 having been invalided as epileptics and the other 2 as having had some kind of seizures. Closely following the article of MacArthur, there appeared a very comprehensive and valuable collection of knowledge on the subject of cysticercosis by Dixon and Smithers (25a & b), who, in an emphatic manner, again called attention to the frequent association of cysticercosis of the nervous system with epilepsy and other neurological conditions, and at the same time decried the fact that even neurological textbooks do not give the disease any prominence as a cause of nervous or mental symptoms.

Chung and Lee (18) have reported on 10 cases of cysticercosis of the central nervous system. Palpable subcutaneous nodules were present in 8 of the ten cases and in the other two cysticerci were seen in the brain at operation or autopsy; epileptiform fits were observed in 8, headache in 6, numbness or paresis in 5, fever in 5, nausea and vomiting in 4, transient motor aphasia, blurred vision, dizziness, drowsiness or eosinophilia in 3. There was a tapeworm in the intestine of 5, leucocytosis in 6, and bilateral papillitis with or without signs in the fundi of 3.

The individual cases of cysticercosis of the central nervous system reported in the literature are too numerous to mention here. The following illustrative cases are among the most interesting and typical:

Luney (54) has reported a case of cysticercosis with symptoms resembling those of "nervous syphilis", such as illusions and hallucinations and complaints of electrical sensations in the hands and feet. The patient was ataxic, with marked Rombergism; knee jerks greatly diminished; pupils sluggish to light and accommodation; paraesthesia of hands and feet; grip of right hand very weak. Laterly he had two epileptiform seizures with frothing at mouth and diffuse clonic convulsive movements on the right side, and died some days later. Autopsy showed *Cysticercus cellulosae* immediately beneath the arachnoid on the under surface of the right frontal lobe. The cyst was flattened out, elongated, and in opposition with the optic nerves and the right olfactory nerve. Three other cysts were found in the subarachnoid space, deep in the sulci on the upper surface of the right cerebral hemisphere in front of the fissure of Rolando, and a fifth cyst occurred in the same region on the left side of the brain.

Equally interesting is the case reported by Broughton-Alcock, Stevenson, and Drought (13). The patient who had been suffering for nearly six years from symptoms of impaired vision of the left eye, attacks of epileptic fit (diurnal and nocturnal), headache, occasional vomiting and mental dullness, died with the following autopsy findings: cysts attached to the dura matter; in the cortex were forty rounded, peasized nodules which showed typical characters of the scolex with hooklets and four suckers; and a very heavy cell infiltration around the connective tissue stroma and extending into the brain substance. The ma-

jority of the infiltration cells were plasma cells with fewer small round cells, and a fair number of endothelial cells were also present, and in one section two giant cells with massed nuclei were seen.

Ch'eng and K'ang (17) have reported a case of very heavy general infection with cysticerci. Starting with symptoms of mental trouble with headache, loss of vision, attacks of unconsciousness and hallucination, the man died of acute opium poisoning four years after the onset of the trouble. Autopsy revealed innumerable cysticerci in the brain and muscles.

Lispcomb (51) has reported a case of cerebral cysticercosis diagnosed *in vivo*. The patient, a soldier, in Punjab, India, was taken to the hospital with symptoms of typhoid fever. He later passed segments of *Taenia solium* and his feces became positive for eggs of the tapeworm. Discharged after 70 days' stay in the hospital, he was taken in again about two weeks later with weakness, headache, and vomiting. Three weeks after the second admission he developed papilloedema with loss of sight in the right eye, the headache and vomiting becoming more severe. In a short time hernia cerebri came on with fever and unconsciousness, and he died 78 days after the second admission. There were 150 cysticerci scattered throughout the brain; none was found elsewhere.

Another case of epilepsy evidently due to cysticercosis has been reported by Holmes (42). The patient, who actually had *Taenia solium* in his intestine, developed disorientation for time and place, loss of memory, dizziness and occasional loss of speech, associated with "little lights" in his eyes whether opened or closed, and epileptic fits accompanied by cyanosis, stertorous breathing, fixed stare and protruded tongue. Small subcutaneous nodules were present. Biopsy of the nodules showed *Cysticercus cellulosae*. X-ray of the skull gave negative results.

The two cases of Hare (39) are both interesting and illustrative of brain cysticercosis. The first had "convulsive seizures, failing vision, headache, amenorrhea and personality changes. Bitemporal hemianophsia, optic atrophy, diminished visual acuity and unequal pupils. Autopsy revealed a large right temporal cyst and multiple small cysticercus cysts". The second one had "convulsive seizures of twenty years' duration, in-

termittent headache for four years, and visual impairment for twelve months. He was admitted to the hospital with signs of meningitis. Death occurred two days after admission. Autopsy revealed basilar meningitis and *Cysticercus cellulosae* in the fourth ventricle."

Marsh (56) has reported a case of cerebral cysticercosis with fever, headache, stupor and signs of insanity. There was a bilateral optic neuritis. At autopsy very many cysticerci throughout and over both hemispheres with a few in the midbrain were found. This author has previously seen ten cases of cysticercosis invalided for epilepsy within a period of eighteen months.

Africa and Sta. Cruz (5a) have reported one case of cerebral cysticercosis in the Philippines. The subject was a male Filipino, 29 years old who died suddenly in his home. Autopsy showed numerous cysticerci in the muscles and brain. In the brain, the cysts had the following distribution: 9 cysts were found scattered on the external surface of the left hemisphere beneath the pia mater; six cysts were similarly distributed on the surface of the right cerebrum. On sections of the brain other cysts were found; one in the left lateral wall of the third ventricle; one in the lower lateral portion of the right thalamus; one in the right caudate nucleus; and one in the hypophysis.

Although occasional reference to signs of involvement of the nervous system is found in the early literature of trichiniasis there are few reports of the actual demonstration of the parasite in the brain. Most and Abeles (61) quote Kratz, who in a review of a three hundred and thirty-seven cases, described patients who exhibited delirium, apathy, insomnia, and anesthesia of the skin. Frothingham (33) was the first to demonstrate the larvae of *Trichinella spiralis* in the brain, as well as the cellular reaction to the parasite. Van Cott and Lintz (86) recovered living trichina larvae from the spinal fluid of a patient who showed neurologic signs and mental symptoms during the course of trichiniasis. Hassin and Diamond (40) found trichina larvae in the spinal fluid removed postmortem from a case in which death was presumably due to a heavy infection of *Trichinella spiralis*. Trichina larvae found in different parts of the brain including the cavity of the fourth and lateral ventricles together with the neuropathological changes that accompanied

the infection form the basis of a comprehensive report by these authors. Most and Abeles (61) have reported two cases of trichiniasis with signs of involvement of the nervous system, of which one terminated fatally, while the other recovered. The pathologic changes seen in the brain of the one that died were in the nature of widespread acute non-suppurative encephalitis. The characteristic changes were disseminated nodules, with or without parasites, and perivascular and meningeal infiltrations, as well as degenerative changes seen in most toxic cases of considerable duration.

What has been said about the larvae of various helminths that migrate through the general circulation with reference to the heart may be mentioned in connection with the central nervous system.

III. TECHNIQUE AND MATERIAL

A general outline of the technique we employed in this investigation has been touched incidentally under the caption: history of the discovery. Briefly it consists of emptying the small intestine of its contents, slitting it open throughout its whole length, and scraping its mucosal lining two or three times with a dull scalpel over an appropriate container with a suitable amount of water. After the resulting mixture has been stirred thoroughly so as to comminute the mucosal scrapings together with whatever particles of food or fecal debris have been included, and after the minute flukes that may be present have been freed from them, it is passed through a series of sieves with from 20 to 100 meshes per linear inch. The sieves are arranged with the coarsest on top *ad seriatim* downward. Without disturbing the arrangement of the sieves, tap water is then poured into the top sieve several times, depending on the consistency of the strained material, in order to free the flukes that may be present from any adhering mucosal particles or fecal matter. The fluid that has passed through the sieves may be discarded. After this procedure, the bottom sieves are rinsed of their adhering particles of mucosal scrapings and food and fecal debris, the whole washing being collected in a large glass jar. The flukes are expected to be found in this fluid, if present.

The examination of the collected fluid is best done fractionally. After the mixture has been stirred, a suitable quantity is taken and placed in a glass receptacle (the body or lid of a moist-chamber is convenient) and examined for the presence of flukes. Each take should be just enough to cover the floor of the glass container to a depth of about 2 cm. to ensure good visibility, since the fluid necessarily contains particles of intestinal villi, and bits of other intestinal tissues, mucous, food particles, and fecal matter. The minute flukes (if present) may be seen congregating just below the water line if the container is tilted to an angle of about 25 to 35 degrees after a little panning movement. A hand lens may be necessary to distinguish them from individual villi and similar objects, but a well-trained and experienced eye does not require this aid, although extreme patience and diligence are necessary. Properly examined, not a single fluke present in each take need escape detection with this process. This fractional examination is continued until the whole fluid is finished. For the detection of these flukes, the intestinal contents need not be examined since most of these parasites are deeply embedded in the intestinal wall or in the crypts of the intestinal glands.

Failure to detect flukes in the intestinal scrapings does not deter us from examining the hearts of cases in which symptoms of cardiac troubles are evident either from the clinical history or from the pathological anatomy of this organ. For example, in one of our cases we failed to recover even a single fluke from the intestinal scrapings, but noting that the clinical diagnosis was cardiac beriberi, which was confirmed by the morgue pathologist, we proceeded to investigate the heart of this case and succeeded in demonstrating eggs associated with lesions characteristic of this infection. On the other hand, the presence of the flukes in the intestine at autopsy always prompts us to investigate the heart for eggs, regardless of whether or not there is evidence of cardiac trouble. For example, in one of our autopsies in which we detected the presence of the parasites in the intestine, we investigated the heart although there was no evidence of trouble in this organ, either clinically or as indicated by the protocol, and we succeeded in finding eggs in the myocardium, but apparently unassociated with any serious lesion.

For rapid detection of eggs in suspected hearts a portion of the myocardium, preferably cut from places where petechial

hemorrhages abound, may be squeezed vigorously and the exuding fluid examined under the microscope. This method failing, more cuts are made from different localities, and the pieces of heart muscle chopped or ground into very fine particles and digested in artificial gastric juice (after the manner of extracting trichina larvae from muscles) at 40 degrees C. for 24 hours or until they are thoroughly digested. The resulting fluid is strained, after stirring, through a sieve 80 meshes per linear inch, and the filtrate centrifugalized at 1000 revolutions per minute for five minutes. The sediment is examined for eggs. After the presence of eggs has been ascertained, blocks are made from different portions of the heart for preparing histological sections.

While in a few of our positive hearts, it did not require so many blocks to encounter lesions characteristic of this infection, in a large number of them as many as from thirty to forty blocks had to be sectioned before we could demonstrate them. One has to explore the myocardium thoroughly in suspected hearts, especially if there are strong indications pointing to this infection, such as the recovery of flukes from the small intestine, before they should be declared negative; because as mentioned elsewhere in this work, in this infection the sites of disturbance are discreet and found only wherever the eggs have caused hemorrhages, emboli or thrombi. In many of our cases the heart became literally honeycombed with cuts before we succeeded in demonstrating chronic inflammatory, or degenerative changes. The search for eggs, or the lesions which they produce, is usually a tedious process. However, in the examination of myocardial sections the microscopist is often greatly aided by the strikingly tinctorial appearance of the reactive cells in the lesion, which contrasts vividly with surrounding tissue. Indeed, time and again we have been guided by this specially stained reactive tissue to the exact spot of trouble in our examination of myocardial sections. Once this characteristic type of tissue reaction is found in a section, careful examination of the series almost invariably ends in the finding of the culpable eggs. The eggs are not found in any special locality with reference to the lesion. They may be found within the mass of the reactive cells, at the edge, or quite remote from the lesion. The same procedure has been followed in the localization of lesions in the brain, spinal-cord, lungs, liver, and spleen.

In this work the small intestines of 297 autopsy cases were examined for the presence of heterophyid flukes. Our examination of the intestines of the first 108 cases was nearly consecutive. During the latter stages of our investigation, however, our examination of the intestines became more or less random because of interference of other work, and, further more, because we became more interested in autopsies in which there were clinical indications of heart condition, or in which heart affection was clearly indicated by the pathological anatomy of this organ. The work was begun early in 1935 and closed temporarily for this report about the middle of 1938.

All these autopsies with a few exceptions were made by the staff of the Department of Pathology and Bacteriology, College of Medicine, University of the Philippines, in the Manila City Morgue. This morgue serves the charity wards of the Philippine General Hospital, an insular institution with about 600 charity beds, which draws patients not only from Manila and suburbs, but also from all sections of the Philippines. The Manila City Morgue also performs autopsies for the Insular Psychopathic Hospital as well as for the Division of Investigation of the Department of Justice in the City of Manila.

Out of these 297 autopsies, 33 were found to be positive for heterophyid flukes in the intestine, either of one species or of two or three species associated together; while in one case, eggs were found only in lesions in the heart, the intestine being negative for the adult parasite. A total therefore, of 34 positive cases are reported in this work, excluding the two hearts from the museum of the Department of Pathology and Bacteriology, from which material for this investigation was also obtained.

Of the thirty-four positive cases that properly belong to this series, eggs associated with lesions characteristic of this infection were found in the heart of 13; eggs unassociated with definite lesions were found in the heart in one case alone; and eggs associated with typical lesions were found in the brain in one; and in the spinal cord in another, which also showed eggs in typical lesions in the myocardium. Eggs associated with lesions characteristic of this infection were also found in the liver, lungs, and spleen of one case, besides in the heart; and in another heart case the eggs were found only in the liver besides the heart.

In this series there were a total of 91 cases with enlarged heart as indicated by the morgue protocols. We attribute this unsually large number of heart cases in the present series to our inclination, which, as previously mentioned, developed in the later stage of our investigations, to examine particularly those cases in which there were clinical indications of heart condition, or in which the pathological anatomy of this organ was obvious. In 13 out of these 91 heart-trouble cases we were able to demonstrate eggs of heterophyid flukes associated with lesions characteristic of this infection in the myocardium, and in the sclerosed mitral valves as well, in three of them. In 5 of these 91 heart trouble cases, flukes were recovered from the intestine, but extensive exploration of the heart failed to demonstrate eggs, or lesions typical of the infection. The hearts in two of these 91 cases which had also signs and symptoms of heart trouble and flukes in the intestine were missed for examination. There were, therefore, 89 enlarged hearts examined in this work. The rest of these 89 heart-trouble cases, or 71, were negative for any sign of the infection either in the intestine or in the myocardium after extensive and intensive explorations.

In this series there were eight cases of cerebral hemorrhage. In one of them, eggs associated with lesions typical of this infection were found in sections of the brain tissue obtained around the blood clot in the right basal ganglion; in the rest no such findings were recorded from the brain tissue around or in the vicinity of the blood clot, or elsewhere in the body.

The histological findings reported in this work are based upon our examination of thousands of histological preparations stained with haemotoxylin and eosin from the various organs, principally, the heart, of the positive cases enumerated above. Since early in this investigation we believed that cardiac and other visceral complications in heterophyidiasis originate from the small intestine where the adult parasites live, it was obviously useless or unnecessary in our opinion to explore the hearts of cases with negative intestine, unless as we have remarked elsewhere, these hearts show suspicious signs or the cases bear clinical history suggesting the condition.

We may add here that it has been impossible for us to cover all the visceral organs of our positive cases in this investigation not only because of lack of adequate personnel, but also because we did not have control over the autopsies, which as pointed

out previously, were mostly performed by the members of the staff of the Department of Pathology and Bacteriology. In many cases, even if we wanted to investigate certain organs we were not able to get hold of them because other parties just happened to be also interested in them in connection with their own investigations. We had difficulty, particularly, in securing the brain and spinal cord of some of our positive cases in which, on account of certain symptoms indicating nervous lesions, we were very much interested, because the morgue pathologist was either not in a mood to open the cranial case and spinal canal, or out of consideration to the feelings of the family of the deceased, was not favorable to further mutilation of the cadaver.

IV. BRIEF PROTOCOLS OF CASES WITH VISCERAL LESIONS

The following are the brief protocols of our fifteen cases in which visceral complications, mostly in the heart, were found:

No. 1. Autopsy P-35-209. Male, 50 years old, found dead one morning. Anatomical diagnosis: Acute cardiac dilatation, right; acute dilatation, stomach; congestion, vicera. Parasitological findings: 21 adult *Spelotrema brevicaeca* recovered from intestine; eggs associated with acute and chronic specific lesions in the myocardium.

No. 2. Autopsy P-35-265. Male, 23 years old, died three hours after admission to hospital with symptoms of failing heart. Anatomical diagnosis: Hypertrophy and dilatation, right ventricle (beriberi). Parasitological findings: 4 adult *Diorchitrema pseudocirrata* and 4 *H. taichui* recovered from intestine. Heart sections showed eggs associated with acute vascular changes and chronic lesions specific or peculiar to heterophyidiasis.

No. 3. Autopsy P-35-321. Male, 62 years old. Died with symptoms of cerebral hemorrhage. Autopsy revealed hemorrhage, cerebral, right basal ganglion; hypertrophy and dilatation, left ventricle; chronic nephritis; arteriosclerosis. A number (undetermined) of adult *Haplorchis yokogawai* and *S. brevicaeca* recovered from intestine. The heart of this case was not seen. Eggs associated with chronic specific lesions identical

to what were seen in the heart of other cases found in sections obtained from the brain around the fatal hemorrhage.

No. 4. Autopsy P-35-326. Male, 35 years old, diagnosed as cardiac decompensation (beriberi) died twelve hours after admission to the hospital. Autopsy revealed acute cardiac dilatation; endocarditis, chronic, with stenosis and calcification of mitral valves. Five specimens of *H. yokogawai* recovered from intestine; sections showed eggs associated with acute vascular changes and chronic specific lesions in myocardium; sclerosis and calcification of mitral valvular leaflets with large number of eggs in the sclerotic areas as well as in the calcified material. Eggs also found in liver, lungs, and spleen.

No. 5. Autopsy P-35-489. Female, 36 years old, brought to the hospital in a dyspneic, semi-conscious, dying condition; died a few minutes after admission. Anatomical findings: Hypertrophy and dilatation, right ventricle (beriberi). One adult specimens each of *H. yokogawai* and *H. taichui* in intestinal scrapings. Eggs associated with acute and chronic lesions in the myocardium.

No. 6. Autopsy P-35-543. Male, 24 years old, diagnosed as peptic ulcer; cardiac beriberi (?). Anatomical diagnosis: Acute cardiac dilatation (all chambers) with slight hypertrophy of right ventricle; myocarditis. Parasitological findings: 3 adult *Spelotrema brevicaeca* and 7 *Haplorchis taichui* recovered from intestines; several adult flukes (specific identity undetermined) in the myocardium and epicardium; eggs associated with acute vascular changes and chronic specific lesions in the myocardium.

No. 7. Autopsy P-35-711. Female, 27 years old, admitted to hospital with symptoms of heart failure and chronic nephritis. Autopsy revealed hypertrophy and dilatation, right ventricle (beriberi). Not a single fluke was recovered from intestine. Eggs associated with acute and chronic lesions characteristic of heterophyidiasis in myocardium.

No. 8. Autopsy P-35-795. Male, 35 years old, with complaints of headache, cough and chilly sensations. Diagnosed in the ward as malaria, acute. Autopsy revealed acute caseous tuberculosis, upper lobes; acute caseous peribronchial glands, right; miliary tuberculosis, pleura. One specimen of *H. yokogawai* recovered from intestine. Eggs found in the myocardium. No chronic lesions found.

No. 9. Autopsy P-35-964. Male, 70 years old, with hypertrophied prostrate and cystitis. Died 38 days after prostatectomy. At autopsy the findings were: Pyonephrosis, bilateral (ascending infection) cystitis, acute parenchymatous degeneration of heart and liver. Twenty-five specimens of *H. yokogawai* recovered from intestinal scrapings; eggs associated with acute and chronic lesions in the myocardium.

No. 10. Autopsy P-35-1110. Male, 17 years old, with signs and symptoms of peripheral neuritis, and cardiac beriberi which were confirmed at autopsy. A lone specimen of *H. taichui* found in the intestine. Eggs associated with acute and chronic specific lesions in the myocardium; also in liver.

No. 11. Autopsy P-36-111. Male, 44 years old, found dead in one of the streets of Manila. No clinical data could be obtained. Postmortem findings: Hypertrophy and dilatation of the heart; sclerosis of coronary vessels; distention and congestion of lungs; congestion of liver, spleen, and kidneys; meningeal hemorrhage, basal, extensive; hemorrhage, dural and subdural, left lateral border of spinal cord at level of lumbar enlargement. Parasitological findings: 23 *S. brevicaeca* and 11 *H. yokogawai* recovered from intestine. Eggs associated with chronic specific lesions in the myocardium; eggs also found in hemorrhages in the left lateral column of the lumbar enlargement; also in chronic specific lesions in this locality.

No. 12. Autopsy P-37-620. Female, 22 years old. Diagnosed as chronic valvulitis with mitral stenosis and insufficiency; cardiac failure, secondary, which were confirmed at autopsy. One lone specimen *H. yokogawai* recovered from intestine; eggs associated with chronic specific lesions in myocardium; eggs also found in sclerotic and calcified areas of mitral valves.

No. 13. Autopsy P-37-705. Male, 21 years old, admitted to hospital with symptoms of heart failure and cerebral embolism. At postmortem were found valvulitis, chronic (rheumatic) with superimposed polypoid vegetations (bacterial) mitral and aortic valves; cardiac hypertrophy and dilatation, secondary; abscesses, or infarctions, spleen, kidneys, lungs, and brain. Two *H. yokogawai* recovered from intestine; eggs in calcified areas of mitral valves; no eggs, but cellular reaction typical heterophyidiasis in the myocardium.

TABLE 1.—*Brief Protocols of Thirty-four Positive Cases (with Parasite in the Intestine or other Viscera or in both).*

No.	Autopsy Number	Flukes Found in the Intestine						Heart Finding	Chief Anatomical Diagnosis	Chief Clinical Diagnosis	Remarks
		S. brevicaeca	*H. taichui*	*H. yokogawai*	*H. vanissina*	*D. pseudocirrata*	*H. calderoni*				
*1	35-209	21						+	Acute dilatation, right heart	Undetermined	
*2	35-265		4			4		+	Beriberi	Cardiac beriberi	
3	35-318	5						—	Malaria acute	Anemia, acute, severe, secondary.	
*4	35-321	14?		4?				Heart was not seen	Cerebral hemorrhage; hypertrophy and dilatation, left ventricle; chronic nephritis, arteriosclerosis	Cerebral hemorrhage right basal ganglion	Chronic specific lesions in the brain tissue around the blood clot.
*5	35-326			5				+	Acute cardiac dilatation	Cardiac decompensation secondary to cardiac beriberi	Lesions also found in liver, lungs and spleen.
6	35-329					5		—	Acute peritonitis	Abscess, acute, appendicial	
7	35-335					5		Heart of this case was not seen.	Chronic endocarditis	Cardiac failure	
8	35-342	1	4			3		—	Lobar pneumonia	Undetermined	

* NOTE: Asterisks indicate cases with visceral complications.

TABLE 1.—*Continued.*

No.	Autopsy Number	Flukes Found in the Intestine						Heart Finding	Chief Anatomical Diagnosis	Chief Clinical Diagnosis	Remarks
		S. breviscaeca	*H. taichui*	*H. yokogawai*	*H. vanissima*	*D. pseudocirrata*	*H. calderoni*				
9	35-403	3						—	Acute meningitis	Meningitis, acute (?)	
*10	35-489		1	1				+	Beriberi	Undetermined	
*11	35-543	3	7					+	Beriberi	Peptic ulcer; cardiac beriberi	
*12	35-711							+	Beriberi	Cardiac failure secondary to chronic myocarditis	Intestine was missed for examination. Lesions found in liver
*13	35-795			1				+	Acute caseous P. T. B.	Malaria, acute; anemia, secondary	
14	35-933	150				5		—	Sub-acute nephritis	Cardiac beriberi	
*15	35-946			25				+	Pyonephrosis, bilateral; parenchymatous degeneration of heart and liver	Hypertrophy, prostate	
*16	35-1110		1					+	Beriberi	Peripheral neuritis, beriberi, cardiac (?)	
*17	36-111	23		11				+	Hypertrophy and dilatation, heart	Undetermined	Chronic specific lesions in spinal cord.

*NOTE: Asterisks indicate cases with visceral complications.

TABLE 1.—*Continued.*

No.	Autopsy Number	Flukes Found in the Intestine						Heart Finding	Chief Anatomical Diagnosis	Chief Clinical Diagnosis	Remarks
		S. brevicaeca	*H. taiohui*	*H. yokogawai*	*H. vanissima*	*D. pseudocirrata*	*H. calderoni*				
18	36-166			17				—	Endocarditis, acute	Cardiac failure secondary to chronic valvulitis	
19	36-168			6				—	Lymphosarcoma, duodenum	Undescended testis, right	
20	36-480	500						—	Portal cirrhosis	Portal cirrhosis	
*21	37-620			1				+	Chronic valvulitis	Cardiac failure secondary to chronic valvulitis	
*22	37-705			2				+	Chronic valvulitis	Cardiac failure secondary to chronic valvulitis	
23	37-745			2				—	Anemia, acute, secondary	Retention, placenta	
24	37-823	21						—	Acute peritonitis	Ectopic pregnancy, ruptured	
25	37-834			2				—	Acute endocarditis	Cardiac failure secondary to chronic valvulitis	
26	37-839					1		—	Gangrenous tonsilitis	Ludwig's angina	
27	37-855				1			—	Hemorrhagic bronchopneumonia	Meningitis, suppurative?	

* NOTE: Asterisks indicate cases with visceral complications.

TABLE 1.—*Continued.*

No.	Autopsy Number	Flukes Found in the Intestine						Heart Finding	Chief Anatomical Diagnosis	Chief Clinical Diagnosis	Remarks
		S. brevicaeca	*H. taichui*	*H. yokogawai*	*H. vanissima*	*D. pseudocirrata*	*H. calderoni*				
28	38-1024			4				—	Cardiac hypertrophy, left	Lobar pneumonia, left	
*29	38-30			2				+	Beriberi, hypertrophy and dilatation, right ventricle	Ascariasis	
30	38-76			3				—	Congestion, brain; status lymphaticus	Undetermined	
31	38-89						6	—	Pericarditis, acute fibrinous	Undetermined	
32	38-141						1	—	Cardiac hypertrophy & dilatation; valvulitis, chronic; myocarditis	Undetermined	No satisfactory examination of the heart was made; the organ was claimed by other interested party.
*33	38-480			4				+	Hypertrophy, left ventricle and dilatation right ventricle; valvulitis, chronic	Undetermined	
34	38-535	370						—	Hypertrophy, left ventricle; hemorrhage cerebral, right basal ganglion	Undetermined	Brain of this case was not seen.

*NOTE: Asterisks indicate cases with visceral complications.

No. 14. Autopsy P-38-30. Male, 17 years old, admitted to hospital with signs and symptoms of beriberi (cardiac). Autopsy revealed hypertrophy and dilatation, right ventricle (beriberi); congestion visceral organs. Two adult specimens of *H. yokogawai* recovered from intestine; chronic specific lesion in the myocardium.

No. 15. Autopsy P-38-480. Male, 48 years old, admitted to hospital with generalized edema, dyspnea and icteric sclera; diagnosed as cardiac failure, secondary to chronic valvulitis with mitral stenosis. Anatomical diagnosis: Hypertrophy, left ventricle, and dilatation, right ventricle; valvulitis, chronic. Parasitological findings: Four specimens of *H. yokogawai* in intestinal scrapings; chronic specific lesions with eggs in myocardium; also fresh hemorrhages associated with eggs. No trace of eggs in sections of the valves.

In addition to these cases we were able to obtain material from two museum hearts labelled H-5-1 and H-5-2 from the Department of Pathology and Bacteriology, College of Medicine, of this university, with hypertrophy and dilatation of the left ventricle, and sclerosis and thickening of the mitral valves (mitral stenosis). Neither the clinical nor the autopsy records were available in either case. The myocardium of these hearts showed the same findings as described in most of the above cases; eggs were found fossilized in the calcified material in the interior of the mitral valvular leaflets in both cases.

V. ETIOLOGICAL CONSIDERATIONS

A. THE FAMILY HETEROPHYIDAE ODHNER, 1914.

The family Heterophyidae, according to Ransom (71) is composed of a number of genera of small flukes, parasitic in the intestine of mammals and birds, usually fish eaters. The family is one of the richest in digenetic trematodes and is fast becoming more and more interesting and important in human and veterinary medicine. Its distribution is world-wide and new species are rapidly discovered in various countries to the further enrichment of the family.

In a monographic study of the family, Witenberg (90a) pointed out the close similarity, both in morphology and life his-

tory of Heterophyidae and members of the Opistorchidae, and advocated the formation of a new superfamily, Opistorchoidea, to include in it both families. He further said that the families "differ from each other mainly in the structure of the terminal portion of the genital ducts and that Heterophyidae parasitise the intestine while Opistorchidae are found in the bile ducts of the final host." The finding of Haplorchis (Monorchotrema) adults and eggs in the bile ducts of cattle egrets and of Stictodora in the pancreas of sea-gulls has removed this physiological difference between the two families and brought them together still closer to justify their fusion. Faust (28a) also erected the superfamily Opistorchoidea, but did not include the family Heterophyidae in it.

