

On the importance of the hyphomycetes in the causation of disease / Otto Lowe.

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ON THE IMPORTANCE OF
THE HYPHOMYCETES IN THE
CAUSATION OF DISEASE.



OTTO LOWE.



1912.

LIVERPOOL.

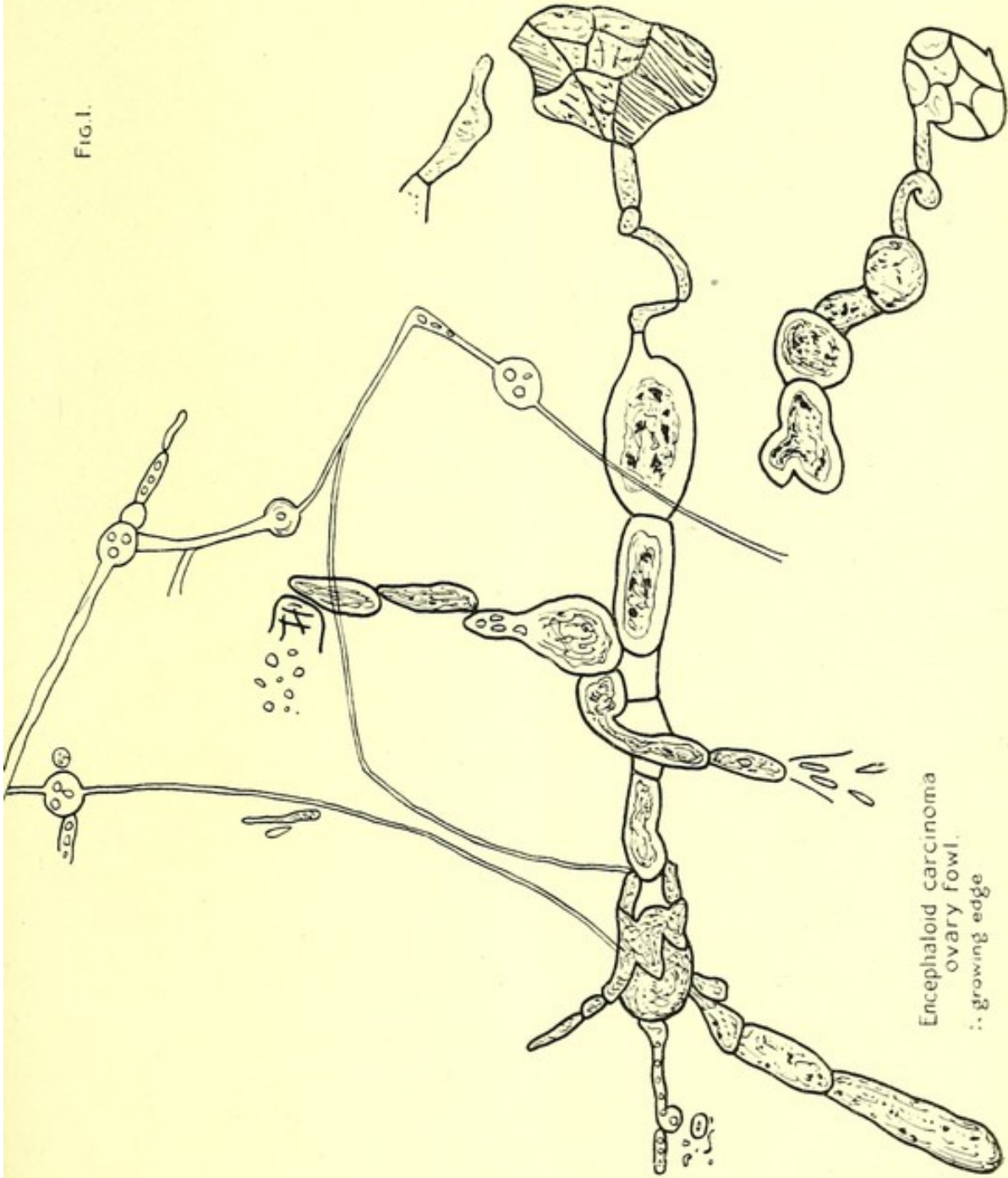
LITTLEBURY BROS., 3 CROSSHALL STREET.