In this work Witenberg's diagnosis and general classification of the family have been adopted. His nomenclature for designating the different parts of the complicated genital sinus, characteristic of but not entirely peculiar to the family, as well as other parts of the reproductive system is also believed to be satisfactory and hence will be followed in this work. His diagnosis of the family Heterophyidae is as follows:—

"Small and very small forms. Pseudodermis covered with scale-like spines. The body is usually divided into two parts. One anterior flattened, free from genitalia and more motile than the posterior part which is oval or round in cross-section and contains the genital apparatus. The oral sucker may be provided with all or a part of the following structures: a contractile dorsal lip-like appendage and rows of circumoral spines.

"Prepharynx and oesophagus vary in different genera and species. Pharynx always present. Intestinal caeca simple, of varying length. Ventral sucker, except in the genus Heterophyes, reduced and included in the modified genital sinus ('ventro-genital sac') or even absent.

"The reproductive organs, except the vitellaria in some genera, are grouped in the posterior part of the body behind the level of the genital aperture which is generally situated near the middle of the body. Testes, two or one, globular or lobed; their situation varies in different genera. The cirrus pouch is absent. The seminal receptacle is voluminous and may be divided into several parts by constrictions. The terminal portion of the seminal vesicle may form a separate vesicle-shaped organ which

is usually provided with chitinished walls; the term 'expulsor' is proposed for the structure (in Heterophyes, Tocotrema, Diorchitrema, etc). Ovary globular or slightly lobed and except in Adleria, is situated in front of the testes. Mehlis' gland present. Seminal receptacle well developed. Laurer's canal usually reduced. The vitellaria are usually situated near the lateral or dorsal surface of the body and the degree of their development varies in different species. The uterus in most cases does not proceed anteriorly to the genital aperture. The latter, except in Heterophyes, open on the inner wall of the ventro-genital sac, which is situated on the middle line or moved towards the lateral border of the body. Near the genital aperture a more or less developed gonotyl is often present. Eggs usually numerous with thick shell 18 to 37 u long. Excretory vesicle usually Y-shaped; the length of the stem varies in different genera and it is either straight, S-shaped, or divided into branches which may reunite (as Scaphanocephalus); the branches may be long, short or entirely absent (as in Galactosomum).

"Adults parasitise the intestines of mammals, birds and rarely fish (*Haplorchis*). Metacercariae encysted in fish. Cercariae, as far as is known, develop in operculated mollusks.

"Type genus:—Heterophyes Cobbold, 1866."

For the history and contents of this family, the reader is referred to Witenberg's (90a) monographic work: "Studies on the Trematode-Family Heterophyidae."

B. LOCAL REPRESENTATIVES OF THE FAMILY

There are eighteen members of the family Heterophyidae Odhner, 1914, so far described or identified in the Philippines. Distributed among seven subfamilies and ten genera they are listed with their corresponding host or hosts as follows:—

I. Heterophyinae Ciurea, 1924.

a) Heterophyopsis Tubangui and Africa, 1938.

Syn. Pseudoheterophyes (Onji and Nishio, 1924) Yamaguti, 1939.

1. *Heterophyopsis expectans* (Africa and Garcia, 1935) Tubangui and Africa, 1938.

Syn. *Heterophyes continuus* Onji and Nishio, 1924; *Heterophyes expectans* Africa and Garcia, 1935;

Pseudoheterophyes continua (Onji and Nishio, 1924) Yamaguti, 1939.
Hosts: Dogs and cats and the bird, *Fregata ariel ariel* (G. R. Gray).

II. Galactosominae Ciurea, 1933.
b) Stictodora Looss, 1899.
2. *Stictodora sawakinensis* Looss, 1899.
Hosts: Dogs and cats.
3. *Stictodora manilensis* Africa and Garcia, 1935.
Hosts: Dogs, cats and sea-gull (*Larus ridibundus* Linn.).
4. *Stictodora guerreroi* Garcia and Refuerzo, 1936.
Hosts: Dogs, cats and sea-gulls (*Larus ridibundus Linn.*).
c) Galactosomum Looss, 1899.*
5. *Galactosomum anguillarum* (Tubangui, 1933) Tubangui and Africa, 1938.
Syn. *Haplorchis anguillarum* Tubangui, 1933.
Host: *Anguilla mauretiana*

III. Cryptocotylinae Luhe, 1899.
d) Scaphanocephalus Jagerskiold, 1903.
6. *Scaphanocephalus adamsi* Tubangui, 1933.
Host: Immature forms encysted in the fins and under the scales *of Lepidaplois mesothorax.*

IV. Apophallinae Ciurea, 1924.
e) Apophallus Luhe, 1909.
7. *Apophallus eccentricus* Africa and Garcia, 1935.
Host: Dogs.

V. Centrocestinae Looss, 1899.
f) Pygidiopsis Looss, 1899.
8. *Pygidiopsis genata* Looss, 1907.
Hosts: Dogs and cats experimentally.
9. *Pygidiopsis marivillai* Refuerzo and Garcia, 1937.
Host: *Haliaetres leucogaster* (Gmelin).
g) Phagicola Faust, 1921.
10. *Phagicola pithecophagicola* (Faust, 1931) Price, 1936.

* In a personal communication Prof. G. Witenberg of the University of Jerusalem seems inclined to think that the genera Stictodora and Galactosomum are identical.

Syn. *Ascocotyle pithecophagicola* (Faust, 1920) Faust and Nishigori, 1926 *Parascocotyle pithecophagicola* (Faust, 1920) Witenberg, 1929; *Ascocotyle* (Phagicola) *pithecophagicola* (Faust, 1920) Travassos, 1930.

Host: *Pithecophaga jefferyi* (monkey-eating eagle).

h) Centrocestus Looss, 1899.

Syn. Stamnosoma Tanabe, 1922.

11. *Centrocestus formosanum* (Nishigori, 1924).

Host: *Bubulcus ibis coromandus* Boddaert and *Pyerreroides manillensis;* dogs and cats experimentally.

VI. Stellantchasminae Price, 1940*

i) Stellantchasmus Onji and Nishio, 1924.

Syn. *Diorchitrema* Witenberg, 1929.

12. *Stellantchasmus falcatus* Onji and Nishio, 1924.

Syn. *Diorchitrema pseudocirrata* Witenberg, 1929.

Hosts: Man, dogs and cats.

VII. Haplorchiinae Looss, 1899.

j) Haplorchis Looss, 1899.

Syn. Monorchotrema Nishigori, 1924.

13. *Haplorchis pumilio* Looss, 1899.

Syn. *Monorchotrema taihokui* Nishigori, 1924.

Hosts: Dogs and cats experimentally.

14. *Haplorchis yokogawai* (Katsuta, 1932) Chen, 1936.

Syn. *Monorchotrema yokogawai* Katsuta, 1932.

Hosts: Man, dogs, cats and the bird, *Bubulcus ibis coromandus* Boddaert; and *Maccacus cynomulgus* experimentally.

15. *Haplorchis taichui* (Nishigori, 1924) Chen, 1936.

---

* Price, E. W.—A review of heterophyoid trematodes, with special reference to those parasitic in man. (Abstract) Report of Proceedings, Third International Congress for Microbiology, New York, 1940.

Syn. *Monorchotrema t[illegible]hui* Nishigori, 1924; *Monorchotrema mi[illegible]chia* Katsuta, 1932.
Hosts: Man, dogs, cats and cattle egret (*Bubulcus ibis coromandus* Boddaert)

16. *Haplorchis calderoni* (Africa and Garcia, 1935) Africa, 1938.
Syn. *Monorchotrema calderoni* Africa and Garcia, 1935.
Hosts: Man, dogs and cats.
17. *Haplorchis vanissima* Africa, 1938.
Host: Man.
18. *Haplorchis sisoni* Africa. 1938.
Hosts: Cats and dogs experimentally.

C. GENERAL LIFE CYCLE OF THE FAMILY

Looss (52) observed that the adult swages of Cryptocotyle and related forms occur only in fish-eating birds and mammals. On the basis of this observation he concluded that the final hosts had acquired the parasites by eating infected fish.

The first worker to confirm this view of Looss was Yokogawa (93a) who recovered a new heterophyid (later named *Metagonimus yokogawai*) from cats and dogs by feeding them with metacercariae encysted in the trout (*Plectoglossus altivelis*). The molluscan host was later found by Muto (65) to be *Melania libertina* in the district of Kaishui, Korea, where from 2 per cent to 50 per cent of this snail were found infected with larval forms. Long-tailed cercariae with oral and ventral suckers and eye-spots, obtained from this snail, were induced to encyst in the tissues at the base of the fins and tails as well as under the scales of previously uninfected gold fishes. Kittens fed with the metacercariae obtained from experimentally infected gold fishes were found to be invariably infected with *M. yokogawai* in from twelve to fifteen days, judged from the eggs found in the stools of the animals. Later researches by the same author (65) apparently show that a minimum of at least twenty days stay in the fish is required by the metacercaria before it becomes mature or infective, proving the absolute necessity of a second intermediate host.

In 1923 Kobayashi (48), evidently influenced by the finding of Onji (68) that the Japanese mullet (*Mugil japonicus*) serves

as the second intermediate host of *Heterophyes nocens*, dissected some Egyptian mullet in Port Said while he was passing through that port, and found in them encysted cercariae, which, judging from their morphology and position in the fish host, he concluded to be metacercariae of some species of Heterophyes. In the same year Khalil (47a) obtained specimens of Heterophyes indistinguishable from *H. heterophyes* from the gut of experimental cats previously fed with metacercaria obtained from mullets (*Mugil cephalus*) from Lake Mensaleh adjoining Port Said. Ten years later this same author (47b) working in the same locality definitely incriminated the snail *Pirenella conica* as one of the molluscan hosts of *Heterophyes heterophyes*.

The life history of *Crytocotyle lingua* has been worked out by Stunkard (80) in a brilliant fashion, proving that the cysts which were previously found infecting the cunner are the metacercariae of this trematode of gulls and terns, and that the larval stages of the parasite occur in the marine snail *Littorina littorea*.

Faust and Nishigori (29) found that the first intermediate host of *Monorchotrema taihokui* (*Haplorchis pumilio*) and *M. taichui* are the snails *Melania reiniana var hidachiens* and *M. obliquegranosa* (fresh-water snails) respectively. These authors were able to recover lophocercous cercariae with pigmented eyespots and a long muscular tail having a fluted keeled margin from both naturally and experimentally infected snails, which could be induced to encyst in the cartilagenous portions of the tails and fins of goldfishes. According to these authors a large number of freshwater fishes in Formosa, distributed among three families, Cyprinidae, Siluridae and Cotilidae, harbor the metacercariae of these flukes.

In 1937 Cameron (14) successfully worked out the life history of *Apophallus venustus* (Ransom, 1920) in Canada. In his own words, the life cycle of this heterophyid trematode is as follows:

"The eggs of the trematode pass into water, embryonate, and are swallowed by the snail, *Geniobasis livescens*. They do not hatch in water. In the snail, multiplication through redia and daughter redia stages takes place, and cercariae, with long flanged tails and pigmented eye-spots, are produced. These escape into water, but have a free life of less than 48 hours. To survive during this period, they must penetrate the skin of a

fish, a great variety of which are successful intermediaries. In the muscle of the fish, the cercaria encysts to become metacercaria, which is however not immediately infective. Infections of the definitive host is by ingestion of uncooked fish."

From the above data obtained from the study of the life cycle of members of five different genera of the family, representing four different subfamilies, it would seem that all the members of the family Heterophyidae have a common type of life cycle, i.e., the miracidium, which escapes from the egg, penetrates the molluscan host where the larval stages are formed; and the cercariae, after leaving the snail, encyst in fishes, the infection being transferred to warm blooded vertebrates (usually fish-eating birds and mammals) when the infected fishes are eaten. Hence the life cycle of the family bears a close analogy to that of the family Opistorchidae. One peculiarity of this group of trematodes consists in the fact that they have little specificity as regards their final hosts. All the species of the genus Monorchotrema (Haplorchis), and Heterophyes that have so far been investigated, aside from occurring as natural parasites in man (as well as in birds, in the case of the former) develop to maturity equally well in the common laboratory animals, cats, dogs, mice, etc. The present authors have succeeded in establishing infection of *H. yokogawai* experimentally in the Philippine monkeys (*Maccacus cynomulgus*). However, from purely biological grounds, (if there is any choice at all) fish-eating birds would seem to offer the most ideal natural host for the maintenance of parasitic cycle since these animals come more closely in contact with streams, lakes, and other bodies of water than any other animals known to be infected with members of this group.

Some authors, when speaking of the life cycle of members of Heterophyidae, show a tendency to qualify the molluscan and piscine hosts with the prefix "fresh-water," evidently implying that the larval stages of this group confine their multiplication and encystment in fresh-water snails and fishes, respectively. This implication is probably misleading; because it is known that some forms of marine fish spawn and leave their progeny in fresh-water streams where the young fishes live for sometime and grow before they migrate to the open sea to spend their adult life. Members of the family Mugilidae, for instance, spend their adult life as marine forms; but when young they

are, as a rule, brackish-water dwellers. On the other hand, some forms of fish (*Chanos chanos*) known to be fresh-water dwellers in their adult stage lay their young in the open sea, their progenies returning after sometime to brackish or fresh-water lakes and streams to grow to maturity. Thus, fishes apparently marine in habitat may get infected with metacercariae during their period of juvenile growth in fresh-water lakes and streams, and fishes known to be fresh-water dwellers may get infected during their early life in the sea. Asada (10) found that the molluscan intermediate host of *Heterophys nocens* is a brackish-water snail (*Tympanotonus microptera*) and that the cercariae of this parasite obtained from this snail die within 20 minutes in fresh-water but live for a long time in saline. Furthermore, according to this author, these do not attain full development in fresh-water fish, but encyst in marine fishes. The snail and fish hosts of *Cryptocotyle lingua, Littorina littorea*, and the cunner, respectively, are both marine forms (Stunkard, 1929). In the Philippines, several marine fishes have yielded upon being fed to experimental animals (as will be seen elsewhere in this work) a large number of heterophyid flukes including members of the genus Haplorchis.

Looss (52) advanced the view that, although flukes found in mammals and birds may appear morphologically indistinguishable, they should be regarded as physiologically different species or varieties. In other words, a single species, according to him, does not parasitise both birds and mammals. To put it in another way, the flukes after passing through their usual developmental parthenogenetic cycle and encysted stage in their molluscan and piscine intermediate hosts, respectively, must be returned to their avian hosts to complete their life cycle; and so *vice versa* in an analogous way with heterophyids infecting mammals. Supporting the idea of Looss, Ciurea (19b) argued that bird parasites, although they may develop in mammals, do not remain long in the intestine and are soon voided. The same results follow, he maintains, when parasites of mammals are acquired by birds. Faust and Nishigori (29) on the other hand maintain that at least in two members of Heterophyidae, *Stamnosoma formosanum* and *Monorchotrema taihokui* (=*Haplorchis pumilio*), the flukes develop equally well in either mammalian or avian hosts. Found naturally as adults in the night heron (*Nycticorax nycticorax*), the life cycles of these hetero-

phyids have been experimentally completed by these authors in various mammals, including man. The same evidence is also obtainable from the data of Ciurea (19b) on *Apophallus mühlingi*, found as natural infection of *Larus ridibundus* and introduced experimentally into the dog; and of Stunkard (80) on *Cryptocotyle lingua* found as natural parasite of gulls and terns and experimentally developed in rats. It is probable that the same is true of other members of the family. There seems, therefore to be no more justification, as Faust and Nishigori (29) have pointed out, for the creation of specific or varietal names for heterophyids which are morphologically identical even though they are found in birds on the one hand and in mammals on the other.

Faust and Nishigori (29), Stunkard (80), and other authors hold the view that probably the heterophyids of birds and mammals are all potential human parasites. On the other hand, the results of feeding experiments in Manila by Vasquez-Colet and Africa (85a & b) seem to present contrary evidence to this view. By feeding dogs and cats with 16 different species of marine, brackish-water, and fresh-water fishes, they were able to recover 13 different heterophyids distributed among 7 genera; but out of these only 4 species so far (*Haplorchis yokogawai, H. calderoni, H. taichui* and *Diorchitrema pseudocirrata*) have been recovered from man in this locality. *Stictodora manilensis, Stictodora guerreroi, Haplorchis sisoni, Haplorchis pumilio, Heterophyes expectans* (*Heterophyopsis expectans*), *Stamnosoma formosanum, Pygidiopsis genata, Pygidiopsis marivillai* and *Microstlistrum* sp. have been recovered in great abundance from experimentally infected laboratory animals, but not a single one of these heterophyids has been encountered in 297 human autopsies performed so far in this work. *Haplorchis pumilio* and *Stamnosoma formosanum*, however, have been experimentally developed in man by Faust and Nishigori (29), and Nishigori (66), respectively, as previously stated. Considering the fact that the majority of these fishes have been found to harbor the metacercariae of a large number of these heterophyids (indeed the Philippine mullet has yielded eight species upon being fed to experimental mammals), and considering further that almost all these forms of fish are eaten raw by a considerable proportion of the natives, it would seem that a greater number of them than has been actually reported in man in the

Philippines should occur in this host if really all of them are potentially capable of establishing infection in man. But in spite of the extensive human autopsies especially performed for the purpose of looking for heterophyid flukes in the Philippines, only five species (including *H. vanissima*) of this group have been so far reported in man in this country.

Of the five heterophyids recovered from the small intestine of man described in this work only the life history of *Haplorchis taichui* has been worked out completely. As already mentioned Faust and Nishigori (29) have determined *Melania oblique granosa* (Smith) as the molluscan (first intermediate) host of *Haplorchis taichui* in Formosa. According to these authors, the miracidium which hatches from the eggs penetrates the tissues of the snail to which it is adapted, and metamorphoses into a sporocyst. (This seems to be a distinct departure from what has been usually observed in the life cycles of other genera of Heterophyidae with respect to the method of infection of the snail host by the miracidium. In the case of *Apophallus venustus*, for example, the eggs, as pointed out previously by Cameron (14), pass into water, embryonate, and are swallowed by the snail, *Geniobasis livescens*. The same is true in the case of *Metagonimus yokogawai* and other heterophyids whose life cycles have been worked out.) Rediae are produced parthenogenetically within the sporocysts, and after a period of five to six weeks mature cercariae develop within the rediae. The cercaria is a lophocercous larva with pigmented eye-spots, and equipped with a long, powerful tail having fluted keeled margin which whips about violently, and seven pairs of cephalic secretory glands. If cercariae freed from the snail are put into a receptacle containing gold fishes, they are soon found to crowd around the fishes and finally invade their tissues. They become encysted on the cartilage of the fins and on the tissue of the palate and gill filaments. According to these authors seven species of fish, collected from the area of Taichu, Formosa, have been found naturally infected with metacercariae of this fluke. They are *Cyprinus carpio* (Linn.), *Carassius auratus* (Linn), *Zacco platypes*—(T. & S), *Pseudorasbora parva* (Schlegel), *Phodeus oceallatus* (Kner), *Gambusia affinis* (Baird and Girard), *Ctenopharyngodon idellus*. In the Philippines, the snail host of *Haplorchis taichui* or of any other heterophyid for that matter is still undetermined, while only one species of fish (Ophicephalus

striatus) has been determined so far to harbor the metacercariae of this particular heterophyid.

The piscine hosts of the majority of heterophyid trematodes so far identified or described in the Philippines are shown in table 2.

D. SPECIFIC ETIOLOGY AND INCIDENCE

Five members of the family Heterophyidae have been identified, or described as new forms from 33 autopsy cases with positive intestines, namely (1) *Haplorchis yokogawai* (Katsuta, 1932) Chen, 1936, (2) *Haplorchis taichui* (Nishigori, 1924) Chen, 1936, (3) *Haplorchis calderoni* (Africa and Garcia, 1935) Africa, 1938, (4) *Haplorchis vanissima* Africa, 1938, and (5) *Diorchitrema pseudocirrata* Witenberg, 1929. These parasites occurred either singly or in parasitic association of two or three species. In addition to these five heterophyids, a member of the family Microphallidae has been found in the intestine, either alone or often associated with heterophyid trematodes. This is *Heterophyes brevicaeca* originally described and assigned by two of us (C. M. A. & E. Y. G.) to the genus Heterophyes, but which upon further study by Tubangui and Africa (83) as stated elsewhere in this work, has been found to be more closely affiliated, and hence assigned to the family Microphallidae and renamed by them *Spelotrema brevicaeca.*

An unidentified species of Plagiorchis was encountered once, and *Echinostoma* (=*Euparyphium*) *ilocanum* twice among our cases positive for heterophyids. These trematodes were recovered from cases in which there were absolutely no indication of visceral complications. They are believed to have no possible etiological relation with the pathological condition we are describing in the present work. It may be remarked further that eggs of these trematodes are easily distinguishable from those of the heterophyids on account of their relatively large size.

Haplorchis yokogawai occurred 16 times in the 33 positive intestines of our series; *Spelotrema brevicaeca,* 11 times; *Diorchitrema pseudocirrata,* 6 times; *Haplorchis taichui,* 5 times; *Haplorchis vanissima,* once; and *Haplorchis calderoni,* twice. *Haplorchis yokogawai* occurred alone in 13 of the cases; *Spelotrema brevicaeca* alone in 6 of the cases; *Diorchitrema pseudocirrata* alone in 1 of the cases; *Haplorchis calderoni* alone in two of the cases; *Haplorchis vanissima* alone in 1 of the cases;

Spelotrema brevicaeca and *Haplorchis yokogawai* together in 2 of the cases; *Spelotrema brevicaeca* and *Haplorchis taichui* together in 2 of the cases; *Spelotrema brevicaeca* and *Diorchitrema pseudocirrata* together in one of the cases; *Haplorchis taichui* and *Haplorchis yokogawai* together in 1 of the cases; and *Haplorchis taichui* and *Diorchitrema pseudocirrata* together in 1 of the cases.

In 12 cases positive for flukes in the intestine and eggs in the heart associated with lesions presumed to be the cause of heart failure in these cases, *Haplorchis yokogawai* occurred alone in 7 of the cases; *Haplorchis taichui* alone in 1 of the cases; *Spelotrema brevicaeca* alone in 1 of the cases; *Spelotrema brevicaeca* and *Haplorchis yokogawai* together in one of the cases; *Spelotrema brevicaeca* and *Haplorchis yokogawai* together in 1 of the cases; and *Haplorchis taichui* and *Diorchitrema pseudocirrata* together in 1 of the cases.

It would thus appear that *Haplorchis yokogawai* is not only the most frequently encountered heterophyid in the human intestine in this country but also the most frequently associated with heart and other visceral lesions. It will also be noted that *Diorchitrema pseudocirrata* has never occurred alone in autopsies in which visceral complications were found. However, this observation cannot be taken as an indication that the latter heterophyid does not actually take part in the production of visceral lesions. The same may be said in the case of *Haplorchis calderoni* and *Haplorchis vanissima*, both of which did not figure at all in autopsies in which visceral complications were noted. To us it seems unlikely that organisms of the same group, more particularly, of the same genus such as the various species of Haplorchis, would behave differently in the same host. For this reason, it seems predictable, that *Haplorchis calderoni* and *Haplorchis vanissima*, which so far have not been recovered in our autopsies with visceral complications, may yet in the future be found involved. As stated previously 34 out of 297 autopsies in our series were positive for heterophyid either in the intestine or in the viscera or in both. From these figures it will be seen that in 11.44 per cent of human autopsies in Manila the bodies are found to be infected with heterophyid flukes. This figure is probably more apparent than real and does not represent the true incidence since, as stated above, our autopsies became more or less random and selected during the latter stage

of our investigation. Our first 108 autopsies, however, were nearly consecutive and uninfluenced or unprejudiced by our heart findings since at the beginning of our investigation we were still unaware of their existence. Nine of these 108 cases were positive for flukes in the intestine, of which five had heart lessons; so 8.33 per cent is probably nearer the actual incidence.

Of the 34 positive cases 15, or about 44 per cent, had been shown to have visceral complications. Of these fifteen cases, one had lesions in the brain; one had lesions in the spinal cord, as well as in the heart; thirteen had myocardial or valvular lesions presumed to be the cause of the heart failure in these cases; while one showed eggs in the heart but apparently unassociated with any serious pathological condition. Since the 89 enlarged hearts due to various causes, including the thirteen presumed to be due to these flukes, have been investigated in this work, it would seem that about 14.60 per cent of heart trouble in charity patients in the Philippines is caused by heterophyid infections.

E. DESCRIPTION OF SPECIES INVOLVED

HAPLORCHIS YOKOGAWAI (Katsuta 1932), Chen, 1936 (fig. 1, plate 2)

Syn.: *Monorchotrema yokogawai* Katsuta, 1932.

Chen (16c) gives the following description of this fluke:

"The worm is generally flattened dorso-ventrally at the anterior half, and is oval at both ends. The body 0.54-0.94 mm. long with an average size of 0.7 × 0.284 mm., and is armed with backwardly directed scale-like spines, either lying flat upon the body or standing up obliquely at an angle. They gradually disappear near or at the posterior tip of the body.

"Oral sucker terminal 0.065 × 0.062 mm. ventral sucker buried in parenchyma closely associated with the genital sucker at the middle of the body to form a ventro-genital-sucker complex. Anterior border of the ventral sucker is armed with numerous tiny spines, very seldom more than 1 u long, uniformly or partially scattered on the surface, surrounded by a semicircular row of the same kind of spines which, because of regional differences, are often more conspicuous. Eccentrically on the spiny surface, or sometimes in the center, there are usually two

chitinous structures with an irregular margin of approximately 5 × 2 u, or there may be a bush of irregular spiny projections instead. These structures may not be seen in many specimens because of the peculiar position of the ventral sucker. They ornament the genital orifice in the genital sinus. The size of the surface covered by the spines is about 0.026 mm. diameter when round, but very often it may tend to be semicircular, or even somewhat irregular.

"Mouth opens into prepharynx about 0.07-0.13 mm. long, intestinal caeca large, reaching the level of the posterior border of the testis.

"Testis large, single 0.142 × 0.119, posterior to ovary. The two are often very close together. Directly or obliquely in front lies the smaller, round or oval ovary about 0.072 × 0.059 mm. Seminal receptacle 0.134 × 0.104 mm. to the right and somewhat posterior. Left of the ovary and anterior is the seminal vesicle which lies diagonally from left to right and often in two constructions, anterior portion 0.07 × 0.053 mm. posterior portion 0.037 × 0.027 mm. A narrow prostate duct goes forward which continues as a short ejaculating duct joining the genital sinus. Uterus sinous and contains numerous eggs. Vitellaria consist of small follicles, all situated behind seminal vesicle. Eggs oval, 28.48-30.26 u long × 14.24-16.02 u wide, often possesses a minute filament at the posterior pole."

HAPLORCHIS TAICHUI (Nishigori, 1924)
Chen, 1936 (fig. 2, plate 2)

Syn.: *Monorchotrema taichui* Nishigori, 1924
Monorchotrema microrchia Katsuta, 1932

The following is Chen's (16c) description of this fluke:

"The worm is flattened and slightly narrowed at the anterior half, but broad and almost cylindrical at the posterior half, with extremities gradually rounded off. Body covered with scales, more conspicuous at the anterior half and diminished in size and number toward the posterior extremity. The average size of nine worms is 0.66 × 0.32, length 0.58-076 mm., width 0.27-0.42 mm. Oral sucker terminal and about 0.06 mm. diameter. Ventral sucker buried in the parenchyma slightly to the right of the body and closely associated with the genital sucker, forming ventro-genital sucker complex. Anterior end of ven-

tral sucker armed with fourteen to twenty, more often fifteen, spines arranged like a fan placed diagonally toward the lower right corner of the sucker. The largest spines which are from 18-21 u long, are at the middle of the fan and those toward the edge become shorter and more slender. Some may be as short as only 1 u, although rarely. The fan is 0.035-0.053 mm. across.

"Prepharynx conspicuous, about 0.02 mm. long. Pharynx is 0.032 × 0.027 mm. Oesophagus slender about 0.09 mm. long. The two intestinal caeca are large and extend to the posterior end of the body. Testis large, 0.11 mm. long by 0.085 mm. wide. In front of it and often close to it is the smaller ovary about 0.065 mm. diameter. To the right and somewhat posterior is a large seminal receptacle 0.107 mm. diameter. Seminal vesicle divided into two parts, the posterior, smaller, 0.036 × 0.046., the anterior one larger 0.07 × 0.09 mm. The two are distinct, having a constriction at the region of junction. They are obliquely placed on the left side of the body just below the ventral sucker. The anterior seminal vesicle is narrowed to form a tubular prostate duct which continues forward as a short ejaculatory duct and opens into the genital sinus. The uterus contains numerous eggs, is much coiled, and after a sinus course reaches the vagina. Vitellaria consist of small follicles located behind the seminal vesicle. Eggs small with a minute filament on the posterior end. They are 29.5 × 15.7 u on the average, the length varying from 27.3-32 u, and width from 14.24-17.8 u."

HAPLORCHIS CALDERONI (Africa & Garcia, 1935)
Africa, 1938 (fig. 3, plate 2)

Syn.: *Monorchotrema calderoni*, Africa & Garcia, 1935.

Africa (6c) describes this fluke as follows:

"Body small, 0.47 to 0.55 mm. long, 0.25 to 0.26 mm. wide, pear-shape, covered with scale-like spines except at posterior end. Oral sucker subterminal, 0.05 mm. in diameter; prepharynx short; pharynx ovoid, 0.03 mm. by 0.027 mm.; oesophagus long and capillary, 0.15 mm. long, 0.015 mm. wide; intestinal caeca tubular, extending to posterior end of body, beyond posterior border of testis.

"Genital sac ringlike, 0.035 to 0.040 mm. in diameter, situated in the median line immediately behind the intestinal bifurcation and occupied by a small protrusible gonotyl ornamented with extremely minute spines generally distributed within a circular area, 0.010 to 0.015 mm. in its central surface. At the bottom of the genital sac and continuous with the gonotyl, is the rudimentary acetabulum, 0.021 to 0.035 mm. in diameter.

"The single, large, spherical or slightly ovoid testis, 0.108 to 0.126 mm. in diameter, occupies the median field of the posterior third of the body. The seminal vesicle consists of three very unequal parts; the first or posterior portion is a small ovoid thin-walled sac, 0.047 mm. long, 0.042 mm. wide, bent under very much larger and longer second sac, or explusor, from which it is separated by a short constriction. The expulsor is enormously long, 0.23 to 0.35 mm. long, 0.035 to 0.56 mm. wide, with a thick (0.0035 to 0.0045 mm.), chitinized wall, running alongside and under the left caecum towards the ventro-genital sac where it terminates in a short ejaculatory duct in common with the vagina. Ovary roundish, 0.055 to 0.080 mm. in diameter, situated in the right side of the body about half way between the testis and the ventro-genital sac. Receptaculum semenis spherical, 0.070 to 0.103 mm. in diameter, situated at the right side opposite the seminal vesicle between the testis and the ovary. The oviduct descends from the inferior border of the ovary and meets the tube coming from the receptaculum seminis to form a common duct which proceeds medially toward the ootype. The uterus descends at the left side of the body, and after describing several coils in the posterior half of the body ascends at the right side alongside the right caecum and then turns medially toward the ventro-genital sac where it terminates in a vagina with denticulated inner lining in common with the ejaculatory duct. The vitellaria are composed of small follicles arranged in groups distributed in the posterior third of the body behind the seminal vesicle. Eggs, 0.021 to 0.025 mm. by 0.011 to 0.015."

HAPLORCHIS VANISSIMA (Africa, 1938)
(fig. 4, plate 2)

Africa (6c) describes this fluke as follows:
"Body ovoid or elongate, 0.375 to 0.512 mm. long by 0.25 to

0.312 mm. wide, covered with minute scale like spines except at posterior extremity. Oral sucker sub-terminal, 0.049 mm. to 0.060 mm. in diameter; prepharynx 0.028 mm. to 0.038 mm. long by 0.018 to 0.035 mm. wide; oesophagus 0.042 to 0.060 mm. long by 0.017 mm. wide; intestinal caeca extending posteriorly a little beyond the posterior margin of the testis.

"Genital sac voluminous, 0.143 mm. to 0.158 mm. long, 0.105 mm. to 0.120 mm. wide, situated transversely across the median field considerably beyond the middle of the body, pushing upward the intestinal bifurcation in most specimens. Genital sac occupied by a large oval and peculiarly ornamented gonotyl, 0.094 mm. to 0.120 mm. long, 0.087 to 0.105 mm. wide. The ventro-genital sac is the most prominent structure in the fluke. Surface of gonotyl partially covered with spines, larger and more thickly set at edge and becoming smaller and rarer centripetally until they abruptly disappear completely in the central area. The spines, which vary in length from 0.0042 to 0.0085 mm, bear a striking resemblance to bamboo shoots being septate, septa two to three, the topmost conical. Left pole of the gonotyl capped with a group of small (0.0015 to 0.0054 mm. in diameter), glistening, white, polygonal plates, plates 28 to 32, with pavement-like arrangement, and apparently held together in position by a pair of large claw-like, chitinous, highly refractile plates (0.033 to 0.042 mm. long from tip to tip, 0.025 to 0.027 mm. at widest point), which lend a grotesque appearance to the fluke.

"The single testis, 0.112 to 0.175 mm. long, 0.070 to 0.155 mm. wide, transversely oval, median in location in posterior quarter of the body, somewhat removed from posterior extremity. Seminal vesicle voluminous, 0.157 mm. long, 0.112 mm. wide, placed on left side between testis and ventro-genital sac. Ovary oval, 0.087 mm. long, 0.057 mm. wide, immediately in front of testis but inclined to right side of body. Receptaculum seminis, 0.054 mm. long, 0.45 mm. wide, placed along left side of ovary but somewhat anterior to latter. Uterine coils all behind the ventro-genital sac. Vitelline glands consist of small follicles arranged in groups, all behind seminal vesicle. Eggs 0.025 to 0.030 mm. by 0.018 to 0.021 mm."

STELLANTCHASMUS FALCATUS (Onji and Nishio, 1916)
(fig. 5, plate 2)

Syn.: *Diorchitrema pseudocirrata** Witenberg, 1929.

Witenberg (90a) describes this fluke as follows:

"They are small worms reaching 0.3-0.6 in length and 0.2-0.3 mm. in breath. The body is almost round in cross section, the anterior portion being narrower than the posterior one. The whole body, except the most posterior part, is covered with small spines.

"The oral sucker is 0.04-0.05 mm. in diameter; the prepharynx is 0.01-0.04 mm. the pharynx 0.03-0.04 mm. the oesophagus 0.07-0.14 mm. in length. The intestinal bifurcation is situated in front of the middle of the body; the intestinal caeca are equal, sometimes thicker than the oesophagus and reach the anterior borders of the testis.

"The testes lie at the same level at the posterior border of the body. They are globular or slightly elongated and measure 0.06-0.12 mm. in diameter. When they are small they are separated from each other by the stem of Y-shaped excretory vesicle, but usually they are large and adjacent.

"The globular ovary, 0.03-0.05 mm. in diameter, lies in front of the testes to the right of the middle line. To the left and a little behind it lies the seminal receptacle, which, according to the amount of distention, may be larger or smaller than the ovary.

"The vitellaria consist of 20 to 40 large elongated follicles dispersed between the dorsal surface of the body and the testes.

"The vasa efferentia open into a small, usually globular seminal vesicle, 0.018-0.037 mm. in diameter, connected with a short tubule with the expulsor. The latter is oval and relatively very large, being 0.07-0.10 mm. long and 0.04-0.06 mm. wide, with very thick walls in which spiral fibers are clearly seen. It lies in the middle portion of the body at the left side and is oblique to the long axis of the body. A short ejaculatory duct rises from the expulsor and unites with the end portion of the uterus. The junction of the uterus and ejaculatory duct is surrounded by a mass of prostatic cells.

---

*In default of Onji and Nishio's original description of *Stellantchasmus falcatus* Witenberg's description of *Diorchitrema pseudocirrata*, which is believed to be an identical species, is used here.

"The uterus in adult specimens fills the whole free space between the expulsor and testes. It joints the ejaculatory duct to form a short hermaphroditic duct opening into the genital aperture. The latter opens on the dorsal wall of the ventro-genital sac at the base of the small ventral sucker, 0.03-0.04 mm. in diameter. The ventro-genital sac lies to the left of the middle of the body.

"The eggs are oval, 0.018-0.021 mm. in length and 0.009-0.012 mm. in width."

*SPELOTREMA BREVICAECA** (Africa and Garcia, 1935) Tubangui & Africa, 1939 (fig. 6, plate 2)

Syn.: *Heterophyes brevicaeca* Africa and Garcia, 1935.

The following is the description given by Tubangui and Africa (83) for this fluke:

"Body pyriform to triangular in outline, thinner anteriorly than posteriorly, 0.5 to 0.7 by 0.3 to 0.4 millimeter; in preserved specimens dorsal surface convex, ventral surface concave, with acetabulum prominently elevated. Cuticle armed with scale like-spines from anterior end to posterior level of vitellaria. Oral sucker subterminal, 0.065 to 0.095 millimeter in diameter; acetabulum slightly larger than oral sucker, 0.080 to 0.105 millimeter across, at middle of body length behind that level in well-extended specimens. Prepharynx very short, in most of the specimens practically absent; pharynx 0.032 to 0.034 by 0.034 to 0.043 millimeter; oesophagus 0.08 to 0.09 millimeter long, with relatively thick walls but narrow lumen; intestinal caeca wide in diameter but short, only 0.15 to 0.19 millimeter long, not reaching posteriorly beyond middle level of acetabulum. Genital pore near left margin of acetabulum, communicating with a small genital sinus.

"Testes globular to oval, postovarial, 0.052 to 0.075 by 0.067 to 0.094 millimeter with zones coinciding and fields widely separated, one on each side of body behind level of acetabulum, and

*This parasite, although not a heterophyid, is included here because it figured among the small trematodes incriminated in this work. Dr. E. W. Price of the Zoological Division, Bureau of Animal Industry, Washington, D. C. suggests the term heterophyoid for flukes which bear strong resemblance to members of Heterophyidae but which can not be included in this family on account of either morphological or physiological reasons.

more or less completely concealed in ventral view by anterior vitelline follicles and uterus. Seminal vesicle large, pyriform, 0.090 to 0.110 by 0.055 to 0.075 millimeter, crowded in between intestinal caeca and acetabulum and slightly overlapped by the latter; in contracted specimens it is displaced posteriorly, dorsal to acetabulum. Seminal vesicle followed by a short prostate and then a long coiled ejaculatory duct which opens into the genital sinus through the apex of a muscular, cone-shaped body (kegelformiger Korper) that measures 0.037 to 0.045 by 0.030 to 0.034 millimeter.

"Ovary slightly oval, usually a trifle larger than the testes, 0.052 to 0.098 by 0.067 to 0.105 millimeter at or near middle of body length, on right side of median line, between acetabulum, right intestinal caecum and right testis. Seminal receptacle absent. Uterus moderately long, loosely coiled, mostly postacetabular, its terminal portion (metraterm) opening into genital sinus near base of conical body and to the left male genital opening. Vitellaria prominent, mostly posttesticular, follicular consisting of two groups of 7 to 9 (usually 8) oval to roundish follicles each. Small vitelline reservoir and shell gland median, immediately behind acetabulum. Eggs small, yellowish, operculated, 15 to 16 by 9.4 to 10 microns."

"Excretory pore dorsoterminal at posterior end of body; excretory bladder V-shaped, its branches reaching anteriorly to level of acetabulum."

F. DESCRIPTION OF THE EGGS

The mature egg of *Haplorchis yokogawai* (fig. 1, plate 3) which appears in the feces is light yellowish-brown almost ovoid, gradually narrowed from the middle toward the opercular pole, its width being greatest at the equator. The egg shell is comparatively thick, its thickness being more or less even throughout except near the opercular area where it widens a bit as it joins the operculum (which is like an inverted watch-glass), and at the abopercular pole where it often thickens to form an external protuberance or tuberculation. Unlike the Clonorchis egg in which the operculum is comparatively smaller thus giving rise to a more exaggerated shoulder, in this egg the operculum is broad and seems exactly to fit the rim of the egg shell proper. For this reason the egg of *Haplorchis yokogawai* has

a more rounded anterior contour than the Clonorchis eggs, although there is also present in the former a slight shouldring. At the posterior end there is, in about 40 per cent of the eggs, a distinct external thickening or tuberculation which reminds one of the Clonorchis egg. This thickening is absent in about 50 per cent and rather exaggerated in about 10 per cent of the eggs examined. Not infrequently the thickening forms a sort of spike which may end in a filament. This latter characteristic may be a sign of immaturity.

The interior of the egg is almost filled up by a larva (miracidium) covered with a number of long delicate cilia except at the anterior conical end. Faust and Nishigori (29) were able to describe two lateral ducts just behind the conical end of the larva which they think are the openings of symetrical unicellular glands, producing histolytic ferments that enable it to penetrate the tissues of the molluscan host. The epithelium of the larva is composed of a number of polygonal cells formed in a definite pattern. These cells are often seen deeply stained and very prominent in eggs found in histological sections of infected viscera stained with haematoxylin and eosin. The eggs measure from 0.028 to 0.030 mm. long, and 0.014 to 0.016 mm. wide.

The above description can be applied to the eggs of other members of Haplorchis except for their differences in size and other minor details. For instance, in *Haplorchis taichui* (fig. 2, plate 3) the thickening at the abopercular end is absent in only 33 per cent of the eggs; a slight thickening is present in 56 per cent; and the thickening is very pronounced or exaggerated in 11 per cent of the eggs examined. The eggs of *H. taichui* are slightly larger than the eggs of *H. yokogawai*, their length varying between 0.027 and 0.032 mm., and their width between 0.014 and 0.017 mm. In general appearance, the eggs of *H. calderoni* and *H. vanissima* are like the eggs of *Haplorchis yokogawai* and *H. taichui;* and, if there is any difference at all, it is only in size, as above stated.

Superficially, the eggs of *Diorchitrema pseudocirrata* look like the eggs of Haplorchis. Closer examination, however, will reveal the complete absence of the thickening or tuberculation at the abopercular end, which, as above stated, is found in about 40 per cent of the eggs of *H. yokogawai* and in about 56 per cent

of the eggs of *H. taichui.* This thickening was not found in more than two-hundred eggs examined. The shouldering at the opercular end is even less conspicuous in the Diorchitrema than in the Haplorchis. The eggs of *Diorchitrema pseudocirrata* are very much smaller than those of the members of the genus Haplorchis involved in this work. Their length measures between 0.018 and 0.021 mm. long and their width between 0.009 and 0.012 mm. wide.

In general appearance the eggs of *Spelotrema brevicaeca* (fig. 3, plate 3) are similar to those of the Haplorchis, but they are apt to be relatively wider and consequently more nearly ovoid than the eggs of the latter. They are also very much smaller, measuring between 0.015 and 0.016 mm. in length and between 0.0094 and 0.010 mm. width. 37.66 per cent of the eggs are without any thickening at the abopercular end; 56.66 per cent have a distinct thickening or tuberculation; while in 8.68 per cent the thickening is very pronounced and apt to end in a filamentous process.

G. DESCRIPTION OF THE METACERCARIA

In general the metacercaria of heterophyid trematodes is an ovoid opalescent body scarcely visible to the naked eye. The locality where it is more abundant varies with the species of fluke and the piscine (second intermediate) host. For instance, the metacercaria of *Haplorchis yokogawai* is more abundant in the muscles of the caudal half of *Arius manillensis* than elsewhere in the body of this fish. The encysted larva is easily teased out from the muscle fibers, there apparently being very little effort, if at all, to encapsulate the larva by fibrosis on the part of the piscine host. When viewed under the microscope, even under low magnification, the larva which it contains is found to be actively moving inside, thrusting its cephalic end now here, then there, its whole body simultaneously contracting and relaxing incessantly, the organism being apparently never at rest while alive. The larva also performs rotatory motions or at times only sways from side to side. For this reason it is hard to make out the internal structures of the larva. In order to immobilize the larva for purposes of study, it is decapsulated by applying a gentle pressure on the coverslip and then the excess fluid (normal saline solution is used for this purpose)

is drained by blotting paper applied at the edge of the coverslip. A good view of the internal structures of the flattened out larva can then be obtained.

The following descriptions of the metacercariae of three flukes involved in this work, namely *Haplorchis yokogawai, H. calderoni* and *Diorchitrema pseudocirrata,* have been based on careful examinations of a considerable number of larvae in the fresh state, which were part of those used for experimental feedings of laboratory animals done in this institute to determine the piscine intermediate hosts of Philippine heterophyid trematodes. The specific identity of each one of these metacercariae has been ascertained by the recovery of their corresponding adults in laboratory animals. The piscine intermediate host or hosts of each of these three heterophyids together with those of other members of this group have been determined by feeding experiments as shown in table No. 2. A more detailed morphological study of the heterophyid metacercariae so far identified in the Philippines is being prepared for publication by Dr. Ana Vasquez-Colet of this institute in collaboration with one of us (C. M. A.).

The Metacercaria of *Haplorchis yokogawai* (fig. 4, plate 3) : The metacercariae of this heterophyid are ovoid, opaque, greyish or pearly-looking bodies, measuring on the average 0.180 mm. long and 0.146 mm. wide. Some of them appear rounded or spherical but this is probably because the cysts were viewed endwise. The cyst wall is relatively very thin hyalin, less than two microns in thickness, and appears as a single line under low magnification. The cysts are apparently very loosely attached to the muscles, since the slightest manipulation of bits of fish flesh cause them to drop to the bottom of the dissecting dish. Within is a motile larva, which is usually doubled up because its length is very much greater than the containing cyst. Although the larva is moving incessantly, under high magnification, the outline of the alimentary system, the two pigmented eye-spots on the anterior end of the larva, and the very prominent and pulsating excretory bladder containing black granules at the posterior region are often distinctly seen. Even the position of the ventro-genital-sucker complex is occasionally revealed, when the gonotyl with its tiny ornamental spines generally distributed over its surface and a pair of shiny plates, frequently with bushy

outgrowths, comes to view. The larva is covered with tiny scale-like spines, except at the very posterior end of the body. The testis and the ovary, although already present at this stage, are often obscured by the excretory bladder.

When the larva is decapsulated and flattened under the coverslip, a more positive view of the internal structures is presented. The excysted larva measures 0.426 mm. long and 0.184 mm. wide. The alimentary system is more or less completely formed, consisting of a mouth surrounded by an oral sucker, a prepharynx, pharynx, oesophagus and intestinal caeca, which reach beyond the testis posteriorly. The excretory bladder, which is very prominent in the encysted larva, has become very much reduced in size and pushed to the posterior extremity. In front of the excretory bladder lies the single testis, which is seen as a large globular whitish or greenish granular body. Immediately in front is a similar though smaller body, the ovary. Midway between the ovary and the intestinal bifurcation lies the ventro-genital-sucker complex. This structure consists of a pear-shaped cellular dorsal portion (the rudimentary acetabulum) buried in the mesenchyma, and a noncellular ventral portion, the gonotyl, which bears numerous ornamental spines with general distribution and a pair of relatively larger and shiny plates which may be plain or provided with bushy outgrowths. It will thus be seen that, even at its encysted stage, the fluke already bears the morphological characteristics of the adult. In fact, no one who is familiar with the morphology of *Haplorchis yokogawai* in its adult stage will upon seeing the character of its metacercarial stage hesitate to connect the two stages. In some of the metacercariae, however, these structures described above are either partially or completely lacking. These are probably the immature individuals which if ingested even by a suitable vertebrate host fail to develop.

The Metacercaria of *Haplorchis calderoni:* The encysted larva of *H. calderoni* is more or less similar to that of *H. yokogawai* in size and general appearance. It measures on the average 0.186 mm. long and 0.142 mm. wide. Examination of decapsulated and flattened larva, however, will reveal specific differences in the internal structures. Whereas in *H. yokogawai* the intestinal caeca reach beyond the posterior level of the testis posteriorly, in *H. calderoni* these organs extend only as far as

the middle of the testis. The very long seminal vesicle which is characteristic of the adult fluke is already very conspicuous in its larval stage. The ventro-genital-sucker complex is also pear-shaped, consisting of a cellular dorsal portion (the rudimentary acetabulum) buried in the mesenchyma and a ventral noncellular portion, or gonotyl, showing on its surface very minute spines which are even smaller than and not so numerous as the spines in the gonotyl of *H. yokogawai.* The pair of plates observed in the gonotyl of *H. yokogawai* is absent in the gonotyl of this fluke. The excretory bladder, testis, and ovary assume the same general characteristics and positions as those in *H. yokogawai.* As in *H. yokogawai* the larval stage typifies the adult in this fluke.

The Metacercaria of *Diorchitrema pseudocirrata:* Macroscopically the cyst of this heterophyid can not be distinguished from those of the Haplorchis. It is an oval body measuring, on the average, 0.268 mm. in length and 0.190 mm. in width. There is a large black mass opposite the oral sucker. The cyst wall is thin hyalin, about 2 microns in thickness, appearing as a single line under low magnification. Under higher magnification, especially in excysted specimens, the difference between this cyst and those of the Haplorchis becomes very evident, because of the two testes, which lie side by side in the same level at the posterior end. Other structures visible are the ovary, the excretory bladder, the large seminal vesicle, of which the middle or expulsor portion bears spiral fibers, the ventro-genital-sucker complex, the excretory bladder, and the completely formed alimentary system.

We have never recovered *Spelotrema brevicaeca* from experimental animals fed with metacercariae obtained from the flesh of Philippine fish, whether fresh or marine forms. In two extensive sets of feeding experiments to determine the piscine intermediate hosts of Philippine heterophyid trematodes performed in Manila (85a & b) which involved sixteen different species of fresh water and marine fish and which yielded the adults of thirteen different species of heterophyids, not a single specimen of Spelotrema was recovered from any one of the experimental animals. This finding is in accord with the view that the microphallids do not utilize fish as second inter-

mediate host. Ochi* (1928) found encysted larval trematodes in the muscles of *Macrobrachium nipponensis* (a species of crab), which, upon being fed to albino rats, puppies, and cats, developed into mature specimens of *Spelotrema* (Levinseniella) *minus*. According to Young (95) the cercaria of *Levinseniella cruzi* (?), which belongs to the ubiquita group of Lebour, inhabits the snail *Olivella biplicata*. From here it passes to the sand crab, *Emerita analoga*, which later, when eaten by the birds, infects them with the adult trematodes. In view of these facts the metacercariae of *Spelotrema brevicaeca* will most likely be found in certain species of Philippine crabs. In this connection it may be mentioned that raw crabs form a substantial item in the diet of many Filipinos.

VI. PATHOLOGICAL ANATOMY

A. SMALL INTESTINE

In no instance does the small intestine show any gross change that would suggest the presence of the flukes in the deeper tissues. The only gross changes noted are slight congestion and petechial submucous hemorrhages, a finding not infrequently encountered in other diseases, although specially common in cases of sudden death and beriberi.

While flukes could be demonstrated in the intestinal scrapings in almost all of the cases studied, lack of definite lesions indicating their presence in a locality does not permit us at this time to observe the local reaction of the intestinal tissues to the presence of the worms. Numerous attempts have been made to study the local reaction against the parasites *in situ* by extensive histological sectioning of the intestine at different levels but so far we have not succeeded. We can, however, surmise from the results of experiments in animals by Yokogawa (93a); Ciurea (19b); Faust and Nishigori (29); and Africa (6a & b) that there probably are not much local reaction in the intestine to their immediate presence. Lack of intestinal symptoms even in our most heavily infected cases may also be taken as an indication that tissue reaction in this organ is insignificant.

* Ochi, Sigeru.—Pri Microphallus minus n.sp. nova trematodos peco, kies la interhusto esos "Palaemon", speco de salikoko (Japan). C. Tokio Izi Sinsi, No. 2578, 1928.

From the results of their experiments in cats, dogs, and rats, Faust and Nishigori (29) surmised that on the whole the pathological changes due to the presence of these trematodes in the intestine are usually negligible, except in cases of very heavy infection in which extensive stretches of the mucosa may become involved and give rise to mild digestive disturbances and even persistent diarrhea. They also mentioned that the intestinal epithelium may become slightly atrophied and wide stretches of solitary intestinal glands are occasionally seen.

Africa (6a & b) in his experiments with pups and kittens involving *Haplorchis yokagawai* (Katsuta 1932) observed very mild tissue reaction around the worms in the intestinal wall. He remarked further that the general absence of attempts to encapsulate the parasites by fibrosis may account for the filtration of eggs into the general circulation observed in human cases. Apart from flattening or pressure necrosis of the epithelium at the bases of the villi or glandular crypts occupied by the worms, and slight endothelial proliferation observed occasionally around the parasites that lie in the tunica propria, and still more rarely, mild fibrosis around the worms, there are no other pathological changes recognizable. Polymorphonuclear leucocytes, especially eosinophiles, are scarce and foreign-body-giant cells are conspicuously absent quite in contrast with what is usually observed in the case of other helminths or their eggs buried in the tissues of the host.

B. HEART

1. Gross Lesions

Grossly, the heart shows nothing definite and specific. It is somewhat dilated, with slight thickening of the musculature, specially noticeable on the right side, which are gross pathological findings on which the diagnosis of cardiac beriberi is usually made. In those hearts, however, with thickening or sclerosis of the mitral valvular leaflets, the hypertrophy is considerably more marked on the left side. Subepicardial hemorrhages, petechial and diffuse, are quite frequent and prominent findings. These may be present in any locality, but are more common and marked on the right side.

When any of the valves are involved, as in five of our cases, the leaflets are thick, hard, and opaque. The contour is

undisturbed. The endocardial surface, except in one case, is not disfigured by ulcerations or scar formation or adhesions between adjacent leaflets, as is commonly observed in active infective endocardial involvement, or in its healed state. On the contrary, the surface of the valve in most of our cases is perfectly smooth and the leaflets are separate and distinct. The valve is distinctly thickened and indurated because of fibrosis, which in the cases studied is confined to the periphery with deposition of calcium in the central interior. These valvular features, characterized by thickened, indurated, or calcified leaflets undistorted and free from adhesions, with perfectly smooth endocardial surfaces, and presenting no evidence that might indicate previous inflammatory endocardial involvement, rheumatic or otherwise, have from time to time prior to this work come under the observation of one of us (W. de L.) at the autopsy table. To this condition, the noncommital diagnosis of valvular sclerosis has been usually given.

2. HISTOPATHOLOGY

(a) Myocardium

Histologically the lesions in the heart can be divided into: (1) acute or of recent development, of a purely vascular nature; (2) relatively chronic but specific, incited by a more or less prolonged residence of the eggs in the cardiac wall; (3) fibrosis following absorption of the specific tissue reaction or of chronic edema.

The acute lesion being in the nature of an acute vascular response is generalized in the entire cardiac area, and, except for the intensity, partakes of the same nonspecific characteristics noted in other vascular changes due to other causes. Its nature can only be diagnosed in association with the findings of eggs in the musculature and with the eventual demonstration of the more specific chronic local tissue reaction. The acute tissue changes are more marked and more easily detected in and around the areas of haemorrhages where eggs are also found in considerable numbers.

The acute lesions consist of (1) marked interstitial and subepicardial edema, (2) intense capillary injection, with haemorrhages in the epicardium and myocardium, and (3) capillary embolism and fragmentation of the muscle fibers.

Edema:—The edema is very extensive, stretching to the maximum all the available spaces that can possibly be flooded. It might be termed dropsy, since the muscle fibers themselves are not much involved. The fluid penetration is so great that the epicardial lining is rendered very thick and the outline of the cells lining the numerous and intricate tissue spaces are rendered definitely visible. The minute spaces between muscle bundles have become very much exaggerated and the delicate fibrous tissue fibrils stand out clearly, definitely, and distinctly, forming a network in the meshes of which the engorged capillaries can be seen as small rounded islets in cross section or as cords in longitudinal section. This marked edema, in the absence of any observable hypertrophy of the muscular fibers, is perhaps mostly responsible for the apparent increase in the size of the heart.

One can not fail to notice, when examining histological sections of these hearts, the intensity of the vascular engorgement. Not only are the larger capillaries found in spaces between muscle bundles affected, but also the very minute one-cell-size capillaries found in between the individual muscle fibers. Under the low power, the latter condition may be taken as intramuscular haemorrhage, but on careful observation under the high power, one can see that the cord of the single row (file) of red cells is well contained in dilated minute capillaries. The injected vessels stand out prominently into the edematous spaces, where their color contrasts markedly with the unstained watery surroundings.

In the epicardial regions, the more superficial and larger vessels, not being amply supported on all sides, break up and a more or less diffuse haemorrhage results which is even more visible grossly on the surface of the heart. Frequently deeper vessels break into haemorrhage, evidently due to the presence of enormous numbers of eggs in their lumen (egg emboli) or to the presence of egg shells (shell emboli) (Fig. 1, plate 5).

Embolism and fragmentation of muscles:—The lesion that is of much significance is the formation of capillary emboli in vessels where eggs are present in sufficient numbers to block the capillaries, forming egg embolism. In some sections such as in (fig. 1, plate 4) there is such an embolus formation, but the capillaries have not as yet been ruptured. In this figure, the blood vessel wall is still intact, but around the eggs the red blood

cells are beginning to show signs of degeneration and clumping. Here and there, in spaces created by the fragmentation and retraction of muscle fibers, are masses of ill-defined conglomerated cells about the eggs. These are taken as disintegrated red cells discharged from the broken capillary, the site of egg embolism. What probably happens is that the eggs upon blocking a capillary vessel, produce sudden ischaemia distad, thereby setting the individual muscle fibers, which depend for their nourishment upon this supply, in violent convulsions, ending in fracture of the individual fibers. The blocked and engorged capillary now lacking support on all sides ruptures and evacuates its contents. This may explain the identical positions of the eggs in the different sections, i.e., ova in spaces between fragmented and retracted muscle fibers and adhering to them are granular debris of conglutinated red cells (fig. 2, plate 4). Not infrequently very large numbers of ova intermixed with granular debris are found packed in wide and long stretches of spaces in between muscle bundles (fig. 2, plate 5). This latter finding may be interpreted as haemorrhages resulting from egg emboli of larger vessels which have dissected apart the muscle bundles. Occasionally also are found what appear to be intravascular clots consisting of fibrin mass and conglutinated remains of disintegrated erythrocytes within larger vessels which in serial sections show encrusted in them here and there at different levels or depths eggs much after the fashion of raisins in bread (figs. 1 & 2, plate 6).