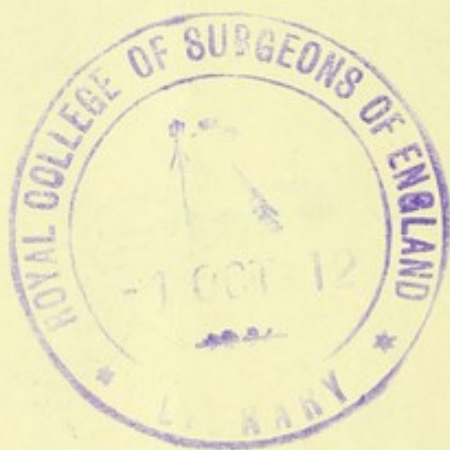


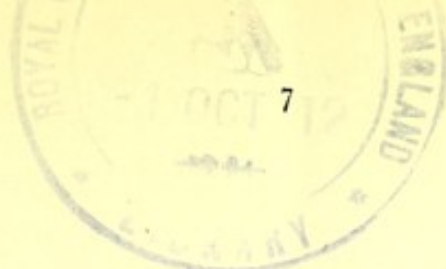
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FIG. 1.







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ON THE IMPORTANCE

OF THE HYPHOMYCETES IN THE CAUSATION OF DISEASE.

This paper is based on a case of Encephaloid Carcinoma of the ovary occurring in a fowl. While engaged upon this I happened to examine a hyphomycete occurring on an Apricot tree. This enabled me to identify the cancer bodies with the hyphal bodies of these fungi. These bodies stain blue with Iodine in certain stages of their development and are probably identical with the Corpora Amylacea of human pathology. About six weeks after the Postmortem Examination of the fowl, I noticed that a slide on which was stretched a piece of the mesentery obtained from this case and kept moistened with glycerine, was developing a crop of moulds. A culture taken from a small tumour of the mesentery at the time of the Postmortem also developed a growth of mould. This culture had been kept at the ordinary temperature of the room. Finally moulds developed on the surface of a solution of Zinc Chloride in which some of the organs from this case of Encephaloid carcinoma of the ovary had been preserved. In this instance a very foul smell of Butyric Acid was present.

All these moulds were very similar in appearance.

While this was in progress I was subject to a slight attack of Arthritis in the left ankle joint.

On examining a film of my blood I found the appearances figured which are obviously characteristic of the development of a hyphomycete and also a triradiate body resembling the feathery form of triple phosphate. These moulds were present in the nasopharyngeal mucus and in the urine which developed a mycelium bearing conidia on standing.

Ever since I can remember I have been subject to symptoms of Irregular Gout which may be grouped as follows—

It is necessary to state that I have never been in the tropics.

History of acute affection of throat a few days after birth, called quinsy which burst and relieved the symptoms.

There is a state of Chronic nasopharyngitis with injection of fauces and back of pharynx with recurring attacks of hypersensitiveness of the mucosa resembling hay fever. Tonsils not enlarged.

The mucosa is covered with a dense hyaline viscid mucus without any trace of purulence. There are recurring attacks of uvulitis in which the uvula enlarges sideways and may vesiculate but never proceeds to suppuration. These attacks may be accompanied by severe vomiting and purging.

TEETH.

Two large central Upper Incisors, four smaller lower. Enamel wanting towards the free edge, dentine stained yellow. The dentine has slowly worn away at the edges and the enamel grown downwards *pari passu*. White dental caries present.

The submaxillary glands were subject to subacute painless enlargement in childhood on catching cold, the symptoms subsided quickly without giving trouble. Thyroid gland palpable.

ALIMENTARY CANAL.

Attacks of acute catarrhal gastritis, acute catarrhal jaundice and intestinal colic are frequent.

AIR PASSAGES.

During childhood attacks of morning hoarseness were observed. These came on suddenly and sometimes proceeded to actual loss of voice. They disappeared as suddenly after a short interval. They were never observed after mid-day. They were evidently analogous to an asthma of the vocal cords. During this period small oval bodies of a whitey brown colour were found in the mouth, after being apparently expelled from the lungs.