Chronic specific lesions:—What we consider here as chronic specific lesions consist of well-circumscribed and well-contrasted sheets or columns of deeply basic staining tissue made up of cells of the monocytic and histiocytic types of endothelial cells in the older ones densely packed in a groundwork of fibrous tissue (figs. 1 and 2, plate 7; fig. 1, plate 8). In the younger lesions intact erythrocytes are seen intermixed with the endothelial reactive tissue cells. While lymphocytes are occasionally encountered among the endothelial cells, polymorphonuclears (both neutrophiles and eosinophiles) are scarce or completely absent. No foreign-body giant cells have been encountered so far in the examination of thousands of histological sections. This peculiar specific reaction seems to be a response to the spilled contents of the eggs, or substance that emanates from them, and not to the presence of intact eggs themselves

as this tissue is spread over a large area where eggs and shells are found, but the reacting cells do not gravitate around them as centers to form typical egg-tubercles, as is usually the case with infection of other helminth eggs, such for instance as those of schistosomes. The eggs or broken shells are within this mass of tissue reaction, but they may be located either in the periphery, in the middle, or in any intermediate position, and the concentration of the reacting cells remains more or less even throughout, unaffected by the number or proximity of the eggs (fig. 1, plate 17). In view of this apparent indifference of the reactive cells to the presence of the eggs themselves in their midst, the ova are considered here to have played a mere mechanical part in the production of these lesions. In other words, the cellular reaction is apparently intended principally to organize and repair whatever damages have resulted from haemorrhages, embolism or thrombosis, presumably caused by the plugging of vessels with ova. The possibility is also suggested that a substance contained in this ova and peculiar to them is diffused from them to the surrounding tissue through impaired opercula or broken shells, and that this substance, by virtue of certain chemotactic influences, invites or incites this peculiar and perhaps specific cellular proliferation.

These lesions stain heavily with haematoxylin, which imparts to them a characteristic tinctorial appearance, assisting greatly the microscopist in spotting them, or the presence of the eggs in them or in their immediate vicinity. Indeed, time and again, as mentioned earlier in this work, we have been guided almost unerringly by this specially stained and peculiar reactive tissue to the exact spot of trouble in our examinations of myocardial sections. Older areas, while retaining the relatively heavy haematoxylin stain, become more frankly fibrous in nature and arrangement apparent even under low magnification (fig. 2, plate 9).

These reacting tissues are found at the sites of haemorrhage or embolic or thrombotic processes and seem to follow the clots even in the remotest regions. We found them, for example, not only at the sites of broken vessels in the interstitial spaces between muscle fasciculi, but also stretching through broken muscle fasciculi to some distance from the main trunk. The contrast that this peculiar reacting tissue makes with its surroundings can be graphically gained through the familiar picture

exhibited when a basal cell type of carcinoma or epidermoid carcinoma sends out compact columns of a deeply staining and a well-circumscribed carcinomatous mass of cells to invade the deeper tissues in the vicinity. This tissue reaction is mostly found in sections near the apex of the heart, where it is surmised, the eggs have more opportunity to become residual by being much removed from the bigger arterial trunks and strong blood currents that can push them off to circulate. In these rather remote positions, possibly aided by gravity, the eggs are able to settle more permanently.

The other chronic histological manifestation that may be considered as part of the process and that follows the lesion just discussed, consists in fibrosis, which, except for some very fine hardly detectable differences, however, can not very well be distinguished from the fibrosis following other inflammatory processes (figs. 2 and 3, plate 11). Were it not associated with specific chronic localized lesions just described, very likely these fibrotic changes would just be taken for any non-specific healed or sclerotic lesions. This fibrosis seems to develop very soon after the absorption of the typical reacting reticuloendothelial cells and to arise from the network of young connective tissue that serves as the groundwork of the reactive cells. It seems to fill exactly the space occupied by the reacting reticuloendothelial cells and shows no evidence of even a mild degree of retraction that usually follows the healing of any injury. In general, the resulting connective tissue sheets that are found in the site of the infection with eggs look very smooth and neatly laid out, homogenous in texture, and lack the ruggedness of the outline and the surface irregularities usually encountered after repair of infectious inflammatory lesions. This irregular architecture of post inflammatory fibrosis in the gross contributes to the scarred appearance of the organ. The smoothness in the fibrous tissue proliferation that follows heterophyid egg infection is probably responsible for the slight but smooth enlargement noted in the size of the heart without the associated irregularity due to the scarring of the surface.

(b) Valves

Histologically, the mitral valves which are involved in five of the positive hearts constituting the present series reveal a

thick external coating of fibrous tissue undergoing different stages of hyalinization converging upon the central areas in which calcification has taken place. Diligent search under the high power revealed the presence of a number of eggs, some still intact, others krinkled and apparently in a stage of long mummification, and still others broken to pieces in various locations, sometimes in the interior of the calcified areas (fig. 2, plate 12), sometimes on the edges of these areas, and at other times in the fibrous-tissue elements (fig. 1, plate 12; fig. 1, plate 13). Many empty eggshells could be demonstrated encrusted in the calcified mass (fig. 2, plate 13), while larger numbers are found in empty spaces evidently vacated by fragments of detached calcified matter which were lost in the technical preparation of the sections. In view of this fact, it is surmised that the number of eggs we have been able to demonstrate in these localities probably does not represent the original number present. The eggs are so minute that they are quite inconspicuous under the low power, especially when enmeshed with calcified masses—a fact which perhaps explains why they have been missed hitherto, despite the countless histological examinations of possibly infected tissues that must have been made in the past. As a matter of fact, two of the hearts considered in this report are old museum specimens from which histological sections must have been prepared and examined in the Department of Pathology and Bacteriology of this same university previously; and the fact that these eggs were missed then, is, to our mind, quite natural, considering the fact that in histological examination of pathological tissues the low power is, as a rule, used to explore the slide, which is usually discarded when no apparent sign of tissue abnormality is present. We have to admit that, were it not for the fact that we strongly suspected the presence of these eggs in the cardiac musculature on account of some very strong clues we mentioned in our first publication on this subject and, further, were it not for our familiarity with the size and appearance of these eggs, we also would probably have missed these ova in our first attempt to demonstrate their presence in the first heart we examined in the beginning of this investigation.

The less hyalinized portion of the fibrous tissue shows edema, and contains capillaries which are just as greatly injected

as are those found in the myocardium. From the presence of such highly injected vessels, one would hardly suspect that the valves were poor in blood supply. Congregations of lymphocytic and plasma cells may be found here and there among the fibrous tissue elements, but the polymorphonuclears and giant cells are again conspicuously absent.

The consensus is that normally the valvular leaflets are absolutely devoid of capillary vessels. This does not seem to be the case, as is shown by histological sections of sclerosed valves in which we definitely found engorged capillaries among the mass of fibrotic tissues that appear to be far within the sclerosed leaflets. Under such condition, however, it would be difficult to determine with certainty the anatomical relations of the different points of the valves. The possibility should be taken into account that what we consider as the interior of the leaflets might in reality be their base pushed centripetally during the course of previous inflammatory processes. But even granting that the possibility was a fact, under such a condition the plugging of the vessels at the base of the leaflets would have had the same effect, if the plugging of the capillaries had occurred in the interior of the valves. It may also be argued that the blood vessels in the valves in question were mere extensions from the myocardium following the formation of rheumatic endocarditic inflammatory processes, and that the heterophyid eggs found mummified in the calcified matter in the interior of the valves had been carried to this locality by the agency of these vessels. In other words, that the presence of the eggs in question did not precede and hence could not have been the cause of the inflammatory processes, but were just incidental to a pre-existing rheumatic endocarditis. Such argument, however, seems to be untenable, at least in so far as the present cases are concerned; because of the absence of any clinical or anatomical evidence of rheumatic conditions, as we will try to show presently.

It will be recalled that we did not find in the valvular lesions of the cases described in our earlier publications the specific cellular response found in the myocardium believed to be characteristic of, and specific to, heterophyidiasis. We attributed the absence of this characteristic and specific cellular reaction in these particular cases to the advanced sclerosis and

calcification noted in them, which we believed had obliterated completely the special types of cells (monocytes and histiocytes) that predominate in younger lesions. Subsequent observations seem to have confirmed this belief; for in one of the two cases considered in our sixth publication (2e) we had found in the sclerosed mitral valves the characteristic cellular reaction observed in the myocardium of our positive cases. However, the sheet of endothelial proliferation observed here has assumed a more compact and fibrous appearance and has lost the capacity to absorb intensely the haematoxylin stain, a capacity which is characteristic of younger endothelial elements; thus there is missing the tinctorial appearance of much younger lesions. The fibrous connective tissues elements are beginning to predominate at the expense of the endothelial cells; so that it is not at all hard to imagine that they will in time lose their characteristic appearance and finally assume the aspect of ordinary healed lesions observed at the termination of any inflammatory process. In fact, were it not for the presence of eggs in the environs of the fibrous connective tissue as well as in the calcified areas we would have hesitated to associate it with this condition.

While, in view of the fact that blood vessels are present even in sclerosed tissue, the possibility may be considered that these ova might have been carried to the interior of the valvular leaflets after sclerosis due to other infections had taken place; yet in the cases here considered such a possibility is held unlikely. On sections of these valves the central or interior portions are found to be calcified here and there, with eggs in the fibrotic as well as in the thoroughly calcified material. The eggs are apparently long dead, some twisted or distorted, others broken to pieces. Some of the eggs are encrusted or fossilized in the calcified matter. The areas where they are found are completely devoid of blood supply. That they arrived in these areas previous to the calcification is obvious. What probably happened is that the eggs carried to this locality by the blood stream precipitated capillary haemorrhages, or embolus formation, which later led to degenerative changes and eventually to hyalinization.

Furthermore, in all the cases in which we have found eggs in the sclerosed and calcified valves, there is no evidence of the presence of Asschoff's bodies in the myocardium. We have ex-

plored the myocardium of our cases thoroughly, because it is very hard to demonstrate or locate the lesions in heterophyidiasis. The lesions are found only in localities where the eggs have by chance happened to cause haemorrhage and other vascular disturbances. We are certain we could not have missed the Asschoff's bodies with the method of exploration we employed, if they were actually present. Instead of finding these bodies in the myocardium of our positive cases, we find the same degenerative lesions in this locality also associated with eggs. In view of these observations we are more inclined to attribute those degenerative changes in the valves to these ova, at least in the absence of contrary evidence or proof that this condition is due to other causes.

The pathological findings so far observed in the myocardium and valves may be summarized as follows:

(1) An acute generalized vascular reaction developed during the attack of heart failure precipitated by the massive arrival of eggs in the myocardium, consisting of injection of blood vessels, extensive edema with embolism, haemorrhages and fragmentation of muscle fibers, specially prominent around areas of haemorrhages where usually a number of eggs can be encountered. In many of our positive hearts, however, only the more chronic types of lesions were encountered.

(2) A more typical reticuloendothelial tissue reaction usually following a more protracted presence of eggs and incited by the spilling of egg contents, a reaction which consists of dense and compact well-circumscribed masses of deeply staining cells that contrast distinctly with the paler eosin-stained surrounding tissue. In the interstices of this tissue are found haphazardly scattered eggs or broken shells. This type of cellular response is considered specific or peculiar to heterophyid infection of the tissue.

(3) The specific tissue reaction is replaced in the healed lesions by the fibrous tissue that insiduously sets in as the specific reaction tissue is gradually absorbed. There is histological evidence that the spaces chronically distended by the edema are also gradually filled in with sheets of fibrous tissue in a similar manner. The replacing connective tissue is characterized by orderliness and smoothness of appearance and homogeneity of texture, and lacks the contraction phenomenon which usually

disfigures and renders the tissues uneven and irregular in an infectious inflammatory process repaired by scar formation.

C. CENTRAL NERVOUS SYSTEM

(1) Brain

Our data concerning lesions in the brain have been furnished by Case No. 3. A male Filipino, 62 years old, who had been suffering from hypertension, presumably due to arteriosclerosis for some time, died of cerebral hemorrhage.

Grossly, both hemispheres of the brain showed much engorgement of the superficial vessels, especially the cerebral branches of the Circle of Willis. The blood vessel walls were very much thickened, and, at various points, before dipping into the substance of the basal ganglia, were found to be friable and easily crushed. The midsagital section of the whole brain revealed a large clot (7 cm. by 5 cm.) in the right basal ganglion involving the lower limb of the internal capsule. The wall surrounding the clot was thrown into irregular and isolated shreds of brain tissue, which had apparently been destroyed or dissected by the onrush of blood from a ruptured vessel.

Sections obtained from different points immediately adjacent to the clot showed numerous fresh perivascular hemorrhages. On examining sections prepared from the posterodorsal wall of the clot in the substance of what appeared to be remnants of the lower limb of the internal capsule, well circumscribed compact masses of deeply staining cells, which under the high power revealed the presence of heterophyid eggs, were seen here and there among the fresh perivascular hemorrhages. The most notable lesions found are essentially identical with those found in the myocardium in our cases of cardiac heretophyidiasis. These lesions, as previously described, consist of compact masses of vesicular or elongated cells with nuclei rich in chromatin, that took the haemotoxylin stain intensely. Under the low power, they might be taken for a massive, focal accumulation of lymphocytes, but well circumscribed. Under higher magnification, the cells in the lesions conformed very well to the description of monocytes and histiocytes that lie in a framework of connective tissue observed in infected hearts (figs. 1 & 2, plate 14). In the younger lesions the

monocytes predominate, and in this stage, it is not very difficult to confuse the cellular picture with that of lymphocytic infiltration, especially when the lesion is relatively minute. In the extensive lesions, however, the very size of the infiltration masses and the very well-circumscribed nature of the lesion will at once throw doubt as to the lymphocytic nature of the infiltration. In much older lesions, the more spindle-shaped histiocytes predominate and, at this stage, the picture of the lesion simulates very much that of young connective tissue (fig. 1, plate 18).

These lesions, which may be considered a typical characteristic tissue reaction in visceral heterophyidiasis, are found mostly in the region of the blood vessels that have been ruptured or thrombosed and from which, of course, the eggs have been scattered. The lesion follows the extent of the distribution of the eggs, usually in the interstitial spaces, but at times dissects the substance of the organ, if the eggs are way-laid in them.

The intense affinity of this tissue for the basic hematoxylin stain renders very easy what might otherwise be a very difficult and tedious search for eggs in the wide, monotonous, pale-staining section of the brain tissue under low magnification, at which range the eggs are hardly visible. The presence of this characteristic reactive tissue, however, with its very characteristic tinctorial reaction that contrasts very vividly with the pale-staining brain tissue makes the localization and search for eggs not so hopeless; for it has been our experience, as stated previously, that the finding of this type of tissue reaction invariably led to detection of eggs or remnants of them in the spot or in its immediate vicinity. This sequence is especially sure if sections are examined serially, in which case eggs at different levels are detected, one after the other.

(2) Spinal Cord

We have been able to demonstrate lesions in the spinal cord only in one of our fifteen cases with visceral involvement. As in the case of the brain, this small proportion has been due, we believe, not so much to the scarcity of lesions in the spinal cords, as to lack of opportunity to investigate them, for reasons already given under the caption "Technique and Material". In fact, many of our heart failure cases presented neurological symptoms such as visual disturbances, unconsciousness, paralysis, di-

minution or total abolition of knee jerk, and absence of Oppenheim's, Babinski's, Gordon's, Kernig's, Chaddock's signs, etc.

Case No. 11 (see protocols) from which our data was obtained involved a male Filipino, 44 years old who dropped dead in one of the streets of Manila, presumably because of heart failure. In his hypertrophied and dilated heart, we were able to demonstrate characteristic lesions of heterophyidiasis, as in the other heart failure cases of our series.

Among the other gross pathological findings were meningeal hemorrhage, basal, extensive; and hemorrhage, dural and sub-dural, left lateral border of the intumescentia lumbalis. Lesions characteristic of heterophyidiasis associated with the presence of eggs were found in the spinal cord at the level of the lumbar enlargement corresponding to the hemorrhage visible at the exterior in this locality. All attempts to find similar lesions at the base of the brain at the site of the meningeal hemorrhages and other suspicious localities failed.

On opening the spinal canal, we found the dura matter from the level of the 5th dorsal to the 3rd lumbar covered with a continuous adherent blood clot. The rest of the spinal cord appeared normal. The subdural space in this portion of the spinal cord was also filled with adherent blood clot, corresponding in extent to the haemorrhage in the surface of the dural coat. The vessels of the arachnoid and pia maters in this region were congested, and there was marked oedema on the left external surface of the intumescentia lumbalis. When the spinal cord proper was freed from the pia mater and from the septum anterius and the legamentum denticulatum, there was noticed on the surface of the left lateral column in this region a dark-brown line of about 1½ mm. maximum width, running parallel with the long axis of the cord, beginning at the level of the 7th dorsal segment where it was most conspicuous, and diminishing gradually posteriad until it became imperceptible at the level of the second lumbar. Microscopic examinations of transverse sections of the cord in this region revealed in the left lateral column a wedge-shaped, dark-brown lesion of about 1½ mm. maximum breadth, with its base towards the left anterior horn of the gray matter on which it slightly encroached in several levels, and with its apex directed towards and reaching as far as the lateral margin. This lesion corresponded to the dark brown longitudi-

nal line observed on the free surface of the left lateral column mentioned above.

Examination of representative sections taken at different levels of the spinal cord, where the lesion is grossly apparent, reveals the following histological changes: The lesion is more prominent and extensive at the level of the 8th dorsal, maintaining the extent uniformly down to the 12th dorsal and from that point gradually diminishing until at the level of the first lumbar the lesion is reduced to one half. The involvement of the cord microscopically gradually disappears lower down where the haemorrhagic streak on the surface of the cord ends.

The lesions are moderately quite acute and, as in lesions reported previously from other organs, consist of marked capillary injection, perivascular and interstitial oedema, capillary thrombosis, multiple capillary haemorrhages, degeneration and rupture of the nerve cells and tissues of the gray substance, and mechanical distortion of the neighboring tissues due to pressure of extravasated blood. The haemorrhages, while confined to a great extent in the gray matter and axial in distribution, can be seen frequently to extend in small tracts across the white matter, sometimes reaching the periphery, either laterally involving the lateral column or dorsally the columns of Burdach and Goll.

Histologically the lesions are pronounced on the left half of the cord involving the entire gray matter and located mainly in the anterior horn, but also encroaching slightly on the posterior. A large zone of white matter laterally adjacent to the gray tissue is also affected. The portion of the cord showing these histological changes corresponds to the half of the cord which grossly shows the haemorrhages on the surface.

The most prominent and extensive lesions are located in the portion of the gray matter. The haemorrhagic processes have extensively destroyed more or less gray tissue in the immediate vicinity in an eruptive manner, creating in the section gaps or spaces partially or fully filled with granular tissue debris or spilled red blood and white cells. The destruction of tissue must have been due to both sudden loss of blood and mechanical pressure caused by the extravasated blood.

In the anterior horn the lesions dissect the nervous tissue up to near the surface of the cord. In the latter location where most of the eggs are found in the haemorrhagic area the lesions are more cellular and compact with less admixture of red cells

and destroyed tissue, and assume more the appearance of the typical specific reactive lesions observed in the brains and hearts and observed also in the heart of this case. In the same segments of the affected side of the cord, which show extensive hemorrhages in the anterior horn, are found definitely circumscribed islands of compact specific reactive tissue entirely in the white matter (fig. 2, plate 18). Compared with the brain and cardiac lesions previously described, the specific tissue reaction observed here is rather loose, although proliferated endothelial cells and histiocytes can be distinguished, which, however, have not assumed the characteristic compactness of cellular arrangement shown by more chronic and older lesions.

The character of the specific tissue reaction in this case is that of a lesion of much more recent date. The most recent lesion here is more centrally located in the spinal gray tissue where purely haemorrhagic lesions can be found. These facts harmonize with our opinion that eggs imprisoned in the reactive tissues can best be seen in the older lesions, because they are caught in the compact tissue and are therefore difficult to dislocate, whereas in the more recent, purely haemorrhagic, lesions where the tissues are loose, the eggs are easily disloged and lost during the technical preparations, unless they are present in exceptional abundance.

The eggs encountered in the lesion are few and far apart. In the examination of the whole series comprising the different blocks prepared from this case, there was no instance when more than one egg could be demonstrated in one serial plane. Judging from their size alone, two types of eggs can be demonstrated, a small one corresponding to *S. brevicaeca* and a larger one corresponding to *Haplorchis yokogawai;* and both types of helminths were recovered from the intestine of this case.

D. LESIONS IN OTHER VISCERA

The lesions observed in the liver (fig. 2, plate 15), lungs, and spleen, the only organs besides the heart and central nervous system in which we have been able to demonstrate the presence of eggs, conform in all essential details with those we have already described in the latter organs.

VII. VISCERAL COMPLICATIONS IN OTHER ANIMALS

Our experience in the dissection and histological exploration of infected dogs and cats is still too limited to draw any conclusion therefrom. Of course, the fact that we have not succeeded in finding lesions similar to those we found in man in the viscera of dogs and cats can not be taken as an indication that such do not actually occur in these animals. Extensive exploration of the viscera of animals with intestinal infections would first have to be made before this question could be settled. In the event that visceral complication were finally proved not to occur in heterophyidiasis of the lower mammals, a very odd biological situation would then be revealed, since it seems to have been conclusively proved by one of us (6a & b) that at least in the case of *Haplorchis yokogawai*, the flukes penetrate the wall of the intestine of dogs very deeply and come to a position where their eggs could easily filter into the lymphatic or portal streams.

Extension of the infection from the intestine to the pancreas (2f) and liver (2g) has been found, however, in certain bird hosts. While examining the various visceral organs of four seagulls (Larus ridibundus Linn.) in whose intestine were found a large number of specimens of Stictodora spp., minute, discreet, bluish-black spots were observed on the surface of the pancreas of one of the birds. When one of these suspicious looking lesions was teased on a slide it gave up a surprisingly large number of eggs the size and appearance of which were identical with the size and appearance of the eggs of the flukes found in the intestine. Paraffin sections of the remaining portions of the organ revealed huge, well-circumscribed collections of the same eggs at various points and depths, surrounded by chronic inflammatory processes consisting of mild fibrosis infiltrated with small round cells, a few plasma cells, and endothelial cells, the last type of which preponderated (figs. 1 & 2, plate 19). Extensive search for the same lesion in other visceral organs was unsuccessful. In view of the heavy collections of eggs found in this organ (which number in thousands in some of them), and in view further of the notable absence of any appreciable vascular disturbances, which would undoubtedly be encountered had these eggs been carried to these localities hematogenously, it is be-

lieved that the infection of the pancreas in this case, had been due to the migration of the adult flukes themselves to this organ from the intestine, either by direct selective tissue penetration, or by way of natural anatomic channels. This view seems to be supported by the presence in these "egg-nests" of what appeared to be the remnants of the soft parts of the worms that have disintigrated and given up their egg contents. At least, it is inconceivable that such a terrific number of eggs could be brought to these localities by the agency of the circulation without a part of them being encountered in other localities. This behaviour does not seem to be foreign to the trematodes. Yokogawa (93b) found that *Paragonimus westermanni* migrate to the lungs by direct selective tissue penetration after excystation in the small intestine, and Yokogawa & Suyemori (94), as mentioned elsewhere in this work, observed that in the great majority of cerebral paragonomiasis the brain lesions are produced by the entrance of partly grown or adult worms through the foramina of the base of the skull, and their subsequent invasion of the brain tissue, and not by emboli composed of eggs. It may also be mentioned here that in one of our human cases adult flukes were found in the epicardial and other superficial parts of the heart.

Similar findings were made in the liver of cattle egrets (*Bubulcus ibis coromandus* Boddaert) in infections of *Haplorchis yokogawai* and *H. taichui.* In three of fifteen birds with intestinal infection by these heterophyids, eggs and sections of adult flukes were found in the biliary passages, but none in other visceral organs. That the flukes encountered in the bile ducts were actually of these species was verified in later dissections when specimens of both these species were squeezed off directly from the liver of this bird.

Grossly the infected liver does not show any abnormality that would differentiate it from an uninfected one. Except in portal areas that happen to contain collection of eggs or, occasionally, what appear to be adult flukes or remnants of them, even the examination of histological sections has failed to reveal any marked abnormality other than evidence of mild degenerative changes due to pressure observed here and there in the parenchyma. Actual hemorrhage or any recent or remote indication of it is conspicuously lacking. The parasites are confined

in the portal area, invariably in the immediate vicinity of the portal vessels (fig. 3, plate 19). No evidence of their presence is found in other localities. These findings suggest that the flukes probably arrived in the liver from the intestine by way of the common bile ducts; although the possibility can not be entirely ruled out that the flukes may traverse the wall of the intestine, attack the surface of the liver from the peritoneal cavity, and reach the bile passages in a way analogous to that which appears to have been found by Sinitzin (77) in the case of *Fasciola hepatica*. As in the case of infection of the pancreas of the sea gull with Stictodora, there seems to be not even a remote indication that these parasites were carried to the liver of the cattle egret by way of the circulation.

Whenever the flukes show evidence of long residence in the locality as indicated by the complete disappearance of any remnants of them except their eggs, a definite chronic inflammatory reaction in the form of fibrotic capsule with leucocytic (mostly of the round cell) infiltrations is observed around the parasites (fig. 4, plate 19). Scattered here and there along the fibrotic wall, mostly on the outside, are proliferated bile capillaries, a histopathological picture analogous to what is observed in infection of the same organ with the opistorchids observed in mammalian hosts. The flukes which were apparently intact and fresh when the sections were made, as indicated by their beautifully stained reproductive glands and well-stained miracidia within their eggs, are seen not to be surrounded by any marked cellular reaction. The bile ducts containing the parasites are greatly dilated and the biliary epithelium is obliterated. There is, if at all, a very scanty fibrotic formation, devoid of leucocytic infiltration around the fluke. The tinctorial masses of endothelial proliferation we found in visceral complications in human infections have not been observed.

VIII. EPIDEMIOLOGICAL CONSIDERATIONS

A. MECHANISM OF INFECTION AND DISSEMINATION OF PARASITES IN THE BODY

Infection of the ultimate hosts (man, other mammals, and birds) with members of the family Heterophyidae occurs upon

ingestion of fish flesh containing the encysted larvae (metacercariae) of the flukes in the raw or semi-raw state. Excystment probably takes place in the upper portion of the small intestine, as shown by Stunkard and Willey (79) in their experiments in rats involving *Cryptocotyle lingua*. Basing their conclusion on data obtained from experimental studies on the development of *Metagonimus yokogawai*, *Apophalus muhlingi*, and *Monorchotrema taihokui* (=*Haplorchis pumilio*), and *M.* (=*Haplorchis*) *taichui* Yokogawa (93a), Ciurea (19b) and Faust and Nishigori (29), respectively stated and unanimously agreed that an intramucosal stage occurs during the development of the worms in the final host, but the flukes upon reaching sexual maturity return to the lumen of the intestine and attach themselves to the free surface of the mucosa. Ciurea believes that this intramucosal stage in the life cycle is characteristic of all members of Heterophyidae. However, Stunkard and Willey (79) failed to demonstrate an intramucosal phase in their experiments in cats and white rats involving *Cryptocotyle lingua*, and inferred from their data that "not all Heterophyidae, as postulated by Ciurea, have an intramucosal stage in the development" and asserted further that "since the life histories of the family are so similar, doubt is cast upon the correctness of the idea advocated by Yokogawa, Ciurea, and Faust and Nishigori" with regard to the existence of an intramucosal stage in the development of heterophyid trematodes in their final host.

Because of the discovery of eggs of certain members of Heterophyidae in the visceral organs of man in this country which have been found in the majority of cases to be associated with definite lesions apparently specific in character, it has got to be postulated *apriori* that an intramucosal stage exists in their development in the final host; for it is obvious that their eggs could not filter into the general circulation unless these flukes themselves had invaded the intestinal wall.

In order to submit this hypothesis under experimental test, and incidentally to gather evidences that might throw some light on the mechanism by means of which these eggs get into the general circulation, one of us (6a & b) undertook a series of feeding experiments using kittens, pups, and birds as experimental animals, and *Haplorchis yokogawai* as the heterophyid to be tested. This heterophyid was particularly selected for these ex-

periments because its metacercaria is always found in great abundance, frequently alone, in the flesh of two common Philippine fishes (*Arius manillensis* and *Clarias batrachus*). Besides, this fluke (as stated previously) has been determined to be not only the most frequently encountered heterophyid in human autopsies in this country but also the one most frequently associated with heart lesions.

These experiments seem definitely to have demonstrated that there is actually an intramucosal phase in the development of *Haplorchis yokogawai* in the final host, and since the life histories of the family are so similar, intramucosal invasion by the young flukes following emmergence from their cysts may be a common occurrence in the development of members of Heterophyidae in general in their final host. However, no evidence was found to substantiate the unanimous claim of Yokogawa, Ciurea, and Faust and Nishigori that the flukes which bore into the mucosa return into the intestinal lumen. On the contrary, evidence gathered so far seems to show that they remain imprisoned in the gut wall, where they grow to sexual maturity, until they die.

Haplorchis yokogawai undergo normal development in experimental animals, the flukes becoming ovigerous on or about the sixth day after infection and attaining complete adulthood in ten to twelve days. Eggs are apparently normally shed upon reaching this stage of development, as shown by their presence in the feces. A large number of the young flukes apparently invade the mucosa soon after excystation. A marked tendency to invade the interior of the mucosa is observed, particularly in the dog. While many flukes are found in the lumen of the intestine in the spaces between the villi more frequently at or near the base of these mucosal projections, many are also found in the lumen of the intestinal glands. The size of the worms being apparently greater than what the glandular tubules can contain, their epithelium is flattened or destroyed completely, perhaps by pressure necrosis, thus allowing the worms in many instances to come in direct contact with or lie within the tunica propria. Whenever this is the case, the body of the worm is adherent to the tunica propria so that no spacing is observed between the parasite and the surrounding tissue, an extremely close contact, not usually the case when the epithelium of the glandular lumen

is intact or just flattened. In the latter case, the worms are found lying freely in the lumen of the glands with ample spacing between them and the epithelial lining, a spacing resultant evidently upon the contraction of the tissues during the technical preparation of the sections. Occasionally the flukes are found even as deep as the muscularis (fig. 4, plate 21). Since the worms found in these situations are almost invariably packed with eggs, the latter containing well developed miracidium in many cases, it seems that the worms do not return to the lumen of the intestine to complete their reproductive activity, contrary to what other authors believe to be true in the case of other members of Heterophyidae closely allied to *Haplorchis yokogawai*, as has been pointed out previously.

The frequent occurrence of adult worms in the lumen of intestinal glands suggests that the usual route of their invasion is through the opening of these glands situated between the bases of the adjoining villi, and not by direct penetration of the mucosa at any point. The invasion of the mucosa is probably made by young worms and probably takes place early after their excystment, when the worms are not yet too bulky to squeeze themselves through the narrow openings of the glands. The worms that fail to enter the glands while still young and small probably remain forever barred from entrance. It is they presumably that are found as full-sized adults occupying distended spaces between the villi or attached feebly on the top of the mucosa (fig. 2, plate 21). These flukes are probably those principally responsible for the eggs discovered in the feces of infected animals; since it is evident that the worms that become imprisoned in the wall of the intestine can expell only with difficulty their eggs into the intestinal lumen.

Aside from flattening or pressure necrosis of the epithelium at the base of the villi or crypts of the intestinal glands occupied by the worms, and slight endothelial proliferation around the parasites observed occasionally, and still more rarely fibrosis around the worms, there are no other recognizable pathological changes in the invaded intestinal wall. Leucocytes of the polymorphonuclear types are scarce and foreign-body giant-cells are not found, they were not, at least, in any one of a considerable number of histological sections examined. The inflammatory reaction, if any at all, is always of the mildest type. It is amaz-

ing how the tissues could tolerate the presence of these worms for long periods without any appreciable attempt to destroy them. Worms showing signs of disintegration are only occasionally found even in five-months' old infection. The worms probably live for a long time within the mucosa. The general absence of any attempt to encapsulate the parasites by fibrotic reaction perhaps accounts for the filtration of eggs into the general circulation. In fact, such filtration would be hard to conceive were the presence of the parasites in the intestinal wall accompanied by fibrotic walling-off processes.

If the evidence of intramucosal invasion manifested in laboratory animals by *H. yokogawai* is also true in man, then the filtration of eggs of members of this family into the general circulation, as has actually been observed in human infections with this fluke and other related species, does not seem hard to explain. The basis for this explanation may be resolved by two principal facts experimentally demonstrated, i.e. (1) the position of the adult flukes in the substance of the mucosa in relation to the terminal tributaries of both the portal and lymphatic streams, and (2) the general absence of fibrotic walling-off processes around the parasites or their eggs that get in the intestinal wall.

In one of our preliminary publications on the subject we advanced the view that the eggs of these flukes which stray into the gut wall are probably freed from the worms not by the natural process of oviposition, but by disintigration and final dissolution of the soft parts of the worms, following their death. We further remarked that these parasites, perhaps, loose their power of natural ovipositing upon transfer to man on the assumption that man is an unnatural host of the heterophyids. This latter view was based upon our failure to demonstrate eggs in the intestinal contents of human cadavers from which we were able to recover adult specimens with their uterus packed full of eggs. Further reference to literature on the subject, however, has disclosed that other workers did not seem to experience any difficulty in demonstrating eggs of heterophyids in the stools of infected persons.* For instance, Faust and Nishigori (29) found the eggs of both *Monorchotrema taichui* and *Monorchotrema taihokui* in

*Eggs have been found recently by us for the first time in the stool of a living case which is not included in this report.

the feces of persons whom they had artificially infected. Alicata and Chattenburg (8) detected an infection of *Diorchitrema pseudocirrata* in a Japanese in Honolulu as mentioned elsewhere in this report by finding the eggs of this fluke in the feces. There seems no longer to be any ground, therefore, for our belief that heterophyids fail to shed eggs naturally on the basis of host-relationship. Perhaps what happens is that during the terminal stages of the infection, providing there has not been any reinfection, very few or no living flukes at all are left in the intestine and these few parasites fail to produce eggs in sufficient number to be demonstrated in the feces. While our view that eggs are probably freed from the worms upon disintigration and final dissolution of their soft parts following their death can not be gainsaid, there are undeniable proofs of the existence of natural oviposition on the part of these heterophyids in the human host. We have, therefore, to attribute our failure to demonstrate eggs in our human autopsy cases either to the small size of the infection existing at the time the autopsies were made, or to faulty technique employed. At any rate, whatever may be the exact manner in which the eggs are freed from the parent worms, the important thing, to our mind, is the general absence of fibrotic walling-off processes around the parasites or their eggs and the position of either or both in relation to the blood and lymphatic vessels of the intestinal wall. This very leniency on the part of the tissues toward these parasites spells, perhaps, the host's own doom in certain cases. The eggs thus freed in the intestinal wall probably find their way into the lacteal vessels or portal venules which are abundant in the tunica propria.

That the heterophyids may be capable of inserting their protrusible genital apparatus into the lumen of the blood and lymphatic vessels in the wall of the intestine and in this manner oviposit directly into the lymphatic and blood streams is another possibility which can not be entirely disregarded in the attempt to explain the dissemination of the eggs of these trematodes to the visceral organs.

As mentioned in our introduction, this is not the first time that eggs of trematodes have been found to invade the systemic circulation. The eggs of schistosomes (*S. japonicum, S. mansoni* and *S. hematobium*) have been reported in the brain and spinal cord of man. More recently Africa and Sta. Cruz (5b)

reported the presence of ova of *S. japonicum* in the myocardium of man, besides in the brain and kidneys, as stated previously. It is presumed that these eggs have been carried to these organs by the arterial blood stream. In the case of *S. hematobium*, which inhabits the systemic veins from the urinary system, the eggs have a direct route to the right heart and lungs. In the case of both the *S. mansoni* and *S. japonicum*, which inhabit the veins of the portal system, it is doubtful whether the eggs of these worms can pass into the inferior vena cava and on into the right heart and lungs without being held up in the sinusoids of the liver, on account of their large size. However, their eggs may escape from the portal veins if collateral circulation has been opened up by dilatation of the oesophageal veins. At any rate, these eggs have to pass the pulmonary filter in order to reach the arterial side of the systemic circulation. Likewise the eggs of *Paragonimus westermanni* have been repeatedly found in the brain, indicating passage through the lung capillaries to the left side of the systemic circulation. As stated previously, however, Yokogawa and Suyemori (94) think that in the great majority of cases of cerebral paragonimiasis the lesions in the brain are produced by the young and adult flukes that invade this organ through the foramina at the base of the skull, and not by egg-emboli.

These facts have been invoked because the eggs of these aforementioned trematodes are about three to six times as large as those of the heterophyids involved in this work. Besides, the eggs of schistosomes are encumbered by a large and sharp spinous process which may cause them to be more easily held up in the capillaries. Considering these facts, it is easy to comprehend how the eggs of heterophyids, which are relatively very much smaller (16 by 10 to 33 by 25 microns) than those aforementioned and provided with perfectly smooth shells unencumbered by any spinous processes, can easily pass through the various capillary filters of the body. It is possible that because of their small size, as well as the smoothness of their shells, the eggs of heterophyids upon reaching the systemic circulation, circulate in the blood stream indefinitely or for some time, until they are held up and filtered out in the different viscera. The heart, by virtue of its peculiar musculature and physiologic activity, perhaps gets a very large share of the circulating eggs.

Besides in the heart, eggs of these flukes have been found in the brain and spinal cord, liver, lungs, and spleen. Their presence in these organs, would of course, indicate their possible occurrence in other parts of the body. At least, there seems to be no valid reason why they can not also occur elsewhere. The finding of ova in the valvular leaflets of the heart, a locality which is believed to be very poor in blood supply, is an indication that these eggs may be found almost everywhere and anywhere in the body.

In one of our previous papers we surmised that the few adult flukes found in the epicardial space of one of the hearts in our series reached that organ through the blood route in a more or less passive manner. We thought this possible on account of their minute size (being only a fraction of a millimeter in length) as well as of their great flexibility which would allow them to be moulded through spaces much smaller than their diameters. On the other hand, the fact that the cuticle of these flukes is provided with sharp posteriorly directed spines makes it hard to conceive that they could pass the hepatic and pulmonary filters without being held up in these localities. However, active invasion of the heart by aberrant worms through direct tissue penetration, analogous to what appears to have been found by Yokogawa (93b) in the case of invasion of the lungs by *Paragonimus westermanni* from the small intestine after excystation, can not be ruled out entirely, and should be regarded as a possibility in heterophyid infections.

B. GEOGRAPHICAL DISTRIBUTION

1. General

Infections with members of the family Heterophyidae are probably world-wide in distribution. They are probably more frequent and varied in regions, such as are found in the tropics, where the temperature is high and more or less uniform throughout the year, conditions which favor the growth of abundant and varied vegetation, and indirectly rich and varied piscine and molluscan fauna. They are found wherever there are piscevorous mammals and birds, but human infections are presumably limited to areas where eating fish in the raw or semi-cooked

state is an established habit among the members of the population.

For example, Professor Jack H. Sandground in a personal communication quotes Dr. Bonne of Batavia, who, after examining heart sections from our cases of cardiac failure, stated that "he feels fairly certain that the condition does not occur in Batavia; for they cut sections of the myocardium and valves in every routine autopsy performed in his (Bonne's) institute (Pathologisch Institute, Geneeskundige Hoogeschool, Batavia, Java) —some 600 yearly—and he maintains that such conspicuous hemorrhage and necrosis would certainly be noticed occasionally if it occurred." Yet *Haplorchis yokogawai* and *Diorchitrema pseudocirrata* have been identified in the material from the intestine of cats sent to us by Professor Sandground from Java. We may state here, that Dr. Bonne's observation could as well be applied to the experience of our pathologists in the Manila City Morgue, who handle about the same number of autopsies every year, and observe the same routine procedure in the examination of the heart, before and after our discovery of the heart lesions due to this infection in 1935. In fact, as mentioned elsewhere in this report, we were able to describe lesions typical of heterophyidiasis both in the myocardium and valves in two hearts labeled "beriberi," which had long been kept in the museum of the Department of Pathology and which, without doubt, had been also submitted under some kind of routine histological examination in that department. We doubt if the class of available material in our morgue at present is different from that which has passed through it since its establishment three decades ago and up to the time of our discovery. If these diseases are finally proved to be actually absent among the people of Java, despite the presence of the same flukes involved in this work in cats and presumably in other fish-eating mammals in that locality, then the following possibilities are patent: (1) the habit of eating raw fish is not practised by the Javanese; or (2) the Javanese eat raw fish but the particular species that harbor the metacercariae of pathogenic heterophyids are not eaten by them in the raw state; (3) or, for physiological reasons, such as the influence of diet, local eating habits, etc. the flukes fail to thrive in the intestines of the Javanese. The

last possibility is, perhaps very remote although we observed that we could establish larger infections of *H. yokogawai* in *Maccacus cynomolgus*, a vegetarian animal, only when we forcibly fed it with meat and milk, indicating that the character of the diet may have something to do in the establishment of heavier infections.

Heterophyes heterophyes which was discovered by Bilharz on April 26, 1851, in the small intestine of an Egyptian boy at autopsy and the first member of this family to be described seems to be a common human infection in Egypt. Khalil (47b) examined 60 school children in an endemic center at Lake Menzaleh adjoining Port Said and found 53 of them infected with this fluke. Cort (20) cites that *Heterophyes nocens* which, according to Leiper (49), is identical with *Heterophyes heterophyes*, occurs in from 22 to 30 per cent of the inhabitants of certain villages in Japan. According to Craig and Faust (21) *Metagonimus yokogawai*, found for the first time in 1911 by Yokogawa in Formosa, is probably the most common heterophyid fluke in the Far East (Sino-Japanese areas and maritime provinces of the U. S. S. R.). It is also found in Korea and the Bankans. It has also been reported in Spain by Lopez-Neyra and Pozo (53).

Stellantchasmus falcatus, originally described by Onji and Nishio (1924) from the cat in Japan, was redescribed by Witenberg (1929) from the dog in Palestine before it was found in the dog and in man (for the first time in the latter host) in the Philippines as natural infection. Alicata and Chattenburg (8), as previously stated, recovered this heterophyid from a Japanese who was born and reared in Hawaii and never traveled away from that territory. Furthermore, they were able to recover adult specimens of this heterophyid from kittens fed with metacercariae obtained from their local mullets.

Haplorchis taichui, described originally in Formosa by Nishigori (66) when recovered from experimental mammals was also reared experimentally in man by Faust and Nishigori (29) in that country before it was found as a natural infection of man and animals in the Philippines (4b). This heterophyid is also present in dogs and cats in Palestine (Witenberg, 1929) and in Canton, China (Chen, 1936a).

Haplorchis yokogawai was originally described by Katsuta (46a) when recovered from experimental mammals fed with metacercariae from mullets in Formosa. It was reported by Chen (1936a) in dogs and cats in Canton, South China, and later determined by us, as repeatedly mentioned in the report, to be the most frequent heterophyid infection of man in the Philippines. *Haplorchis pumilio (Monorchotrema taihokui)* is a frequent parasite of mammals and birds in the Near East. It is also present in these animals in Formosa and experimentally developed in man in that country together with *Haplorchis taichui* (29). Chen (16a) also found it to be a frequent parasite of dogs and cats in Canton. Natural infection with this heterophyid has never been encountered yet in the Philippine mammals and birds or in man, but it has been recovered a number of times from kittens and pups (85b) fed with metacercariae from both fresh water and marine fishes in this country.

Haplorchis calderoni, which was described as taken from the dog in the Philippines and later encountered twice in man as natural infection, has not yet been reported outside the Philippines. Nor has *Haplorchis vanissima*, which was recovered (and described) from the small intestine of a native Filipino at autopsy (6c). Other potential human parasites yet to be generally recognized in the Far East are *Stamnosoma armatum* and *Stamnosoma formosanum*. The latter has been recovered from experimentally infected animals in the Philippines. Likewise, *Spelotrema brevicaeca (=Heterophyes brevicaeca)*, originally thought to be a heterophyid, but recently assigned by Tubangui and Africa (83) to Microphallidae (as mentioned elsewhere in this work) is a frequent parasite of the human intestine in the Philippines and figures among the flukes that have been incriminated in the production of visceral lesions. Indeed it is very likely that the distribution of *Spelotrema brevicaeca* is not limited to the Philippines. Closely allied species, such as the *Spelotrema minus*, *Spelotrema capellae*, and *Spelotrema longicolle*, have been described or reported in Japan (92).

2. Local

In the basis of present data, it is difficult to determine the local distribution of the heterophyids so far described or identi-

fied in the Philippines. Although our human autopsy cases consist of natives who apparently came from different sections of the country, it is impossible to determine when and where they contracted their infection, especially when we consider the fact that infected persons apparently harbor their infection for long periods. Until extensive dissections of animals (cats, dogs, etc.) can be made in different localities to determine their heterophyid parasitic fauna, it would be neither wise nor profitable to attempt to ascertain exact local distribution. We believe, though, that most of these heterophyids have a more or less general distribution in the Philippines. We base this assumption on the fact that our piscine and molluscan fauna are more or less generally distributed throughout the archipelago, and, further, on the fact that many of our heterophyids are also found in Formosa, which is closely adjacent to us in the north.

C. ENVIRONMENTAL AND HUMAN FACTORS

Heterophyidiasis is contracted solely by eating fish infected with the encysted larvae, or metacercariae of the flukes in the raw or semi-raw state. Consequently, it is absent in man wherever this habit is not indulged in or practised by the inhabitants, even in places where infected fish are abundant, and in such localities only piscevorous animals such as dogs, cats, rats, foxes, and other fish-eating mammals, as well as fish-eating birds, harbor the infection. In the Philippines this group of trematodes, including those which have been incriminated in this work as producing visceral lesions, has been found to use freshwater, brackish-water, and marine fishes as second intermediate hosts.

1. *Piscine Intermediate Hosts:*—In table 2 will be seen the kinds of Philippine fishes which have been determined by feeding-experiments as second intermediate hosts of heterophyid trematodes with the corresponding flukes recovered from laboratory animals fed with metacercariae obtained from each kind. Those which have been recovered from man in this country as natural infection are marked with asterisks. *Haplorchis pumilio and Stamnosoma formosanum* are potential human parasites, since they have been experimentally developed in man in

TABLE 2.—*List of Philippine Fishes Harboring Metacercariae of Heterophyids*

Name of Fish	Native Name	Habitat	Name of Flukes
1. *Ophicephalus striatus* Bloch	"dalag"	fresh water	*Haplorchis calderoni** *Haplorchis yokogawai** *Haplorchis pumilio* *Haplorchis taichui** *Stamnosoma formosanum*
2. *Glossogobius giurus* Buchanan & Hamilton	"bia" or biyang-puti	fresh water to brackish water	*Haplorchis calderoni* *Haplorchis pumilio* *Stamnosoma formosanum*
3. *Therapon plumbeus* Kner	"ayuñgin" of Laguna de Bay	fresh water	*Haplorchis sisoni* *Haplorchis pumilio* *Stamnosoma formosanum*
4. *Gerris kapas* Bleeker	"malakapas"	salt water to brackish water	*Haplorchis yokogawai* *Heterophyopsis expectans*
5. *Gerris filamentesus* Cuvier & Valenciennes	"malakapas"	salt water to brackish water to fresh water	*Stictodora manilensis* *Haplorchis calderoni* *Haplorchis pumilio* *Heterophyopsis expectans*
6. *Creisson validus* Jordan & Seals	"bia ng sapa"	fresh water to brackish water	*Haplorchis calderoni*
7. *Anabas testiduneus* Bloch	"martiniko"	fresh water	*Haplorchis calderoni* *Diorchitrema pseudocirrata** *Stamnosoma formosanum*
8. *Pelates quadrilineatus* Bloch	"babansi"	salt water to brackish water occasionally to fresh water	*Stictodora manilensis* *Haplorchis calderoni*
9. *Amphacanthus javus* Linnaeus	"samaral"	salt water occasionally to brackish water	*Haplorchis calderoni* *Haplorchis pumilio* *Heterophyopsis expectans*
10. *Eleutheronema tetradactyla* Shaw	"mamale"	salt water occasionally to brackish water	*Haplorchis calderoni*

* NOTE: Asterisks indicate flukes that have been recovered from the intestine of man in the Philippines.

TABLE 2.—*Continued.*

Name of Fish	Native Name	Habitat	Name of Flukes
11. *Atherina balabacensis* Seale	"guno"	salt water brackish water occasionally to fresh water	*Stictodora guerreroi* *Stictodora manilensis* *Haplorchis calderoni* *Heterophyopsis expectans*
12. *Hemiramphus georgii* Cuvier & Valenciennes	"cansusuit" or "buguing"	salt water to brackish water occasionally to fresh water	*Stictodora guerreroi* *Haplorchis calderoni* *Heterophyopsis expectans*
13. *Mugil dussumieri* Cuvier & Valenciennes	"talilong" or "banak"	salt water to brackish water to fresh water	*Stictodora guerreroi* *Stictodora manilensis* *Haplorchis calderoni* *Haplorchis yokogawai* *Diorchitrema pseudocirrata* *Heterophyopsis expectans* *Pygidiopsis marivillai* *Pygidiopsis genata*
14. *Ambassis buruensis* Bleeker	"lañgaray"	fresh water to brackish water to salt water	*Stictodora guerreroi* *Stictodora manilensis* *Haplorchis calderoni* *Haplorchis pumilio* *Heterophyopsis expectans* *Microlistrum sp.*
15. *Clarias batrachus* Linnaeus	"hito"	fresh water	*Haplorchis yokogawai*
16. *Arius Manillensis* Cuvier & Valenciennes	"kanduli" of Laguna de Bay	fresh water	*Haplorchis yokogawai*

Formosa (29). The first has not been recovered in the Philippines as natural infection either in man or animal, while the second has been encountered in birds (*Bubulcus ibis coromandus* and *Pyrrerodios manillensis*) as natural infection. The rest, with the exception of Microlistrum sp., have been encountered also in dogs and cats, as well as in birds under natural condition. It is possible that some heterophyids we have hitherto recovered only from mammals and birds may yet be encountered among the Filipinos.

In the list of Philippine fishes (see table 2) serving as second intermediate hosts of heterophyid trematodes in this country *Nos. 1, 2, 3, 4, 5, 6, 10, 13, 14, 15,* and *16,* be marked as common and popular, with extensive distribution throughout the archipelago. They all figure prominently in the daily diet of the Filipinos especially of the middle and lower classes. The natives are specially fond of broiled, semi-cooked or fermented *Ophicephalus striatus* ("dalag"), *Clarias batrachus* ("hito") *Mugil* sp. ("talilong" and "banac"). According to information gathered from native Filipinos of the different sections of the country, there is hardly any doubt that the habit of eating raw fish is common here, particularly in certain regions, such as the Visayas and Ilocano provinces.

2. *Resistance of the Metacercariae:*—One of us has made a study on the resistance of the metacercaria of *Haplorchis yokogawai** to various physical and chemical agents, with the end in view of obtaining pertinent information that may prove useful in the prophylaxis against heterophyid infections in general. *Haplorchis yokogawai* was chosen because the metacercariae of this fluke occur abundantly, frequently alone, in the flesh of *Arius manillensis.* Moreover, this fluke, as mentioned elsewhere in this report, is not only the most frequently encountered heterophyid in man in the country but also the most frequently involved in our heart failure cases. The criterion used for testing the viability of the larvae after exposure of chopped pieces of fishes containing the larvae to various physical and chemical agents usually employed by the Filipino house-

* This fluke was erroneously identified as *Monorchotrema taihokui (Haplorchis pumilio)* in the original paper.

wife in preparing fish for the table was their ability to excyst and develop into the sexually matured flukes in the intestine of white rats, an animal that has been previously found to permit full development of this heterophyid if fed with untreated metacercariae.

Assuming that the metacercariae of the different heterophyid flukes have more or less the same resistance against physical and chemical agents, as appears to be reasonable, the data gathered in these experiments may serve as a guide for the house-wife in preparing fish for the table without jeopardizing the health of her family. For example, refrigerator temperature (around ten degrees centigrade) has been found to have practically no lethal effect on the larvae, even after twenty-four hours, but may kill all the larvae in from three to four days. Moist heat seems to be the most practical way of rendering the metacercariae uninfective, as they all seem to be killed at a water-bath temperature of 55°C. applied for ten minutes; the thermal death point of the larvae probably lying between 50°C. and 55°C. This point conforms with the finding of Ochi (67), who ascertained that the infectivity of the metacercariae of *Heterophyes heterophyes* is lost if the fish is plunged into water at a temperature of 50°C. and kept there for seven minutes. Practically the same result was obtained by Witenberg (90c), who found that three minutes' exposure to a temperature of 60°C. kills the metacercariae of *Heterophyes heterophyes*. Table salt applied to the point of saturation at room temperature is only partially effective in killing the larvae after two hours, but may kill all the larvae within four hours. As raw fish is usually prepared by the natives immediately before serving, this result indicates that salting alone is not an efficient means to prevent infection unless consumption is delayed for more than four hours after preparation. This efficacy of delay also indicates that "bagong" (native name for raw, fermented, salted fish) is quite safe for human consumption in so far as this infection is concerned; since it is usually sold in the market after long storage, which is said even to improve its flavor. The combination of either vinegar, ginger, or garlic in liberal amounts with table salt applied to the saturation point seems to be more lethal to the metacercariae than table salt

alone, but the fish must be prepared at least three hours before serving, in order to render it safe. Fish flesh salted to the saturation point and exposed to direct action of sunlight (34°) may be safe for consumption after three hours exposure. In connection with this fact, however, the common practice among the natives must be noted, which is to dry whole fishes under the sun; in this case, the lethal effect of the sunlight against the metacercariae would depend to a great extent, not only on the duration of exposure, but also on the size and character of the fish. Dried fish sold in the market are probably safe for consumption as they are as a rule dried in the sun for days, and even undergo storage for long periods before they are ready for the stalls.

Further data* of Ochi (67) are equally interesting; he found that encysted cercariae live for 13 hours in soja sauce, 24 hours in vinegar, 48 hours in miso, 36 hours in sour miso and 4 days in 5 per cent salt solution. A 10 per cent solution kills in 4 days and a saturated solution in 2 days. Infectivity is lost if the fish is plunged into boiling water and left for twenty seconds; in water 80°C. for three minutes; or at 50°C. for seven minutes (as cited above). Metacercariae isolated from the fish remain alive from 3 to 7 days in fresh water, from 4 to 7 days in sea water, and after 18 hours in active gastric juice.

3. *Reservoir Hosts:*—With the exception of *Haplorchis vanissima* all the heterophyids so far found in man in the Philippines as natural infection have been recovered from the intestine of dogs and cats, either experimentally or under natural conditions. We venture to predict that this fluke will also be found to be parasitising our dogs and cats, and also fish-eating birds. It is probable that many other piscevorous mammals in this country harbor these trematodes. *Spelotrema brevicaeca* (which is not a heterophyid but included in this work because it seems to be involved in the production of visceral lesions herein described) has not been recovered yet from dogs, or cats either experimentally or as natural infection; but it is a frequent para-

* As there seems to be some discrepancy between our data and those of Ochi, particularly in so far as the effect of exposure to vinegar and saturated salt solution is concerned, we tried to look into the methods used by this author in his experiments but his original paper was not available at this writing.

site of the bird *(Sterna albifrons sinensis)*. *Haplorchis yokogawai, H. taichui, H. calderoni* and *Diorchitrema pseudocirrata* occur in from 2 to 9.5 per cent of the street dogs in Manila (Refuerzo and Garcia, 1936). They often occur in hundreds, or even thousands in young dogs caught in the towns bordering Laguna de Bay, a fresh water lake about twenty-five kilometers south of Manila. In that locality, nearly all the dogs we examined harbor these flukes, *H. yokogawai* being the most common and abundant of them all. *Ophicephalus striatus* ("dalag") which harbors among others the metacercariae of *Haplorchis yokogawai* and of *H. taichui*, and *Arius manillensis* ("kanduli") and *Clarias batrachus* ("hito"), both of which harbor the encysted larvae of *H. yokogawai* frequently alone in great abundance, are among the most common fishes in that locality. A few of our positive human autopsies including one with serious cardiac lesions associated with eggs have been traced to that same area.

Cattle egrets *(Bubulcus ibis coromandus)* and a pelican (*Pyrreroidios manillensis*) are frequently upon dissection found infected with *Haplorchis yokogawai* or *Haplorchis taichui*, or the two together, in the small intestine (2g). These birds, which are voracious fish-eaters, most likely act as the natural reservoir hosts of these two important heterophyids in that area, and perhaps also in other parts of the Philippines. It may be of interest to mention here that parthenitic larval stages including a lophocerous cercariae with a long keeled fluted tail, secretory cephalic glands and pigmented eye-spots answering in all essential details those described by Faust and Nishigori (29) in their life history work in *H. pumilio* and *H. taichui* in Formosa have been observed by us during the dissection of an unidentified melanid snail which is very abundant in Laguna lake. Dogs and cats as well as other fish-eating mammals may act as reservoir hosts, also.

4. *Age:*—Age is probably not a factor in the epidemiology of heterophyidiasis, excepting to the extent that, as in many other infections, the exposure is greater and the infection correspondingly more frequent during the more active years of life. In our series of thirty-four positive autopsies seven occurred in subjects between the ages of 11 and 20; nine between 21

TABLE 3.—*Distribution of Cases in 297 Autopsies According to Sex and Age Groups*

Age Groups	Cases Examined						Infected Cases					
	Sex				Total	Per cent	Sex				Total	Per cent
	Male	Per cent	Female	Per cent			Male	Per cent	Female	Per cent		
1—10	5	3.06	2	1.49	7	2.04	0	0	0	0	0	0
11—20	24	14.72	23	17.6	47	15.84	5	14.70	2	5.88	7	20.58
21—30	31	19.01	44	32.83	75	25.83	5	14.70	4	11.76	9	26.47
31—40	25	15.32	27	20.14	52	17.54	5	14.70	3	8.82	8	23.52
41—50	29	17.79	16	11.94	45	15.17	5	14.70	2	5.88	7	20.58
51—60	21	12.88	9	6.71	30	10.14	1	2.94	0	0	1	2.94
61—70	20	12.27	7	5.52	27	9.13	2	5.88	0	0	2	5.88
71—80	1	0.61	3	2.23	4	1.37	0	0	0	0	0	0
81—90	1	0.61	0	0	1	0.35	0	0	0	0	0	0
Undetermined	6	3.68	3	2.23	9	3.05	0	0	0	0	0	0
TOTAL	163	99.95	134	99.95	297	99.91	23	67.62	11	32.34	34	99.97

and 30; eight between 31 and 40; seven between 41 and 50; one between 51 and 60; and two between 61 and 70. It will thus be seen that this infection is apparently more common during the more active years of life than during childhood and old age. However, as will be seen in table 3, autopsies under 10 years and over 70 years of age were relatively fewer than in other age groups in the present series.