During sleep there is a tendency for the nasal passages to become choked towards early morning, resulting in mouth breath-

ing and the formation of a scum on the lips and tongue. This scum contains squamous cells, mould spores, and crystals.

CIRCULATORY SYSTEM.

Slight anaemia pulse slow—58—tendency to subnormal temperatures. Resistance to septic infection very high.

JOINTS.

The jaws, carpus, thumbs, knees, ankles, metatarsi, and great toes are subject to sudden attacks of arthritis. The neighbouring tendons may be affected. The symptoms are usually slight and consist of a feeling of weakness, resembling a subluxation or a slight stiffness. Sometimes they may swell slightly. These attacks are accompanied by obstinate constipation and subside when a free action of the bowels is obtained. Grating obtained in both shoulder joints.

NERVOUS SYSTEM.

Neuritis of ulnar at elbow joint, threatenings of sciatica and calcaneodynia, Metatarsalgia have been observed at different times.

SKIN.

Urticaria affecting the neck, back of hands and legs above ankles.

Herpes zoster of lower intercostals on one occasion.

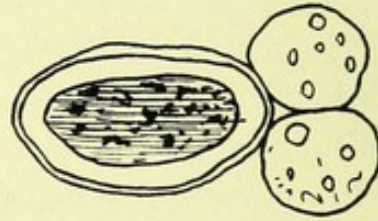
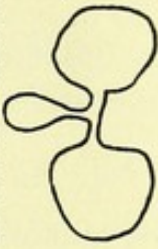
KIDNEYS AND URINE.

Enuresis as a child, bladder irritable. No pus, blood sugar or albumen ever observed. During arthritis it deposits a somewhat thick mucus cloud and pink urates. At this period the urine is scanty, highly coloured, and keeps a long time without putrefying. It also develops a growth of mould which commences as a hyaline ring round the junction of vessel and urine followed by an eruption of scattered islets over the surface which finally become confluent, forming a pellicle. Attacks resembling renal colic have been observed. These start as a colicky pain in the loin followed by contraction of the dartos drawing the scrotum up into the groin and passage of a large quantity of clear pale urine when the symptoms subside ; no stone or gravel has been ever passed.

FIG. 2.

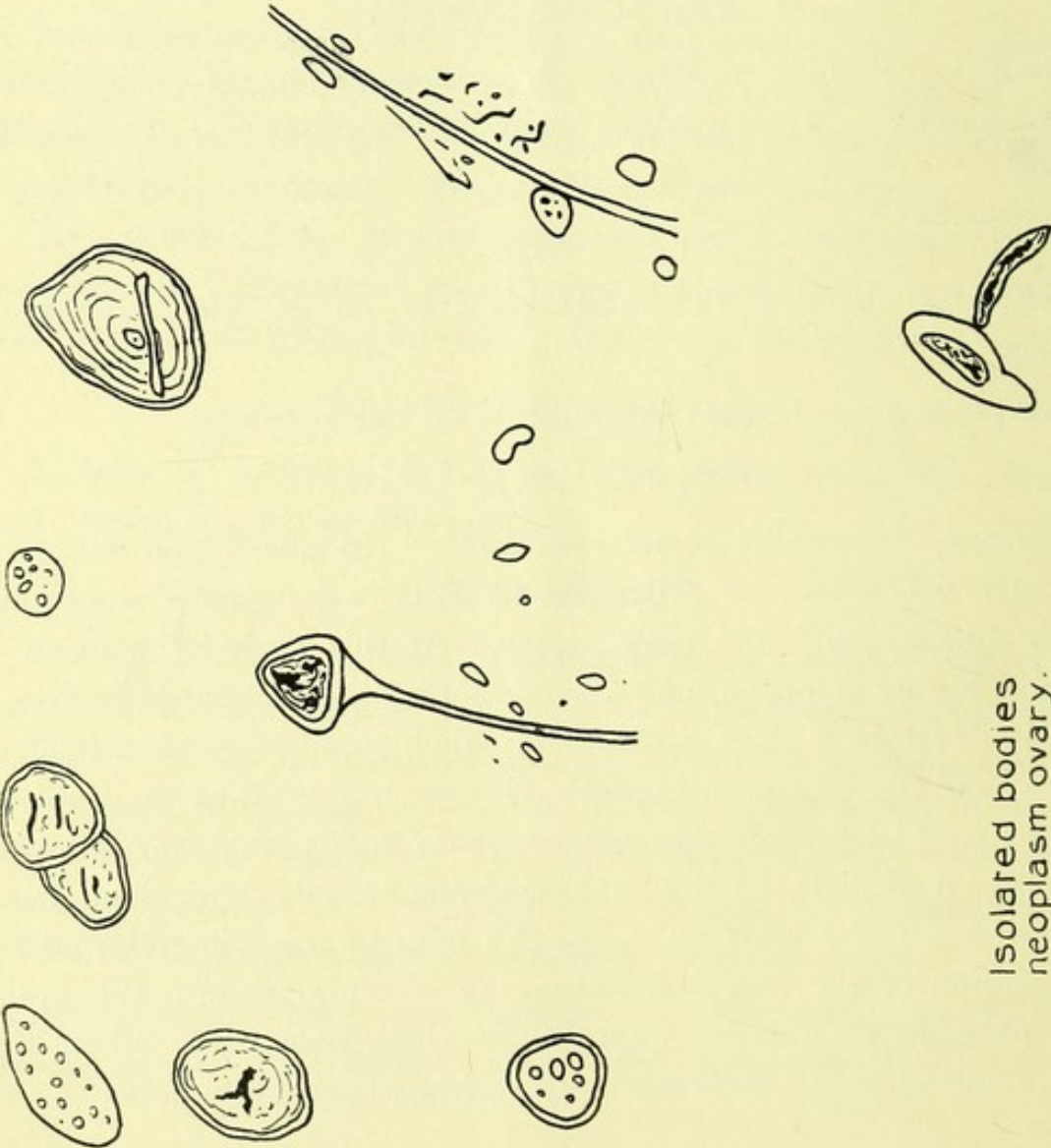


Development Crescent body
after Manson



Conjugating hyphal bodies of
Entomophthorae

Thaxter - from Cooke Introduction to
Study of Fungi



Isolated bodies
neoplasm ovary.

I have observed a somewhat similar organism in fowls in association with asthmatic symptoms and loss of voice and the occurrence of tumours in the mesentery. The organism was found in the blood, kidneys and lungs, the blood developing a growth of mould on drying.

In asthma the occurrence of this characteristic viscid sputum has long been recognised. It is this secretion that produces the symptoms of the attack which is in fact gout of the lungs. Its association with hay fever gives the clue to the path of infection.

There is another condition connected with gout which remains to be considered, this is glycosuria which seems to form a connecting link with Diabetes and also with Grave's disease in which glycosuria may also occur and in which gastro-intestinal disturbance is almost always present. Uric acid is not responsible for the symptoms of Gout except in so far as it acts as a foreign body. It is the accumulation of this acid and possibly other products of katabolism of the infective agent that brings the attack to an end and the excretion of these products by the host prepares the way for a fresh attack.

When the excretion proceeds *pari passu* with the production we get the chronic manifestations.

The organism in the blood somewhat resembles a giant yeast cell. It is characterised by the peculiar distinctness of its markings. The hyphal bodies appear to split and segment and the contents arrange themselves into a looped or twisted skein very much as in the figures of mitosis. In fact, many of the appearances figured as mitosis are due to the invasion of cells by hyphomycetes. These pseudo-mitotic figures break up into irregular fragments which seem able to start an independent existence.

Some of the phases of development are remarkably similar to those of the malarial parasite. It is my opinion that Malaria and possibly even trypanosomiasis are allied organisms and should be included in the Vegetable kingdom. It would be interesting to enquire if fowls take any part in the dissemination of tropical diseases.