5. *Sex:*—Sex is probably not a factor either excepting again to the extent that, as in many other diseases, the exposure is greater and the infection correspondingly more frequent in the male than in the female. In this same series of 34 positive autopsies more than two-thirds (twenty-four) were males, and less than one-third (ten) were females despite the fact that there is very little discrepancy in the number of autopsies between the two sexes. Again in our fifteen cases with visceral lesions only three were females, the rest being all males.

6. *Occupation:*—Occupation probably affects to a certain extent the incidence of this disease. Fishermen, boatmen, hunters, mining prospectors, rangers, and other persons whose occupations bring them in close association with marine life are probably more prone to eat fish in the raw state than are people engaged in other occupations. The absence of cooking facilities for the roving workers may also induce these people to eat uncooked fish. Our cases, however, have all come from among people of the lower presumably more static land classes, where many of the different occupations offer similar types of exposure and where the vocation is often changed from day to day.

7. *Customs and Habits:*—The habit of eating raw or semi-cooked fish is undoubtedly an important factor in the epidemiology of this disease. One will easily appreciate this fact by referring to table 4. In this table it will be seen that over fifty per cent of our thirty-four positive autopsies came from the Visayan and Ilocano regions of the archipelago, where the eating of raw fish is admittedly more common and heavy than in Central Luzon inhabited mostly by the Tagalogs, who as a group are known to be less inclined to eat raw fish than are people of other areas. It is true that in area and in the number of population the combined Visayan and Ilocano regions are

TABLE 4.—HETEROPHYIDIASIS: *Distribution of Cases According to Nativity*

No.	NATIVITY	A. No.	SEX	AGE		
* 1	San Jose del Monte, Bulacan	35-795	M	35	47.06 per centum	CENTRAL LUZON
* 2	Balañga, Bataan	38-30	M	17		
* 3	San Roque, Cavite	35-321	M	62		
* 4	Biñan, Laguna	35-946	M	70		
5	Sta. Cruz, Laguna	37-834	F	20		
6	Quiapo, Manila	38-89	M	38		
7	Sta. Mesa, Manila	38-141	M	26		
8	Bacolor, Pampanga	35-329	M	48		
9	Bacolor, Pampanga	35-335	F	30		
10	Cainta, Rizal	38-76	M	12		
11	Cardona, Rizal	36-168	M	35		
*12	Makati, Rizal	37-705	M	21		
13	Mariquina, Rizal	38-480	M	41		
14	Mariquina, Rizal	37-745	F	33		
15	Tagig, Rizal	37-1024	M	35		
16	Luchan, Tayabas	36-166	M	23		
17	Libon, Albay	35-403	M	11	26.47 per centum	VISAYAN REGION
*18	Calivo, Capiz	35-326	M	60		
*19	Barugo, Leyte	35-265	M	23		
*20	Barugo, Leyte	35-711	F	27		
21	Ormoc, Leyte	35-342	M	19		
*22	Cotabato, Mindanao	37-620	F	22		
*23	Oroquieta, Mindanao	35-1110	M	17		
*24	Borongan, Samar	35-543	M	24		
25	Sibuyan, Romblon	37-855	M	37		
26	Pangasinan	38-535	F	44	23.51 per centum	ILOCANO REGION
27	Calasiao, Pangasinan	37-389	F	48		
28	Mangaldan, Pangasinan	35-933	F	36		
*29	Batac, Ilocos Norte	36-111	M	44		
30	Candon, Ilocos Sur	35-318	F	18		
*31	Bacnotan, La Union	35-489	F	35		
*32	San Fernando, La Union	35-209	M	50		
*33	San Fernando, La Union	36-480	M	45		
34	Hilo, Hawaii	37-823	F	23	Foreign	

PHILIPPINE ISLANDS

*Note: Asterisks indicate cases with visceral complications.

greater than Central Luzon; but Manila, where our autopsies were performed, lies in the heart of the Tagalog region and for this demonstration the Tagalogs of any chosen group would likely be amply representative in number and be correctly proportional to the total Philippine population. Yet infected Tagalogs are few; though the great majority of the charity patients admitted to the Philippine General Hospital are from this Central Luzon region. Indeed it is probable that the Visayan and Ilocano subjects we have investigated in this work represented for the most part the Visayan and Ilocano elements of the Philippine metropolis only, to which they have drifted. We can not pass over the fact that these elements naturally bring along with them, as all folk do, their folk habits, and among these no doubt, their habit of eating raw fish. It is also significant that ten out of our fifteen cases with visceral complications came from the Ilocano-Visayan group. To our mind this fact suggests that continuous and heavy eating of raw fish favors the adverse if not mortal involvement of the visceral organs, since a very large percentage of the most popular local fishes are naturally infected, as has been indisputably shown.

IX. SYMPTOMATOLOGY

A. INTESTINAL HETEROPHYIDIASIS

According to Khalil (47b) Heterophyes infection in man occasionally produces diarrhea, which may be accompanied with blood. The course of the infection is of a chronic and intermittent nature. Neurasthenia is sometimes observed among the patients. Practically the same symptoms are observed in Metagonimus infection.

Analysis of the clinical record of the majority of our thirty-three cases from which flukes were recovered in the intestine at the time of their confinement in the hospital did not show intestinal symptoms that could be clearly attributed to the presence of the worms even in the most heavily infected ones. The patients evidently sought admission to the hospital for other reasons. We have not yet seen any antemortem infection

by the flukes involved in the present work to justify discussion of the symptoms of uncomplicated intestinal infections. Faust and Nishigori (29) experimentally infected human beings with Haplorchis, but unfortunately, no clinical records of their experiment are available. There can not be any doubt, however, that Haplorchis infection could produce intestinal disturbances such as colicky pains and mucous diarrhea, judging from the location of the parasites in the mucosa as observed in experimental animals (6a & b). The degree of these disturbances would, most likely, depend upon the number of worms that had invaded the glands of Lieberkuhn and the extent of penetration, or of the destruction or necrosis of the epithelium occasioned by the presence of the worms. On the whole, these intestinal disturbances, except in very heavy infections, are perhaps so mild that they may be considered negligible clinically.

B. CARDIAC HETEROPHYIDIASIS

Analysis of the clinical records of the thirteen cases in our series in which death was attributable to cardiac complications of intestinal heterophyidiasis, or in which serious lesions evidently due to the presence of eggs of the flukes in the myocardium (and mitral valves in some) have been observed, shows that in two of the cases death was apparently sudden; in three, death ensued soon after admission to the hospital; and in almost all of the cases which were admitted to the hospital and lived long enough for clinical observation, the patient showed symptoms of failing heart on admission, and had been suffering from this condition for some time previously.

The most important signs and symptoms observed in the ward in the order of their frequency are: enlarged heart, dyspnea and cyanosis, easy fatigability, cough, palpitation and arhythmia, edema of the lower extremities and face, numbness of the lower extremities, diminution or total abolition of knee jerks and other reflexes, ascitis, enlarged liver, systolic murmur, accentuation of the second pulmonic sound, pre-systolic murmur and other abnormal heart sounds, anasarca and fornication.

That cardiac heterophyidiasis may be comfounded with dropsical beriberi is evinced by the fact that in the ward four of our cases were diagnosed and treated as such; while eight of the cases were given the same anatomical diagnosis. When val-

vular involvement is present, besides the myocardial lesions, the condition may pass for any endocardial affection due to other causes. It may be mentioned that in the ward, clinicians not infrequently meet cases presenting symptoms of cardiac beriberi which are absolutely refractory to the administration of vitamin B_1.

Because of the possibility of the wide dissemination of eggs throughout the body, concomittant with the heart condition (as has been demonstrated in one of our cases in which eggs were found in the liver, lungs, and spleen, besides in the heart) cardiac heterophyidiasis may present protean manifestation.

X. DIAGNOSIS

In very young infections, or in cases of recurrent ones, diagnosis is based on the finding of eggs in the feces. The eggs must be very carefully differentiated from those of the opistorchid trematodes (*Chlonorchis sinensis* and *Opistorchis felineus*) which they closely resemble. We have not detected eggs of these flukes *(heterophyids)* in the feces of cadavers examined in the present series. We attribute this failure either to faulty technique employed or to the scarcity of eggs due to the small size of infection in the majority of the cases. In many cases we were able to recover only a few flukes from the cadavers. With the exception of *Spelotrema brevicaeca,* of which as many as 500 specimens were recovered in a single autopsy, only a few flukes (refer to table 1) were obtained in the majority of our positive autopsies. We doubt whether the egg output of such small numbers of flukes would be sufficient to be demonstrated in the feces by the ordinary method of fecal examination. In fact, in one of our heart-failure cases not a single fluke was found in the intestine at autopsy. Furthermore, the parasites that get imprisoned in the lumen of the intestinal glands, or in the tunica propria can expel their eggs into the intestinal lumen only with great difficulty. For this reason we believe that diagnosis *in vivo* of advanced cardiac heterophyidiasis, or of other visceral complications would be rather problematical unless some kind of skin test is developed in the future. Clinically, cardiac heterophyidiasis has to be differentiated from

wet beriberi, and other organic heart diseases, such as restricted specific valvular troubles, chronic myocarditis, and the like.

XI. COURSE, DURATION, AND PROGNOSIS

As in other helminthic infections in which there is no multiplication of the parasites in the body of the host, the course, duration, and prognosis of this disease naturally depend upon the size and age of the infection, upon how many times reinfection has occurred, and upon the degree of involvement of the viscera. Heterophyidiasis is primarily an intestinal infection, and visceral complications, perhaps, occur only under certain conditions. If the intestinal infection is slight, providing no reinfections occur, the patient may probably eventually get rid of his infection without developing visceral lesions, or at least the visceral lesions may not become serious enough to show external manifestations. Visceral complications probably set in in subjects who are frequently exposed to the larvae (metacercariae) through eating uncooked fish, for long periods of time. Once serious lesions in the heart are produced, the course, duration, and prognosis are probably the same as in other organic heart diseases.

Theoretically, a single massive dose of eggs may overwhelmingly embarrass the heart (specially if they happen to plug important vessels, or annihilate extensive vascular areas) and bring about a fatal acute heart attack. However, in many of our cases in which lesions attributable to this infection and presumably the cause of cardiac dysfunction, were found, only the specific type of lesions and the very chronic ones (sclerosis and calcification) could be demonstrated, indicating that probably in many cases the condition is a chronic one, resulting from recurrent hemorrhages in the myocardium, or valves, mechanically produced by the eggs of the parasites.

XII. TREATMENT

Administration of tetrachlorethylene recommended by other authors for the treatment of Metagonimus and Heterophyes infections may be tried to expell the flukes in the intestine and prevent possible visceral dissemination of the eggs. Every intestinal infection should be considered potentially dangerous. Reinfection should be avoided by abstinence from eating any

kind of fish in the raw or semi-raw state in order to limit the size of the infection already present in the intestine and to frustrate possible visceral involvement, or prevent its aggravation if already present. Once the symptoms of failing heart supervene, the treatment would be in the same line as in other organic heart diseases, or symptomatic. Perhaps in no other disease is the adage "an ounce of prevention is worth more than a pound of cure" more applicable than in this infection in reference to its serious visceral complications.

XIII. PROPHYLAXIS

Absolute prevention of the infection is possible if the people could abstain from eating fish of any kind in the raw or improperly cooked state. We do not subscribe to the opinion of other authors that, fundamentally, control involves the sanitary disposal of human feces, because other mammals (dogs, cats, foxes, etc.) and birds are infected heavily with this heterophyids in endemic areas. It is probable that these animals and not the infected human population, mainly disseminate the eggs that infect the molluscan hosts. Mass education especially along the line of drying, seasoning and cooking fish properly before consumption so as to render it free from viable larvae will greatly help to minimize the incidence or intensity of the infections in endemic localities.

XIV. COMMENTS

One will note in our protocols the paucity of worms recovered from the intestine of individual autopsies. Indeed, as previously stated, not a single fluke was recovered from the intestine of one of our heart-failure cases in which ova were found associated with degenerative changes in the myocardium. Superficially it would really seem far-fetched to associate the presence of a few worms in the intestine of these cases with the cardiac dysfunction observed in them. We believe, though, that the few worms recovered from these cases did not represent the actual number of flukes present in the intestine at the time of autopsy, since some of the parasites could have been easily lost during the process of recovering the others. This loss can well be appreciated by having in mind the small size of these trema-

todes, which measure on the average only a fraction of a millimeter in length. Furthermore it has to be considered that these worms do not multiply in the intestine of the host. The number of worms that an individual harbors can not be any greater than the number of encysted larvae (metacercariae) previously ingested by him. Yet a person may ingest dose after dose of the infective larvae at varying intervals for long periods, so that batch after batch of new worms may arrive successively in the intestine, take their position in the intestinal wall, mature, die and disappear from the scene, but leave their eggs in favorable situations, whence they can easily filter into the lymphatic and blood streams. The number of worms found at autopsy can not then be taken as an index of the size of the infection or of "successive infections" that the subject had had in life.

The above view will also help explain the apparent absence of visceral complication in over one half of our positive autopsies in which the flukes were recovered from the intestine. Of course, in some of these cases eggs might have also been present in certain visceral organs but perhaps in such negligible number that their presence could neither give rise to observable external manifestations nor be detected with the method we used. Had the subjects not died of other intercurrent diseases, or had they lived long enough to permit their heterophyid infection to run its course, it is probable that some of them would likewise have developed visceral heterophyidiasis.

The extent and severity of visceral complications in heterophyidiasis perhaps depend upon the size and duration of the original infection and upon how many times reinfection has occurred. If the intestinal infection is slight, providing no reinfections have occurred, the patient probably gets rid of his infection eventually without developing visceral lesions; or the visceral lesions, if already present, may not become serious enough to produce observable external manifestations. While every existing intestinal infection is not necessarily followed by visceral complications, nevertheless any infection should always be regarded potentially dangerous. Visceral complications probably occur in persons addicted to the eating of raw fish in endemic areas; in other words, in individuals exposed to large doses of larvae for long periods, the long periods favoring cummulative deposits of ova in the intestinal wall. This observation seems to be supported by the fact that the great majority of

our autopsies with cardiac complications occurred as we have repeatedly said among the Ilocanos and Visayans, who eat more raw fish than other Philippine population groups.

There seems to be no doubt that the lesions we have demonstrated in the myocardium and valves of our heart-failure cases are caused specifically by the heterophyid ova with which they are usually found associated. That these lesions eventually lead to the formation of scar tissue and other degenerative changes seems to have been demonstrated in this work. However, whether these lesions have been primarily responsible for the cardiac dysfunction observed in these cases, or whether they only contributed with other coincidental pathological conditions to bring about the final breakdown of the circulation are questions which are not yet fully settled. In fact, according to MacCallum* (1928) there is still much dispute as to the effect of scars in the myocardium, or rather of the injuries which give them origin, upon the muscular power of the heart. While conceding that the destruction of the heart muscle and its replacement by rigid scar tissue must deprive the heart of some of its strength, he believes that the reserve power of this organ is so extraordinary that a great deal may be destroyed before the circulation is impaired. He cites Aschoff and Tawara, who lay little stress on such scarring of the heart as a cause of the failure of the circulation, and states further that most clinical writers also agree that even extreme degrees of fibrous alterations may exist for a long time without giving rise to any symptoms. MacCallum is also uncertain whether the conversion of a part of the heart muscle into scar tissue is followed by hypertrophy of the rest of the muscle, so as to enlarge the whole heart; because, according to him, the condition seldom occurs without other changes within or outside the heart, which could also be concerned in causing cardiac hypertrophy.

But whatever may be the exact mechanism of cardiac failure it is difficult for us to dissociate the lesions in the myocardium and valves, which we believe are specifically produced by heterophyid ova, from the cardiac dysfunction in our cases. This conviction is particularly strong in connection with those cases where in addition to the scarring of the myocardium the

* MacCallum, W. G.—A text book of pathology, fourth edition, W. B. Saunders Company, Philadelphia and London, 1928.

mitral valves were so thickened by sclerosis and calcification that the cardiac hypertrophy, followed by the final breakdown of the circulation observed in them, was pretty obviously due to these anatomical changes.

The possibility that the cardiac hypertrophy and failure of the circulation in these cases is independent of, or unrelated to, the lesions specially produced by the ova in question, and that they have been due to other coincidental pathological conditions seems to us highly improbable even from purely statistical grounds alone. Coincidence may occur in a few cases, but hardly in such a relatively large number of instances. In this work, we have extensively and painstakingly explored histologically the hearts of 89 unselected cases of cardiac trouble without regard to their clinical or anatomical diagnosis, and irrespective of the presence or absence of the worms in the intestines. The primary causes of death in these 89 cases with enlarged hearts were as follows: Cardiac dilatation with hypertrophy of the right ventricle (beriberi), 10 cases, or 11.23 per cent; chronic interstitial nephritis with hypertrophy and dilatation of the left ventricle, 15 cases, or 16.85 per cent; chronic valvulitis with mitral stenosis and insufficiency, 27 cases, or 30.33 per cent; acute or subacute endocarditis, 6 cases or 6.74 per cent; cerebral hemorrhage, 8 cases or 8.89 per cent; aortitis, syphilitic with secondary cardiac dilatation, 2 cases or 2.4 per cent; acute or chronic myocarditis, 20 cases or 22.47 per cent. It is interesting to note that in 13 of these 89 cases with enlarged heart in which the ova of the parasites were found associated with serious lesions in the myocardium and valves, the adult worms could also be demonstrated in the intestine except in one case; whereas in 71 cases of these series in which the heart was enlarged but found after exhaustive histological explorations to be without any evidence of the presence of the ova, or lesions which may be specifically attributed to them, the intestine was likewise invariably negative for flukes. In these 13 cases with myocardial and valvular involvement the cause of death was attributed to cardiac beriberi in 9, to chronic valvulitis in 3, and to acute pyonephrosis in 1. These attributions seem significant; because, if these changes in the heart (which we believe are caused specifically by heterophyid ova) were only coincidental with other pathological conditions which were really responsible for the final breakdown of the circulation in these cases, the

changes should have been found more or less evenly distributed among the different conditions above enumerated. As it is, they seem to show a tendency to occur in cases which to the pathologist grossly appear as cardiac beriberi, thus indicating the existence of a pathological condition which although unrecognizable grossly from the real beriberi, is nevertheless distinct from and quite independent etiologically of the latter. It is true that in 5 cases of this series we failed to demonstrate the presence of eggs or lesions characteristic of this infection in the heart in spite of the presence of the worms in the intestine. However, failure to demonstrate them does not mean that they were actually absent; and the failure consequently can not constitute a negative evidence, since as stated previously, in this infection the places of the specific lesions are difficult to find and are discovered only wherever the eggs happen to be lodged. To eliminate heterophyidiasis completely as a possible etiologic factor even in these five cases it would necessitate the satisfactory demonstration of the presence of other causes. We may add that if not associated with ova or with the characteristic reactive cellular elements which we consider specific to this helminthic infection, the non-specific lesions in heterophyidiasis (such as, the very acute, or those of purely vascular nature, and the very chronic, or terminal degenerative changes) can not very well be distinguished respectively from the acute vascular changes and sclerosis due to other causes, and can be mistaken for any acute vascular condition or for any non-specific healed or sclerotic lesions.

Although we think that our knowledge of this infection is still very limited, nevertheless we feel that we are now in a position to advance at least seven main propositions as a working basis for further study, as follows:

(1) That heterophyidiasis is primarily and essentially an intestinal infection; but because of an unbalanced parasitic relationship between the human host and the parasites, the parasites wander into the deeper layers of the wall of the small intestine, where they become imprisoned and die.

(2) That because of the position assumed by the parasites in the intestinal wall in relation to the terminal tributaries of the portal vein and lymphatic vessels, and because of the general lack of fibrotic walling-off processes on the part of the host

tissue, the eggs of the worms that degenerate get into the blood and lymphatic streams and are carried into the different viscera.

(3) That in the viscera these eggs may precipitate in a mechanical manner hemorrhages and other vascular disturbances of varying degrees of intensity which later may provoke a cellular reaction hitherto unknown and peculiar or specific to heterophyidiasis.

(4) That these specific tissue changes are eventually replaced in the healed lesions by the proliferation of fibrous tissue that insidiously sets in as the specific reaction tissue is gradually absorbed, the total activity leaving an inflammatory residue quite unrecognizable, in the absence of eggs, from the terminal inflammatory processes due to other infections.

(5) That the nature, as well as the extent and severity of the visceral complications, depends upon the organ or organs receiving the largest number of eggs, which in turn depends upon the size and duration of the original infection and upon how many reinfections have occurred.

(6) That if the intestinal infection is slight, providing no reinfections occur, the patient may get rid of his infection, eventually, without developing visceral lesions; or the visceral lesions, if they develop, may not become serious or extensive enough to produce observable external manifestations.

(7) That while every existing intestinal infection is not necessarily followed by visceral complications, nevertheless any infection should always be regarded as potentially dangerous.

XV. GENERAL SUMMARY

It is the purpose of this entire paper to embody in one volume all the pertinent observations we have made so far in human heterophyidiasis since our discovery in 1935 of visceral complications in this helminthic infection heretofore believed to be restricted to the small intestine. However, it was realized that in order intelligently to present our findings in man the different phases of this infection as observed in animals both under natural and experimental conditions as well as the systematic position of the flukes concerned should be dealth with at some length. Hence special reference has been made to the family Heterophyidae as a whole; such as,

the general description of this family; its local representatives in the Philippines; their life cycle in general and the local fishes that convey the infection to the ultimate hosts; the mechanism of infection and dessemination of the parasites (particularly their eggs) in the body; the description of the varying species involved; their behavior in avian hosts, and whatever else seemed germane. In order to provide a background to the present work there have been included a brief history of the discovery of complications in the heart. and a survey of local trematode infections, and a review of other pertinent literature on the subject, including other helminths that have been previously found to lodge in the heart and central nervous system.

The technique we have employed in this investigation has been fully described for the convenience of other workers who may want to amplify on the little start we have made in the Philippines, or as an invitation for other institutions similarly situated to confirm our findings.

The present work is mainly a report on visceral complications in intestinal heterophyidiasis observed among thirty-four positive autopsies in a series of two hundred ninety-seven cases performed in the Manila City Morgue. Visceral complications were found in fifteen: heart (including the mitral valves in several), fourteen times; brain, once; spinal cord, once; liver, twice; lungs, once; spleen, once. In thirteen cases with heart lesions associated with heterophyid eggs, cardiac symptoms were observed in life, and death was attributed to heart failure.

Heterophyidiasis is primarily an intestinal infection. Intestinal infection occurs in about 8.33 per cent of autopsies in charity patients in Manila. About 44 per cent of intestinal infections develop visceral complications. The adult flukes parasitise the mucosa of the small intestine; but apparently because of an unbalanced parasitic relationship between the human host and these worms, the latter wander into the deeper layers of the intestinal wall, where they become imprisoned and die. Because of general lack of fibrotic walling-off processes on the part of the host tissues, the ova in the bodies of these flukes that degenerate filter into the lymphatic or blood streams, and are carried to the different organs of the body. Recurrent hemorrhages and other concomitant vascular changes precipitated by these eggs from time to time in the heart during the

course of intestinal infection result in the formation in the myocardium and valves, in a proportion of cases, of lesions of varying grades of chronicity. Except for the presence of the eggs, the acute stages, which are purely of vascular nature, and the very chronic or terminal stages of the inflammatory processes can not be differentiated from those of other infections. In between these two extremes, however, the lesions partake of the nature of typical reticuloendothelial proliferation with very little or none at all of the other cellular elements usually found in other helminth infections. This type of lesion, which is found almost invariably wherever the eggs of these flukes have lodged for some time, is considered specific or peculiar to heterophyidiasis, and is a newly discovered and newly described pathological condition. Such lesions apparently lead eventually to the formation of fibrous tissues or scars and other degenerative changes in the myocardium, or valves, which may become extensive enough to impair seriously the function of the heart and to bring about an acute fatal heart attack.

If the lesions in the myocardium, or valves, in thirteen of our fatal heart cases could be taken as primary contributing factors to the death of these individuals, as seems reasonable from the apparent absence of any other probable factors then it would seem that around 14.60 per cent of heart disease in charity patients in the Philippines is occasioned by heterophyid infection. At any rate, it seems that one previously undiscovered cause of heart trouble has been found and that a distinct specific pathological condition hitherto unrecognized has been demonstrated, appropriately to be called—cardiac heterophyidiasis.

Broad generalization can not be deduced from our limited data on the complications of this infection in the central nervous system, in the liver, the lungs, and spleen. Nevertheless, the lesions we have described in the brain and spinal cord caused by the presence of eggs in these localities present unequivocable evidence to support the contention that serious neurological disturbances may also occur as complications of intestinal heterophyidiasis.

The paucity of our data concerning lesions in the central nervous system and other viscera is in our opinion more apparent than real and is due largely to lack of means as well

as to lack of opportunity to examine such organs as extensively and as intensively as we have examined the heart.

Included in this treatise are short discussions on the symptomatology, diagnosis, course, duration and prognosis, treatment, and prophylaxis of heterophyidiasis, particularly the cardiac form.

PAPERS CITED

1. Africa, C. M., Garcia, E. Y., and De Leon, W. Intestinal heterophyidiasis with cardiac involvement: A contribution to the etiology of heart failure. Phil. Jour. Pub. Health, v. 2, Nos. 1-2, (1935).

2a. Africa, C. M., de Leon, W., and Garcia, E. Y. Heterophyidiasis II: Ova in sclerosed mitral valves with other chronic lesions in the myocardium. Jour. Phil. Is. Med. Ass'n., v. 15, No. 11, (1935) pp. 583-592.

b. Heterophyidiasis III: Ova associated with a fatal hemorrhage in the right basal ganglia of the brain. Jour. Phil. Is. Med. Ass'n. v. 16, No. 1 (1936).

c. Heterophyidiasis IV: Lesions found in the myocardium of eleven infested hearts including three cases with valvular involvement. Phil. Jour. Pub. Health, v. 3, Nos. 1-2, (1936).

d. Heterophyidiasis V: Ova in the spinal cord of man. Phil. Jour. Sci., v. 62, (1937) pp. 393-399.

e. Heterophyidiasis VI: Two more cases of heart failure associated with the presence of eggs in sclerosed valves. Jour. Phil. Is. Med. Ass'n. v. 9, No. 10 (1937).

f. Somatic heterophyidiasis in fish-eating birds: I, Ova associated with chronic lesions in the pancreas of a sea-gull (*Larus ridibundus* Linn.). Phil. Jour. Pub. Health, v. 3, Nos. 1-2 (1936).

g. Somatic heterophyidiasis in fish-eating birds: II, Presence of adults and eggs in the bile ducts of the cattle egrets (*Bubulcus ibis coromandus*, Boddaert). Phil. Jour. Sci., v. 61, No. 2 (1936).

3. Africa, C. M. and de Leon, W. Observations on the mechanism of phagocytosis of various helminth ova. Livro Jubilar Prof. Travassos, Rio de Janeiro, Brazil III (1938).

4a. Africa, C. M. and Garcia, E. Y. The distribution of schistosomiasis japonica in the Philippines. Phil. Jour. Pub. Health, v. 2, Nos. 1-2 (1935).

b. Various heterophyid trematodes from man and dogs in the Philippines with description of three new species. Phil. Jour Sci., v. 57, No. 3 (1935).

c. Two more new heterophyid trematodes from the Philippines. Phil. Jour. Sci., v. 57, No. 3 (1935).

d. Plagiorchis sp., a new trematode parasite of the human intestine. Papers on helminthology published in commemoration of the 30-

year jubileum of the scientific, educational and social activities of the honoured worker of science, K. J. Skrjabin, M. Ac. Sci. and of the fifteen anniversary of the All Union Institute of Helminthology, Moscow (1937).

5a. Africa, C. M. and Cruz, J. Sta.—*Cysticercus cellulosae* in man. Jour. Phil. Is. Med. Ass'n., v. 7, (1927).

b. Ova of *Schistosoma japonicum* in the human heart. Volumen jubilare pro Prof. Sadao Yoshida, v. 2, Osaka, Japan. March, (1939).

6a. Africa, C. M. Evidence of intramucosal invasion in the life cycle of *Haplorchis yokogawai* (Katsuta, 1932), Chen 1936 (Heterophyidae). Jour. Phil. Is. Med. Ass'n., v. 17, No. 12 (1937).

b. An attempt to elucidate the filtration of eggs of certain heterophyid trematodes into the general circulation. Phil. Jour. Ani. Industry., v. 5, No. 2, (1938).

c. Description of three trematodes of the genus Haplorchis (Heterophyidae) with notes on two other Philippine members of this genus. Phil. Jour. Sci., v. 66, No. 3, (July, 1938).

d. Parasitological oddities. Jour. Phil. Is. Med. Ass'n., v. 17, No. 2, (1937) pp. 83-93.

7. Agote, L. and Bianchi, A. E. Echinococcosis in the heart: case at autopsy. Rev. Soc. Med. int. and tisiol, v. 3 (1927) pp. 469-514.

8. Alicata, J. E. and Chattenburg, O. L. A case of intestinal heterophyidiasis of man in Hawaii. Jour. Am. Med. Ass'n., v. 110, No. 14, (April 2, 1938).

9. Anderson, A. M. and Patterson, S. W. Hydatids of heart and hydatid emboli. Med. Jour. Australia, v. 1, (1924) pp. 41-44.

10. Asada, J. Determination of the first intermediate host of *Heterophyes heterophyes* occurring parasitic in human body in Japan and an experimental investigation on its development. Tokio Iji Shinsi (Tokio Med. News), March No. 2564. Summarized in Japan Med. World, v. 8, No. 5, (1928) p. 134.