Similar spores and mitotic figures are present in glycerinated calf lymph. In connection with the theory of immunity it is

important to remember the centrifugal concentric habit of growth which is so marked in the fungi and is well seen in the formation of fairy rings. This would seem to indicate the accumulation of the products of Katabolism which renders the central area unsuitable to the growth of the fungi. It is worthy of remark that the age incidence of Carcinoma commences as that of Ringworm and the acute specific fevers ceases.

These Hyphomycetes are rife in the vegetable kingdom. Of the uredineæ there are upwards of 1,200 species known which attack various plants and some unfortunate hosts are the victims of two or three distinct species all of which defy the ingenuity of man to eradicate them.

Equally disastrous in their effects and persistent in their attacks are the rotting moulds or Peronosporaceæ of which the potato disease is a form. (Cooke, introduction to the study of Fungi).

They also seem to be the cause of the damping off of seedlings and cuttings.

In the animal world they are responsible for the silkworm disease, for the salmon disease and for the fly rot, and parasitic mange.

In man they are the cause of Madura foot and many skin diseases of the ringworm type.

Aspergillus has been found in the external auditory meatus and in the lungs especially in diabetics. Zenker described multiple abscesses of the brain in a child affected with thrush in which he demonstrated germinating spores of *oidium albicans*. Gröhe was led by these observations to investigate the subject. Experimentally he introduced the spores of the mould fungi into the blood vessels of rabbits and found that a fatal disease then attacked the animals. Further enquiry by Grawitz, Gaffky and Koch, Lichtheim and Leber led to the discovery of some varieties of mould fungi which thrive at the body temperature and are capable of further growth in warm blooded animals and therefore possess pathogenic properties. These are :—

Aspergillus fumigatus.

„ *flavescens*.

Mucor Rhizopodiformis.

„ *corymbifer*. (Thoma. Text book of Pathology.)

Thoma observed small rounded bodies resembling spores in human carcinoma and in chronic catarrhs of the uterine mucous membrane.

Ruffer pointed out the resemblance of cancer bodies to the rosette stage in the malarial parasite. Recent observers (Roncali, Plimmer) have identified the cancer bodies with parasitic fungi. Plimmer has indeed succeeded in isolating certain fungi from cancers which cause death when inoculated intraperitoneally with the production of endothelial tumours and that cultures from these growths produce similar results. (Green's Pathology-ed Montague Murray).