11. Bacaloglu, C., Balan, N., Ballif, L. and Vasilescu, C. Echinococcosis of heart, pathologic study at autopsy. Ann. de Med., v. 26, (1929) pp. 242-268.

12. Boettiger, C. and Werney, J. *Ascaris lumbricoides* found in the cavity of the human heart. Jour. Am. Med. Ass'n., v. 93, No. 32, (July 6, 1926).

13. Broughton-alcock, Stevensons, and Drought, W. Cysticercosis of the brain, with report of a case. Brit. Med. Jour., v. 2, (1938) pp. 980-982.

14. Cameron, Th. W. N. Studies on the heterophyid trematode *Apophallus venustus* (Ransom 1920) in Canada. Canada Jour. Research, v. 15, No. 2. (February, 1937).

15. Chandler, A. C. Introduction to Human Parasitology. 5th edition. New York John Wiley & Sons, (1936).

16a. Chen, H. T. Helminths of cats in Fukien and Kwangtung provinces with a list of those occurring in China. Lingnan Sci. Jour., v. 13, (1934) pp. 261-273.

b. Helminths of dogs in Canton with a list of those occurring in China. Lingnan Sci. Jour. v. 13. (1934) pp. 75-87.

c. A study of the Haplorchinae (Looss, 1899) Poche. 1926 (Trematoda: Heterophyidae), Parasit., v. 28, (1936) pp. 10-55.

17. Ch'nd, L & K'ang, H. J. Cysticercosis cellulosae in man, report of case with very severe infestation especially in brain. Chinese Med., v. 50, (February, 1936) pp. 137-139.

18. Chung, H. L. & Lee, C. U. Cysticercosis cellulosae in man with special reference to involvement of central nervous system. Chinese Med. Jour., v. 49, No. 5, (February, 1935) pp. 429-445.

19a. Ciurea, J. Uber einege neue Distomen aus dem Darm unserer Haustiere und des Pelikans für welche die Fische als Infectionsquelle zu betrachtchen sind. Zeit. Infektionskr. Haustiere, Bd. 16, (1915) S 445-458.

b. Heterophyides de la faune parasitaire de Roumanie. Parasit., v. 16, (1924) pp. 1-21.

c. Les vers parasites de l'homme, des mamiferes et des oiseaux provenant des poisons der Danube et de la mer noire. Arch. roumaines path. exptl. Microboil., v. 6 (1933), pp. 4-134.

20. Cort, W. W. Proceedings of the Helminthological Society of Washington. Jour. Parasit., v. 7. No. 4, (1921) pp. 120-186.

21. Craig, C. F. and Faust, E. C. Clinical Parasitology. Philadelphia, Lea and Febiger, (1937).

22. Crowell, B. C. and Hammack, R. W. Intestinal parasites encountered in five hundred autopsies with reports of cases. Phil. Jour. Sci., v. VII-B, (1913) pp. 157-174.

23. Day, H. B. and Kenway, M. R. Bilharzial myelitis; a case. Trans. Roy, Soc. Trop. Med. & Hyg., v. 30, (July 1936) pp. 223-224.

24. Dickerson, R. E. Distribution of life in the Philippines. Monograph No. 21, Bureau of Science, Manila, P. I. (1928).

25a. Dixon, H. B. and Smithers, D. W. Cysticercosis (*Taenia solium*). Jour. Roy. Army Med. Corps, v. 65, Nos. 1 & 2 (1935) pp. 28-34; 91-98.

b. Cysticercosis *(Taenia solium)*. Jour. Roy. Army Med. Corps. v. 64, Nos. 4, 5, & 6, (1935), pp. 227-234; 300-306; 375-380.

26. Edgar, W. H. Epilepsy due to infection of *Schistosoma japonicum*. Jour. Roy. Nav. Med. Service, v. 22, (1936) pp. 150-153.

27. Elera, C. de Catalogo sistematico de toda fauna de Filipinas: Moluscos y Radiados.—Colegio Universidad de Sto. Tomas, Manila, v. III, (1896).

28a. Faust, E. C. Human Helminthology. Philadelphia, Lea and Febiger, (1929).

b. Notes on trematodes from the Philippines. Phil. Jour. Sci., v. 17, No. 6, (1920) p. 627.

29. Faust, E. C. and Nishigori, M. The life cycle of two new species of Heterophyidae parasitic in mammals and birds. Jour. Parasit., v. 13, (1926) pp. 91-128.

30. Ferguson, H. Eggs of *Schistosoma hematobium* in brain and spinal cord; report of a case. Glasgow Med. Jour., v. 79 (1913).

31. Finney, C. M. Echinococcosis of the heart. Brit. Med. Jour. v. 2, (September, 1934) p. 465.

32. Fleming, M. B. and Bury, C. W. A case of primary hydatid disease of brain. Lancet, v. 2, (December 27, 1919) p. 1186.

33. Frothinghan, C. A contribution to the knowledge of the lesions caused by *Trichinella spiralis* in man. Jour. Med. Research, v. 15 (1906) p. 483.

34. Garcia, E. Y. and Refuerzo, P. G. Two more species of the genus Stictodora Looss, 1899, in the Philippines with description of a new species. Phil. Jour. Sci., v. 60, (1936) p. 137.

35. Garcia, E. Y. Studies on the resistance of the metacercariae of *Monorchotrema taihokui* to different physical and chemical agents. Jour. Phil. Is. Med. Ass'n., v. 16, No. 9, (September, 1936).

36a. Garrison, P. E. The prevalence and distribution of the animal parasites of man in the Philippine Islands, with a consideration of their possible influence upon public health. Phil. Jour. Sci., v. III-B, (1908) pp. 191-210.

b. A new intestinal trematode of man (Fascioletta ilocana, gen. nov., sp. nov.). Phil. Jour. Sci., v. III-B, (1908) pp. 385-393.

37. Goldsworthy, N. E. A case of hydatid infection involving myocardium. Med. Jour. Australia, v. 1, (January, 1925) pp. 110-111.

38. Gonzales, R. and Mosto, D. Echinococcosis in patient with clinical and electrocardiographic picture of myocardial infarct; a case. Prensa. Med. Argentina, v. 24, (1937) pp. 308-318.

39. Hare, C. C. *Cysticercus cellulosae* of the brain. Jour. Am. Med. Ass'n., v. III, No. 6, August, 1938.

40. Hassin, G. B. and Diamond, I. B. Trichinosis encephalitis; pathologic study. Arch. Neurol. & Psychiatry, v. 15, (January, 1926) pp. 34-47.

41a. Herre, A. W. C. T. The Philippines as an ideal site for a biological station. The Scientific Monthly, v. 17, No. 3, (September, 1923) pp. 206-215.

b. Distribution of the true fresh-water fishes in the Philippines: The Philippine Cyprinidae. Jour. Sci., v. 24, No. 3, (March, 1924).

42. Holmes, F. Cysticercosis, case with epilepsy. Jour. Roy. Army Med. Corps, v. 62 (April, 1924) pp. 296-298.

43. Hynd, D. Echinococcus of heart, Brit. Med. Jour., v. 2, (August, 1924) pp. 277.

44. Jesus, Z. de. *Lymnaea philippinensis*, an intermediate host of *Fasciola hepatica* in the Philippines with some observations on the

bionomics of the parasite. Phil. Jour. Sci. v. 58, (1936) pp. 299-316.

45. Jurgensen, Th. Von and Schotter, L. Trichina larvae in the pericardium. Diseases of the heart in Nothnagel's Encyclopedia, v. 12, (1908) p. 824.

46a. Katsuta, I. Studies on trematodes whose intermediate hosts are fishes, from brackish waters of Formosa. (IV Report). On a new trematode *Monorchotrema yokogawai* of which the mullet is the second intermediate host. Jour. Med. Ass'n., Formosa, v. 31, (1932) pp. 253-265.

b. Studies on trematodes whose second intermediate hosts are fishes from brackish waters of Formosa, (V Report). Taiwan Igakkai Zasshi (Jour. Med. Ass'n. Formosa) v. 31, No. 4, (April, 1932).

47a. Khalil M. A preliminary note on the second intermediate host of *Heterophyes heterophyes* in Egypt. Jour. Helminthology, v. 1, No. 3, (1923) pp. 141-142.

b. The life history of human trematode parasite, *Heterophyes heterophyes* in Egypt. Lancet, v. 2, p. 537, (September, 1933).

c. Hydatid cyst of heart as a cause of sudden death. Jour. Egyptian Med. Ass'n., v. 17, (September, 1934) pp. 796-798.

48. Kobayashi, H. A distomid larva infesting the Egyptian mullet. Jour. Helminthology, v. 1, No. 3, (1923) pp. 97-98.

49. Leiper, R. T. Medical helminthology: A Review. Part I. Trop. Dis. Bull., v. 19, (1922) pp. 361-365.

50. Leon, W. de and Leiva, L. Echinococcus cyst in human lung. Phil. Jour. Sci., v. 27, (1925) pp. 531-369.

51. Lipscomb, F. M. Case of cysticercosis *(Taenia solium)*. Jour. Roy. Army Med. Corps, v. 65, (December, 1935) pp. 397-400.

52. Looss, A. Weiters Beitraege sur kenntniss der Trematoden Fauna Aegypticus. Zool. Zahrb. Jena, Abt. f. Syst., v. 12, (1899) pp. 521-784.

53. Lopez-Neyra, C. R. and Pozo, D. G. Nuevo trematode intestinal humano en Europa. Bol. de la Soc. Esp. de Hist. Nat., v. 32, (1932) pp. 297-304.

54. Luney, F. W. Cysticercus of *Taenia solium* in human brain. Canad. Med. Jour., v. 14, (Feb. 1924) p. 143.

55. MacArthur, W. P. Cysticercosis as seen in the British army with special reference to production of epilepsy. Trans. Roy. Soc. Trop. Med. Hyg., v. 27, (January, 1934) pp. 342-363.

56. Marsh, E. B. Cysticercosis, interesting case. Jour. Roy. Army Med. Corps, v. 62, (April, 1934) pp. 294-296.

57. Martin, R. H. and de Crespigny. Notes on a case of hydatid of the heart. Brit. Med. Jour. Australia, v. 1, (April, 1921) p. 287.

58. McMullen, D. B. The life histories of three trematodes parasitic in birds and mammals, belonging to the genus Plagiorchis. Jour. Parasit., v. 23, No. 3, (1937) p. 235.

59. Mendoza-Guazon, M. P. Schistosomiasis in the Philippine Islands. Phil. Jour. Sci., v. 21, (1922) pp. 523-567.

60. Morquino, L. Primary echinococcosis of myocardium rupturing into left ventricle. Bull. Soc. de Pediat. de Paris, v. 31 (October, 1933) pp. 422-428.

61. Most, H. and Abeles, M. M. Trichiniasis involving the nervous system: A clinical and neuro-pathologic review, with report of two cases. Arch. Neuro. Psych., v. 37, (1937) pp. 589-616.

62. Mueller, J. F. and Van Cleave, H. J. Parasites of Oneida Lake Fishes. Part II. Descriptions of new species and some general taxonomic considerations, especially concerning the trematode family Heterophyidae. Roosevelt Wild Life Animals, v. 3, No. 2, (1932).

63. Mueller, H. R. and Stender, A. Bilharziasis of the spinal cord simulating complete transverse myelitis, a case. Arch. Schiffs u. Tropen-Hyg., v. 34, (1930) pp. 327-538.

64. Musgrave, W. E. Paragonimiasis in the Philippine Islands. Phil. Jour. Sci., v. B-2, (1907) pp. 15-63.

65. Muto, M. The first intermediate host of *Metagonimus yokogawai.* Kyoto Igaku Zasshi. Kyoto Jour. Med. Sci. v. 14, No. 1, (1917) pp. 115-134.

66. Nishigori, M. Two new trematodes of the family Heterophyidae found in Formosa. Jour. Med. Ass'n., Formosa, No. 237, (1924) pp. 569-570.

67. Ochi, S. Experimentalle untersuchungen ueber die Widerstand fahigkiet der encystierten Cercarien von *Heterophyes heterophyes.* Okayama Igakai Zasshi (Zent. d. Okayama Med. Gasellsch) v. 42, No. 3, (1930) pp. 617-626.

68. Onji, Y. and Nishio, K. General observations on new flukes. Igakii Chyn Zasshi (Japanese text) (1915) pp. 875-883.

69. Phalen, J. M. and Nichols, H. J. Notes on the condition of the liver in schistosomiasis. Phil. Jour. Sci., v. III-B, (1908) pp. 223-228.

70. Pico Duni, R. J. Cerebral and cardiac hydatids. Rev. Med. Latino Am., v. 14, (September, 1929) pp. 1493-1499.

71. Ransom, B. H. Synopsis of the trematode family Heterophyidae with descriptions of a new genus and a new species. Proc. U. S. Nat. Mus., v. 57, (1920) pp. 527-573.

72. Ransom, B. H. and Foster, W. D. Recent discoveries concerning the life history of *Ascaris lumbricoides*. Jour. Parasit., v. 5, (1920) pp. 93-99.

73a. Refuerzo, P. G. and Garcia, E. Y. Metazoan intestinal parasites of street dogs in Manila and environs: A preliminary report based on two hundred autopsies. Phil. Jour. Pub. Health, v. 3, Nos. 1 & 2, (March-June, 1936).

b. *Neodiplostomum larai*, a new trematode parasite of the cattle egret *(Bubulcus ibis coromandus,* Boddaert). Phil. Jour. Sci., v. 62, No. 2, (February, 1937.

c. Refuerzo, P. G. and Garcia, E. Y. *Pygidiopsis marivillai*, a new heterophyid trematode from the Philippines. Phil. Jour. Sci., v. 64, (1937) p. 359.

74. Schwartz, B. and Tubangui, M. A. Uncommon intestinal parasites of man in the Philippines. Phil. Jour. Sci., v. 20, (1922) pp. 611-614.

75. Shimamura, S. and Tsunod, T. Pathology of katayama disease; supplementary report on the cause of Jacksonian epilepsy and emboli of cerebral artery. Kyoto Igakai Zasshi (Kyoto Jour. Med. Ass'n.) v. 2, N.o5, (1905).

76. Shuman, J. W. Hydatid brain cyst. Med. Jour. Record, v. 120, (July, 1924) p. 73.

77. Sinitzin, D. Th. Liver fluke *(Fasciola hepatica)* in Moscow District. Rpts. Zemstro, Moscow District, No. 14, (1915) pp. 1-42 (Russian.)

78. Strong, R. P. Medical survey of the town of Taytay. Phil. Jour. Sci., v. IV-B, (1909) pp. 201-210.

79. Stunkard, H. W. and Willey, C. H. The development of Cryptocotyle Heterophyidae) on its final host. Am. Jour. Trop. Med., v. 9. No. 2, (1929) pp. 117-128.

80. Stunkard, H. W. The life history of *Cryptocotyle lingua* (Creplin), with notes on the physiology of the metacercariae. Jour. Morph. and Physiology, v. 50, (1930) pp. 143-191.

81. Supplement to the Report of the Twelfth Annual Meeting of the American Society of Parasitologists. Report of the Committee on Terminology: Infection vs. Infection; Host-parasite Specificity; the Terms Symbiosis, Symbiont and Symbiote. Jour. Parasit. 1937, v. 23, No. 3, (1937) pp. 325-326.

82a. Tubangui, M. A. The molluscan intermediate host in the Philippines of the oriental blood fluke *Schistosoma japonicum* Katsurada. Phil. Jour. Sci., v. 49, (1932) pp. 295-304.

b. Trematode parasites of Philippine Vertebrates VI. Descriptions of new species and classification. Phil. Jour. Sci., v. 52, (1933) pp. 169-197.

83. Tubangui, M. A. and Africa, C. M. The systematic position of some trematodes reported from the Philippines. Phil. Jour. Sci., v. 67, No. 2, (Oct. 1938).

84. Turner, M. and Leiper, R. T. On the occurrence of *Coenurus glomeratus* in man in West Africa. Trans. Roy. Soc. Trop. Med. & Hyg. v. 13, (1919) pp. 23-24.

85a. Vasquez-Colet, A. and Africa, C. M. Determination of piscine intermediate hosts of Philippine heterophyid trematodes by feeding experiments. Phil. Jour. Sci., v. 65, No. 4, (April, 1938).

b. Determination of piscine intermediate hosts of Philippine heterophyid trematodes by feeding experiments. Progress report. Phil. Jour. Sci., v. 70, No. 2 (October, 1939).

86. Van Cott, J. M. and Lintz, W. Trichinosis. Jour. Am. Med. Ass'n., v. 62, (February, 1914) p. 680.
87. Vosgien, Y. "Le cysticercus cellulosae chez l'homme at chez les animaux" These de Paris, (1911).
88. Wharton, L. D. *Opistorchis wardi*, a new species of liver fluke from cat in the Philippines. Phil. Jour. Sci., v. 19, (1921) pp. 243-144.
89. Willets, D. C. Intestinal helminthiasis in the Philippine Islands as indicated in examinations of prisoners upon admission to Bilibid Prison, Manila, P. I. Phil. Jour. Sci., v. IX-B, (1914) pp. 233-240.
90a. Witenberg, G. Studies on the trematode family Heterophyidae. Ann. Trop. Med. & Parasit., v. 23, (1929) pp. 131-230.
b. Correction to my paper, Studies on the trematode family Heterophyidae. Ann. Mag. Nat. History. Series, v. 10, No. 5, (1930) pp. 412-414.
c. Fish as a source of worm diseases in man. Harefuah, Jerusalem, v. 6, No. 3, (1932) pp. 127-139. (English summary).
91. Woolley, P. I. The occurrence of *Schistosoma japonicum vel cattoi* in the Philippine Islands. Phil. Jour. Sci., v. I-B, (1906) pp. 83-90.
92. Yamaguti, Satyu. Studies on the helminth fauna of Japan. Part 25. Trematodes of birds, IV. Japanese Journal of Zoology, v. 8, No. 2, (March, 1939).
93a. Yokogawa, S. Ueber einen neuen Parasiten *Metagonimus yokogawai*, der die Forellenart Plectoglossus altivelis (Temminick) zum Zwischenwirt hat. Bildung einer neuen Gattung. Centr. Bakt, u. Parasit., Abt, Originale 82, (1913) pp. 158-179.
b. Yokogawa, S. Life history of lung fluke. Taiwan Igakai Zasshi Jour. Med. Ass'n. Formosa, Nos. 201-202 (1919) pp. 731-733 & 827-875.
94. Yokogawa, S. and Suyemori, S. An experimental study of intracranial parasitism of human lung fluke, *Paragonimus westermanni*. Am. Jour. Hyg., v. 1, No. 7, (1921) p. 63.
95. Young, R. T. The Biological Bulletin, v. 74, No. 2 (April, 1938).

ILLUSTRATIONS

PLATE 1

FIG. 1. *Stictodora manilensis* Africa and Garcia, 1935.
FIG. 2. *Heterophyopsis expectans* (Africa and Garcia, 1935) Tubangui and Africa, 1938.
FIG. 3. *Haplorchis pumilio* (Looss, 1899).
FIG. 4. *Stictodora guerreroi* Garcia and Refuerzo, 1936.
FIG. 5. *Pygidiopsis marivillai* Refuerzo and Garcia, 1937.

PLATE 2.

FIG. 1. *Haplorchis yokogawai* (Katsuta, 1932) Chen, 1936.
FIG. 2. *Haplorchis taichui* (Nishigori, 1924) Chen, 1936.
FIG. 3. *Haplorchis calderoni* (Africa and Garcia, 1935) Africa, 1938.
FIG. 4. *Haplorchis vanissima* Africa, 1938.
FIG. 5. *Stellantchasmus falcatus* Onji and Nishio, 1924.
FIG. 6. *Spelotrema brevicaeca* (Africa and Garcia, 1935) Tubangui and Africa, 1938.

PLATE 3

FIG. 1. Egg of *Haplorchis yokogawai.*
FIG. 2. Eggs of *Haplorchis taichui.*
FIG. 3. Egg of *Spelotrema brevicaeca.*
FIG. 4. Metacercaria of *Haplorchis yokogawai.*
FIG. 5, 6, 7 and 8. Different types of *H. yokogawai* egg.

PLATE 4

FIG. 1. Eggs blocking a capillary vessel in the myocardium (Case No. 1).
FIG. 2. Eggs in a space where a blood vessel has ruptured and the musculature disintegrated with red cell debris around the ova and evidence of much congestion and edema (Case No. 6).

PLATE 5

FIG. 1. Another capillary hemorrhage in the myocardium, evidently due to an egg-embolus, showing intense hyperinjection of the capillaries between individual muscle fibers (Case No. 1).
FIG. 2. A large number of eggs intermixed with red cell debris in an interstitial space between distinctly edematous muscle fasciculi. Note again the hyperinjected capillaries that stand out in bold relief between individual muscle fibers like cords (Case No. 1).

PLATE 6

FIG. 1. A mass of fibrin clot and conglutinated red cells in an empty space, between muscle fasciculi in which many eggs are enmeshed (Case No. 7).
FIG. 2. A thrombus with an egg (indicated by arrow) in an interstitial space which is greatly infiltrated with fluid. A serial study of this block disclosed the presence of many more eggs as well as the relation between this thrombotic formation and a blood vessel (Case No. 6).

PLATE 7

FIG. 1. A segment of a longitudinally cut mass of young reticuloendothelial cells in a young fibrous tissue groundwork apparently plugging what was once the lumen of a blood vessel between muscle bundles. Eggs (indicated by arrow) are found here and there all along this deeply staining mass of reactive tissue (Case No. 4).

FIG. 2. A large sheet of very compact and dense proliferated reticuloendothelial cells in the subepicardial space, with eggs (scarcely visible under the low power) interspersed irregularly among them. The center of the mass has become frankly fibrotic. (Case H-5-1).

PLATE 8

FIG. 1. Another mass of highly tinctorial reactive tissue consisting of young endotheliocytes and histiocytes in a young fibrous tissue groundwork evidently occupying what was once the site of extravasated blood. Note that it communicates with another mass of the same cellular composition in a neighboring inter-fascicular space. The eggs are scarcely visible (Case No. 4).

FIG. 2. Circumscribed masses of proliferated reactive cells that have thrown the myocardium into shreds. Appearing like abscesses under the low power, their nature becomes more apparent as the usual characteristic cellular elements with eggs or bits of them scattered around come to view under higher magnification (Case No. 7).

PLATE 9

FIG. 1. Streaks of the same typical reactive tissue following the course of the inter-fascicular spaces in the myocardium. Note points that have become definitely fibrotic. Eggs are often seen snugly enclosed in the fibrotic areas such as the one indicated by arrows but are hardly visible in the photomicrograph (Case No. 6).

FIG. 2. The same characteristic lesion as the one above but more extensive in distribution (Case No. 10).

PLATE 10

FIG. 1. A typical chronic specific lesion. Clumps of eggs (indicated by arrows) are discernable even under the low power (Case H-5-$_1$).

FIG. 2. Chronic specific lesions dissecting muscle bundles. These sheets of endotheliocytes and histocytes if followed throughout their full length will lead to points where the reactive cells are still intermixed with red blood cells. The leucocytes, specially the polymorphonuclears, are amazingly rare, and foreign-body giant-cells absent as they are from all the rest of histological sections examined (Case No. 9).

FIG. 3. Microdrawing under the oil immersion of an area indicated in fig. 2, (this plate) showing the types of reactive cells, (a) histocytes, (b) endotheliocytes, (c) lymphocytes, (d) fibroblasts, common to all chronic specific lesions described in this work.

PLATE 11

FIG. 1. Chronic specific lesions in the myocardium which while still retaining distinctive cellular features, have become definitely fibrotic in certain points (Case No. 5).

FIG. 2. A section of the segment shown in fig. 1 (this plate) under the high power showing an egg (indicated by arrow).

FIG. 3. Showing the specific reactive cells being replaced by scar formation. (Note an egg indicated by arrow). After the complete disappearance of the characteristic reactive cells, such scars would just appear like any healed lesions due to other causes (Case No. 4).

PLATE 12

FIG. 1. Histological section of leaflet of the mitral valve showing eggs (indicated by arrows) still clinging to strands of sclerotic tissue apparently in the path of an advancing hyalinization. At the periphery of the microscopic field on one side may be seen the same deeply-stained reactive cells found in the myocardium (Case No. 4).

FIG. 2. Typical eggs fossilized in a mass of calcified material in the interior of a sclerosed leaflet of the mitral valve (Case H-5-$_1$).

PLATE 13

FIG. 1. Sclerotic interior of a leaflet of mitral valve showing fragments of broken eggs. Note presence of blood vessels around (Case No. 4).

FIG. 2. Portion of a calcified interior of mitral valve showing eggs fossilized in the calcified matter indicated by arrows (Case No. 4).

PLATE 14

FIG. 1. Chronic specific lesion identical with those found in the myocardium in a section prepared from the wall of a fatal hemorrhagic clot in the right basal ganglion. Note an empty egg at the edge of the lesion near the normal brain tissue (Case No. 3).

FIG. 2. Another section from the same neighborhood as the above, showing an intact egg in the interior of the reactive cellular elements.

PLATE 15

FIG. 1. Another well circumscribed mass of proliferated deeply staining endotheliocytes and histiocytes in a fibrous tissue groundwork, marking the site of what appears to be an old perivascular hemorrhage. An empty egg is discernible at the edge of the lesion (Case No. 3).

FIG. 2. Chronic specific lesion in the liver, showing the same character of reactive cells found in lesions of the heart of the same case (Case No. 10). An egg is indicated by arrow.

PLATE 16

FIG. 1. Water color microdrawing (under the low power) of the same section represented in the photomicrograph (fig. 1, plate 10).

FIG. 2. Water color microdrawing (high power) of the same section represented in the photomicrograph (fig. 1, plate 7).

PLATE 17

FIG. 1. Water color microdrawing under the high power of a section of the myocardium showing a chronic specific lesion which has become more frankly fibrotic. The eggs are indicated by arrows (Case No. 6).

FIG. 2. Water color microdrawing (high power) of a section of the brain showing a chronic specific lesion in which fibrotic changes are already evident in certain points. An egg is indicated by arrow (Case No. 321).

PLATE 18

FIG. 1. Water color microdrawing (low power) of a section of the brain showing the lesion in marked contrast with the normal brain tissue. An egg is indicated by arrow (Case No. 3).

FIG. 2. Water color microdrawing (high power) of a section of the spinal cord, showing the same characteristic lesions found in the heart and brain. An egg is indicated by arrow (Case No. 11).

PLATE 19

Photomicrographs of Histological Sections of Pancreas and Liver of Birds Showing Heterophyid Adults and Eggs.

FIG. 1. A large collection of eggs of Stictodora in the pancreas of a sea gull *(Larus ridibundus Linn.)*

FIG. 2. Edge of the egg collection showing the nature of cellular reaction.

FIG. 3. Portal area of the liver of a cattle egret *(Bubulcus ibis coromandus)* showing sections of adult Haplorchis in the bile ducts.

FIG. 4. Eggs of Haplorchis in a bile duct of cattle egret showing the character of the reactive tissue.

PLATE 20

FIG. 1. Water color microdrawing of a huge collection of eggs of Stictodora in the pancreas of a sea gull.

FIG. 2. Water color microdrawing of a section of the liver of a cattle egret showing section of Haplorchis in the bile duct.

PLATE 21

Photomicrographs of Histological Sections of the Small Intestine of Dogs Experimentally Infected with Haplorchis yokogawai.

FIG. 1. A fully developed adult fluke in the space between the villi.

FIG. 2. An adult fluke causing pressure necrosis at the base of two adjoining villi.

FIG. 3. An intestinal villus showing a section of a fluke inside. Note the absence of tissue reaction around the parasite.

FIG. 4. A section of an adult fluke in the substance of the tunica propria very near the muscularis. Note again the absence of reactive tissue around the parasite.

PLATE 22

FIG. 1. *Clarias batrachus* Linnaeus ("hito")

FIG. 2. *Arius manillensis* Cuvier & Valenciennes ("kanduli")

FIG. 3. *Ophicephalus striatus* Bloch ("dalag")

FIG. 4. *Mugil dussumieri* Cuvier & Valenciennes ("talilong")

FIG. 5. *Gerris filamentosus* Cuvier & Valenciennes ("malakapas")

PLATE 23

FIG. 1. Laguna de Bay, Laguna Province, Philippines.

FIG. 2. Drying fish on the shore of Laguna de Bay, Biñan, Laguna Province, Philippines.

PLATE 1.

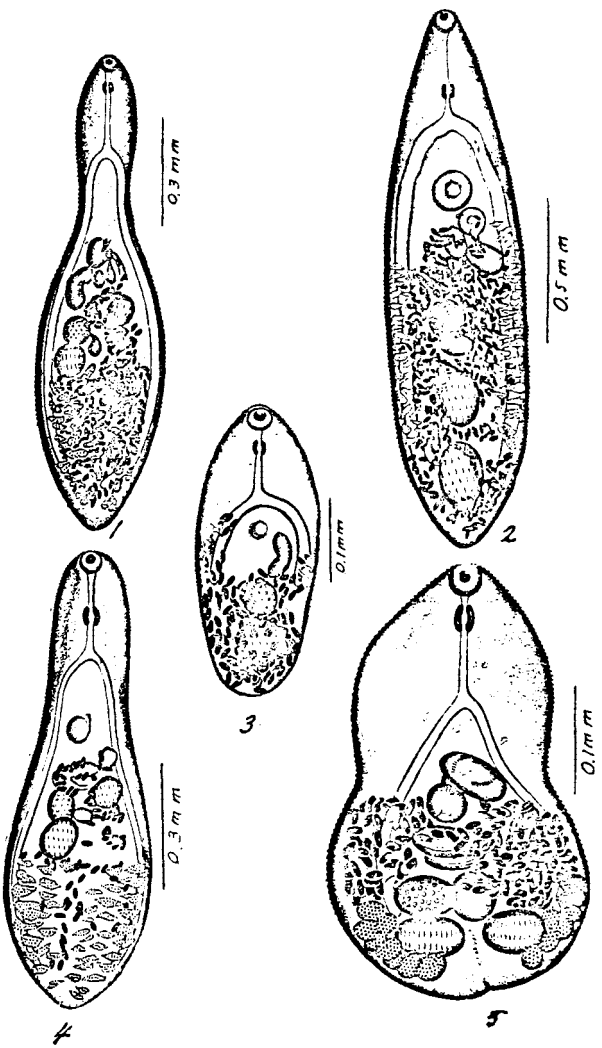

PLATE 2.

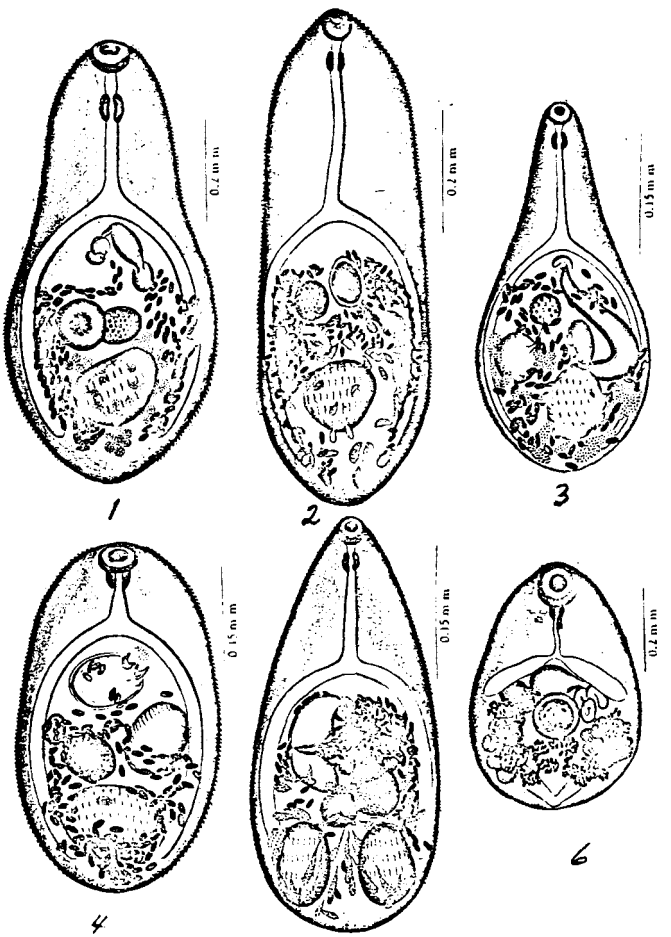

PLATE 3.

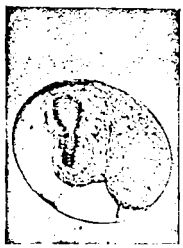

FIG. 4

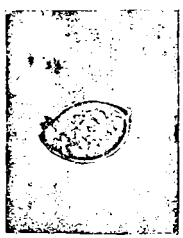

FIG. 3

FIG. 2

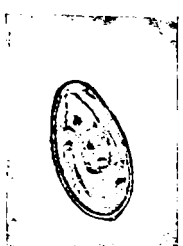

FIG. 1

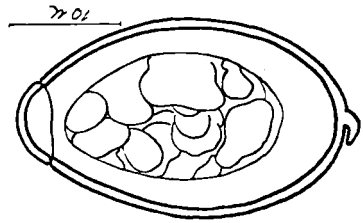

FIG. 8

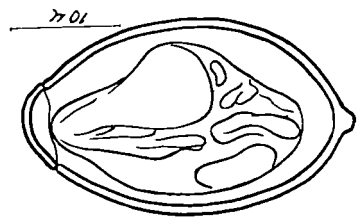

FIG. 7

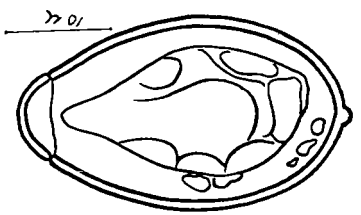

FIG. 6

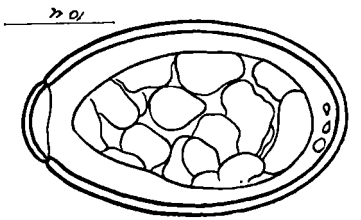

FIG. 5

PLATE 4.

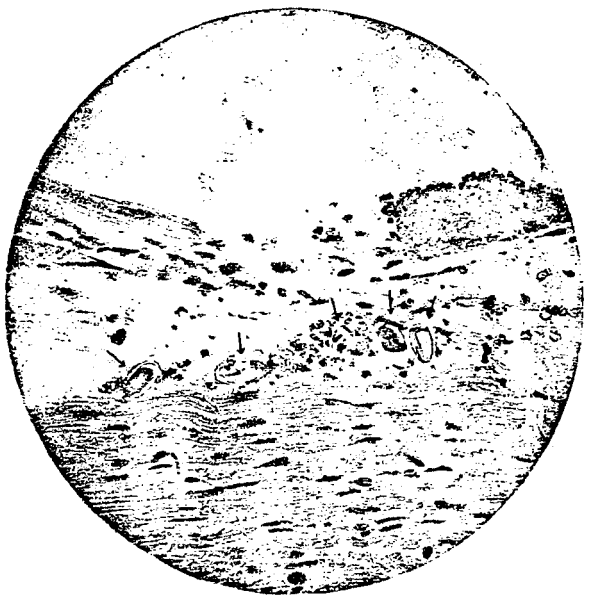

FIG. 1

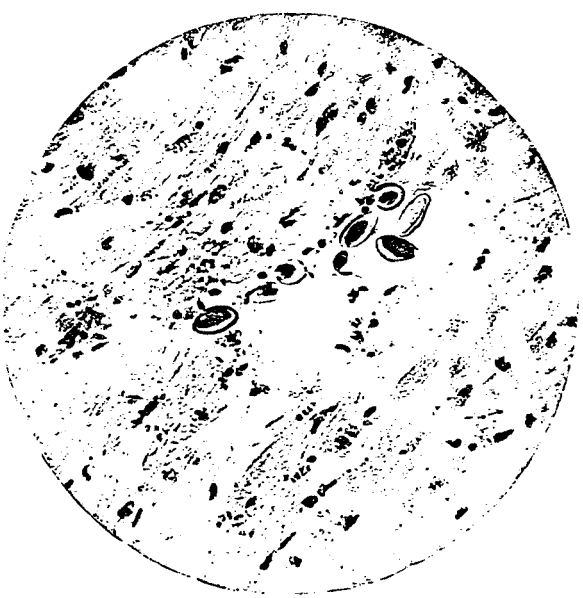

FIG. 2

PLATE 5.

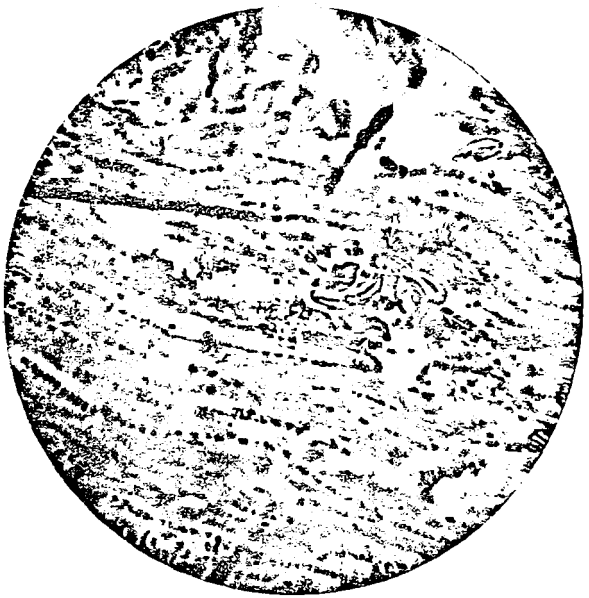

FIG. 1

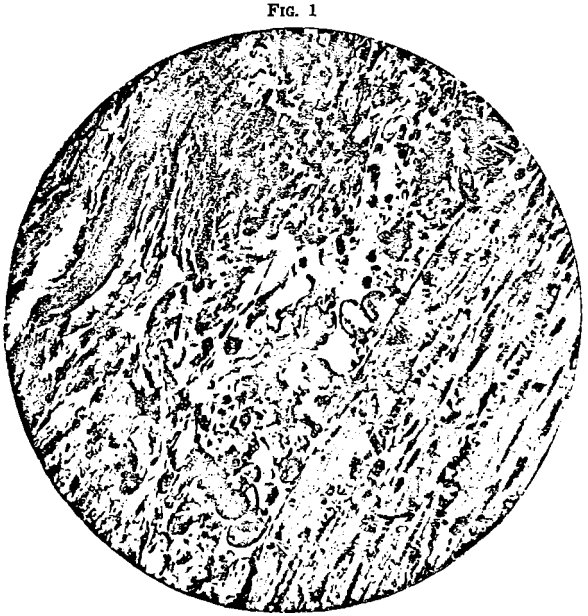

FIG. 2

PLATE 6.

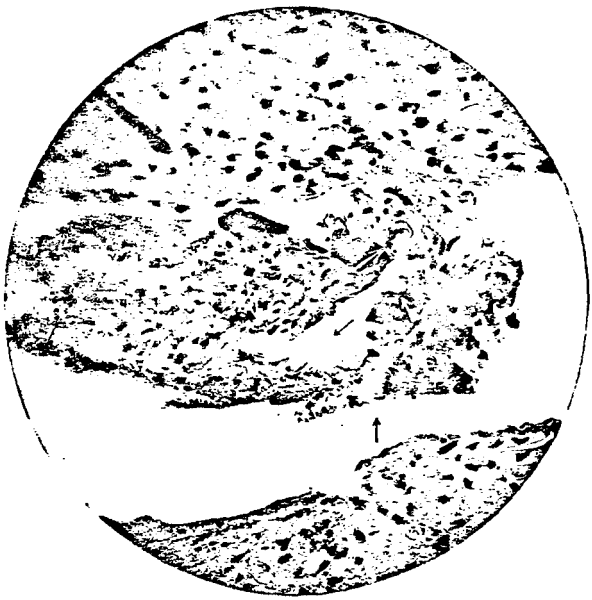

FIG. 1

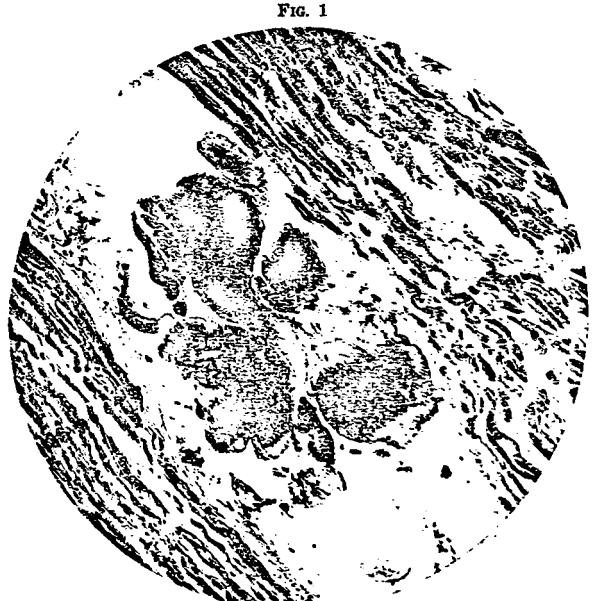

FIG. 2

PLATE 7.

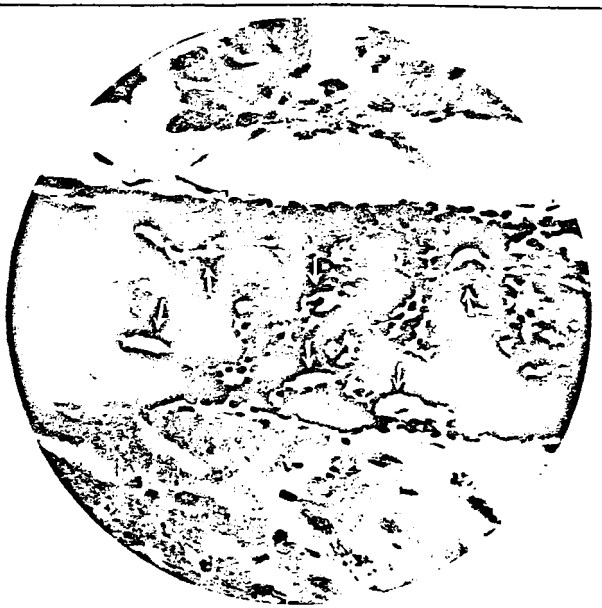

FIG. 1

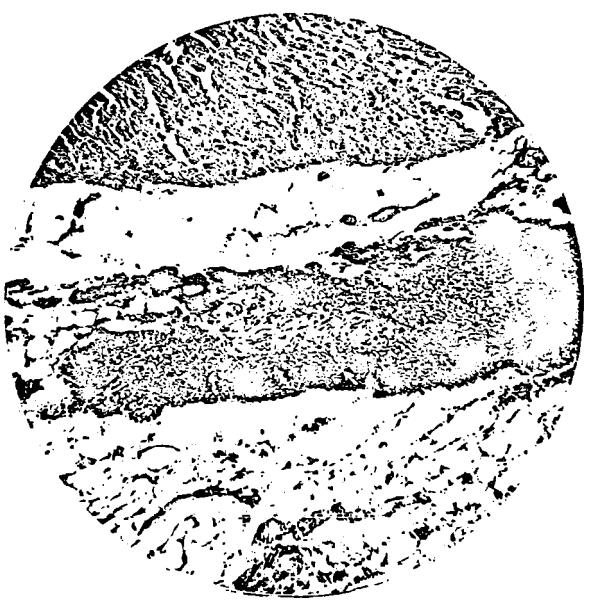

PLATE 8.

FIG. 1

FIG. 2

PLATE 9.

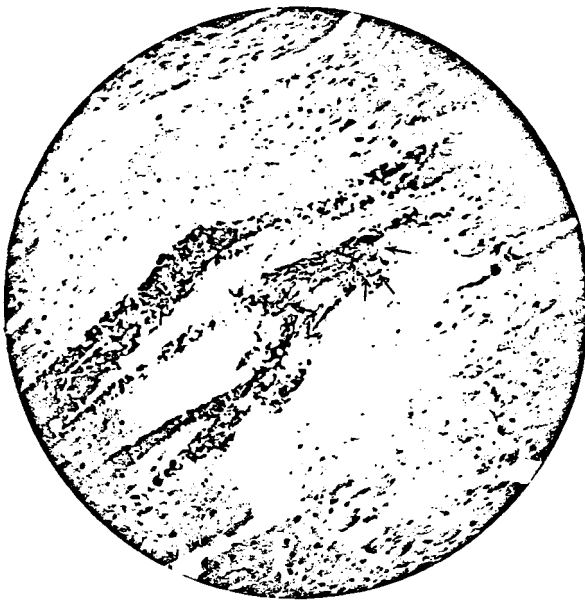

FIG. 1

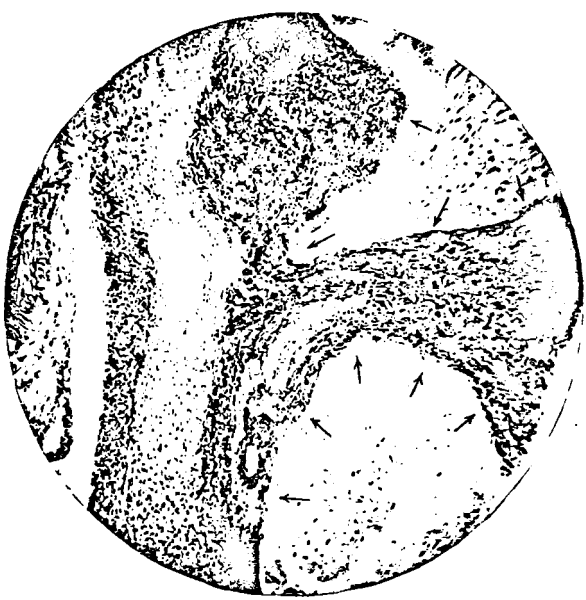

FIG. 2

PLATE 10.

FIG. 1

FIG. 2

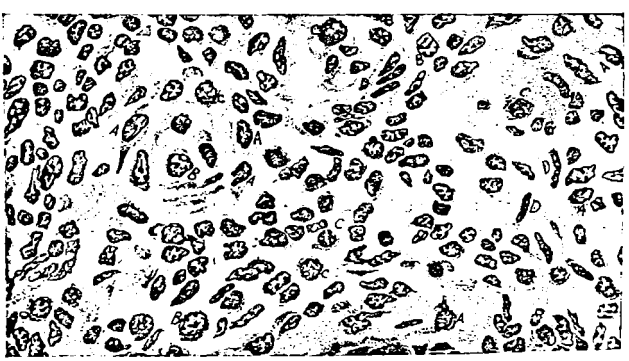

FIG. 3

PLATE 11.

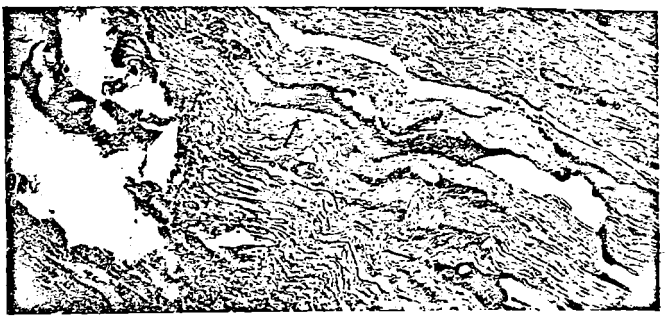

FIG. 1

FIG. 2

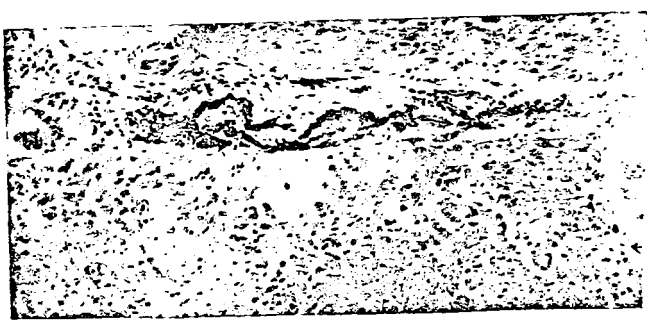

FIG. 3

PLATE 12.

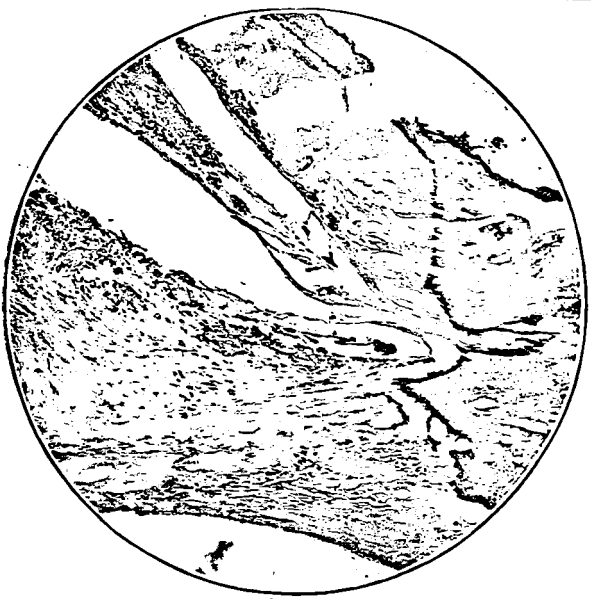

FIG. 1

FIG. 2

PLATE 13.

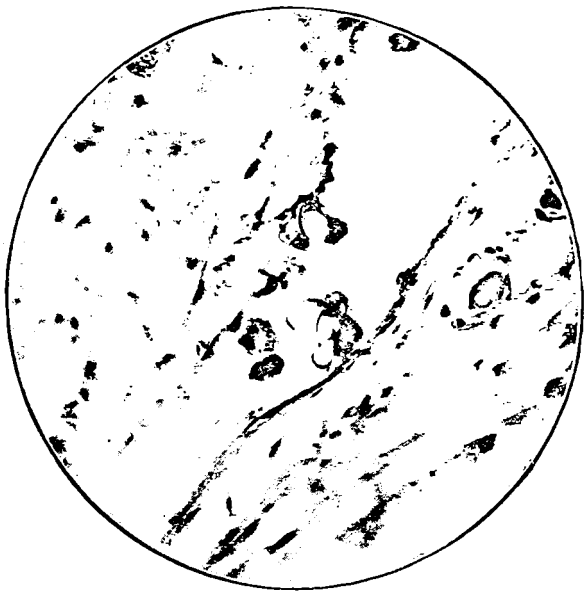

FIG. 1

FIG. 2

PLATE 14.

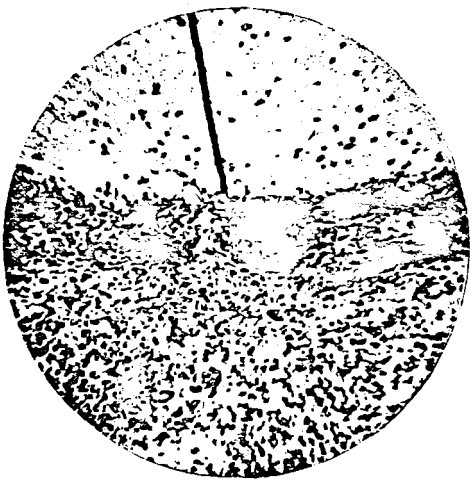

FIG. 1

FIG. 2

PLATE 15.

FIG. 1

FIG. 2

PLATE 16.

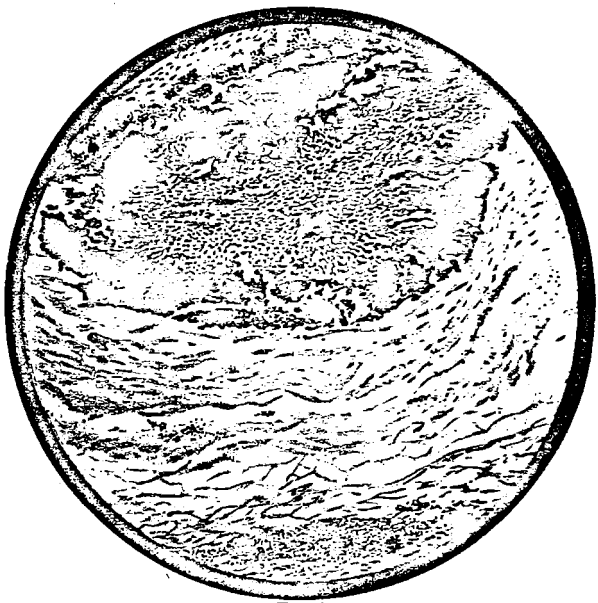

FIG. 1

FIG. 2

PLATE 17.

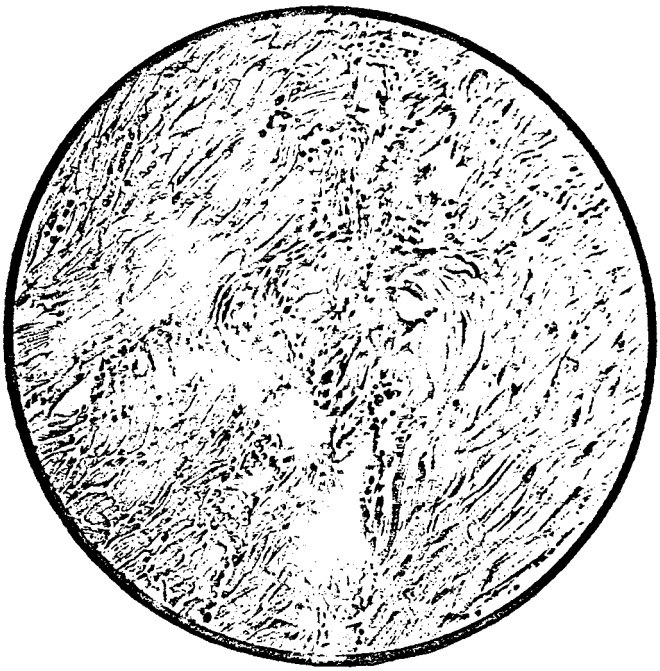

FIG. 1

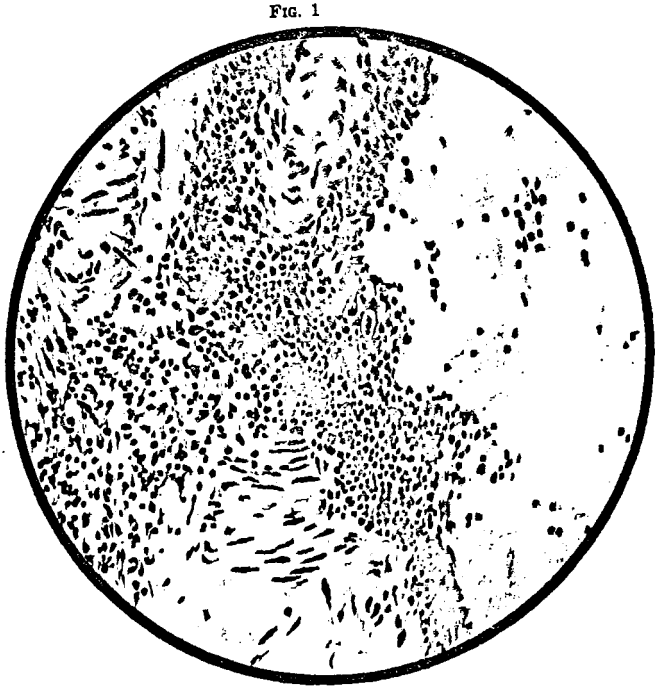

FIG. 1

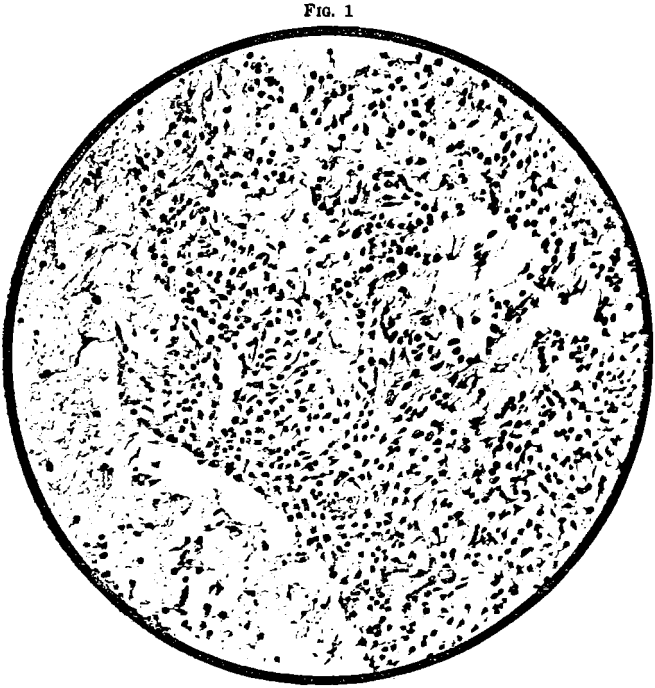

FIG. 2

PLATE 19.

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1

FIG. 2

FIG. 1

FIG. 2

FIG. 3

FIG. 4

PLATE 22.

FIG. 1

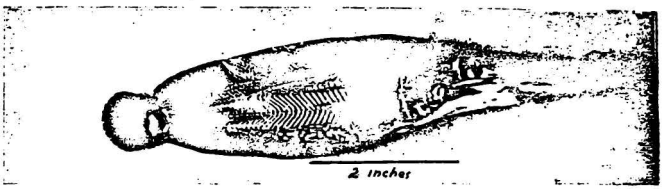

FIG. 2

FIG. 3

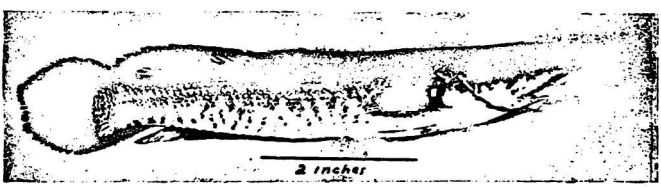

FIG. 4

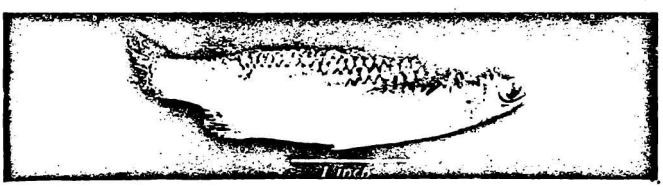

FIG. 5

PLATE 23.

FIG. 1

FIG. 2

The price of this monograph per copy is ₱2.50 Philippine Currency ($1.25 U. S. Currency) plus the regular postage charges for orders from foreign countries. Remittances should be made payable to the University of the Philippines and sent to the Business Manager, ACTA MEDICA PHILIPPINA, P. O. Box 126, Manila, Philippines.