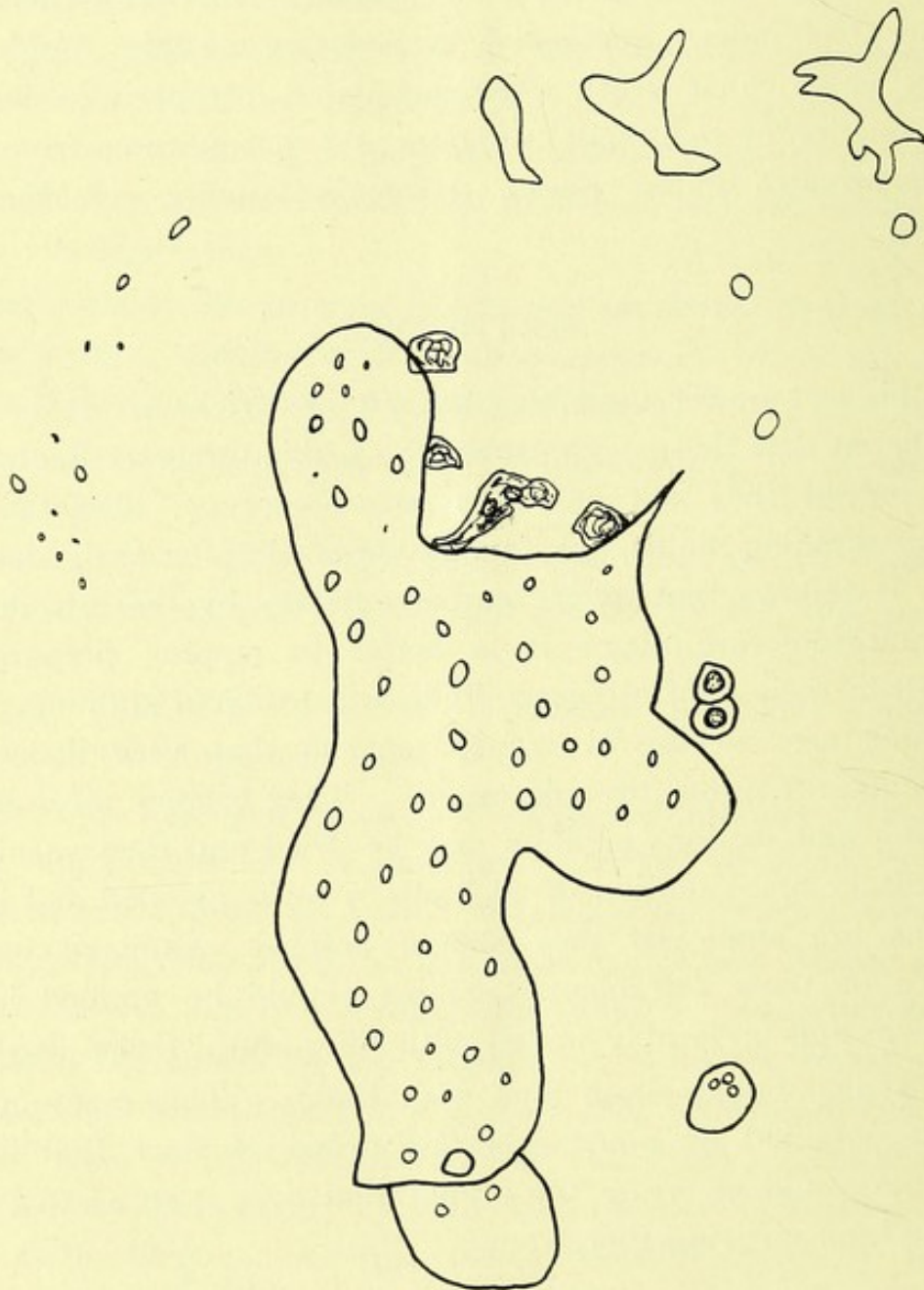
METHODS.

The highest power used was the 7A of Reichert. It is to be remembered that these organisms are as ubiquitous as Bacteria of which indeed they appear to be the prototype, also that the ordinary staining fluids are favourable media for their development. It follows that to prevent any fallacy by the introduction of adventitious organisms it is better to employ preparations mounted in their natural tissue fluids and to avoid staining. The organisms are excessively transparent so that very little light must be admitted into the microscope. They become more visible by drying and sections or films may be dried and then varnished. Unnecessary manipulation of all kinds is to be avoided and if any solutions are employed they should first be examined for the presence of these organisms. Stains should be applied in the solid form and preferably mixed with the natural tissue fluids.

The hyphal bodies stain blue with Iodine. This reaction may be best obtained by pouring a few drops of tinct Iodi into a watch glass and inverting the preparation over it so as to expose it to the fumes arising therefrom.

Soft tissues may be crushed or rubbed into a film. Firmer tissues may be teased or a washing made by raising or lowering the cover glass several times. The films are allowed to evaporate spontaneously and are not to be heated. They may be examined in the dry state and without the appliance of any mounting medium.

FIG 3



from ovary.

ENCEPHALOID CARCINOMA IN A DOMESTIC FOWL.

Towards the latter end of February one of my fowls was observed to be losing condition. Up to that time she appeared to be in good health though she was not laying, but as she was an old bird no importance was attached to that.

She rapidly became weaker, the comb turned yellow, and she was killed. Compared with the gravity of the condition revealed postmortem the dispersity of the symptoms was very striking. She was very thickly feathered and was infested with Lice. On opening the Abdomen a large quantity of clear yellow fluid escaped. There was an entire absence of fat throughout the body. The Abdominal Cavity was almost completely occupied by a tumour springing from the ovary, the intestines were empty and contracted.

The tumour was cystic and was composed of individual Ova varying in size from small shot to that of a pigeon's egg, some were firm and solid filled with a clear yellow fluid, some contained hæmorrhages.

At the upper portion was a mass of Neoplasm white and resembling brain substance.

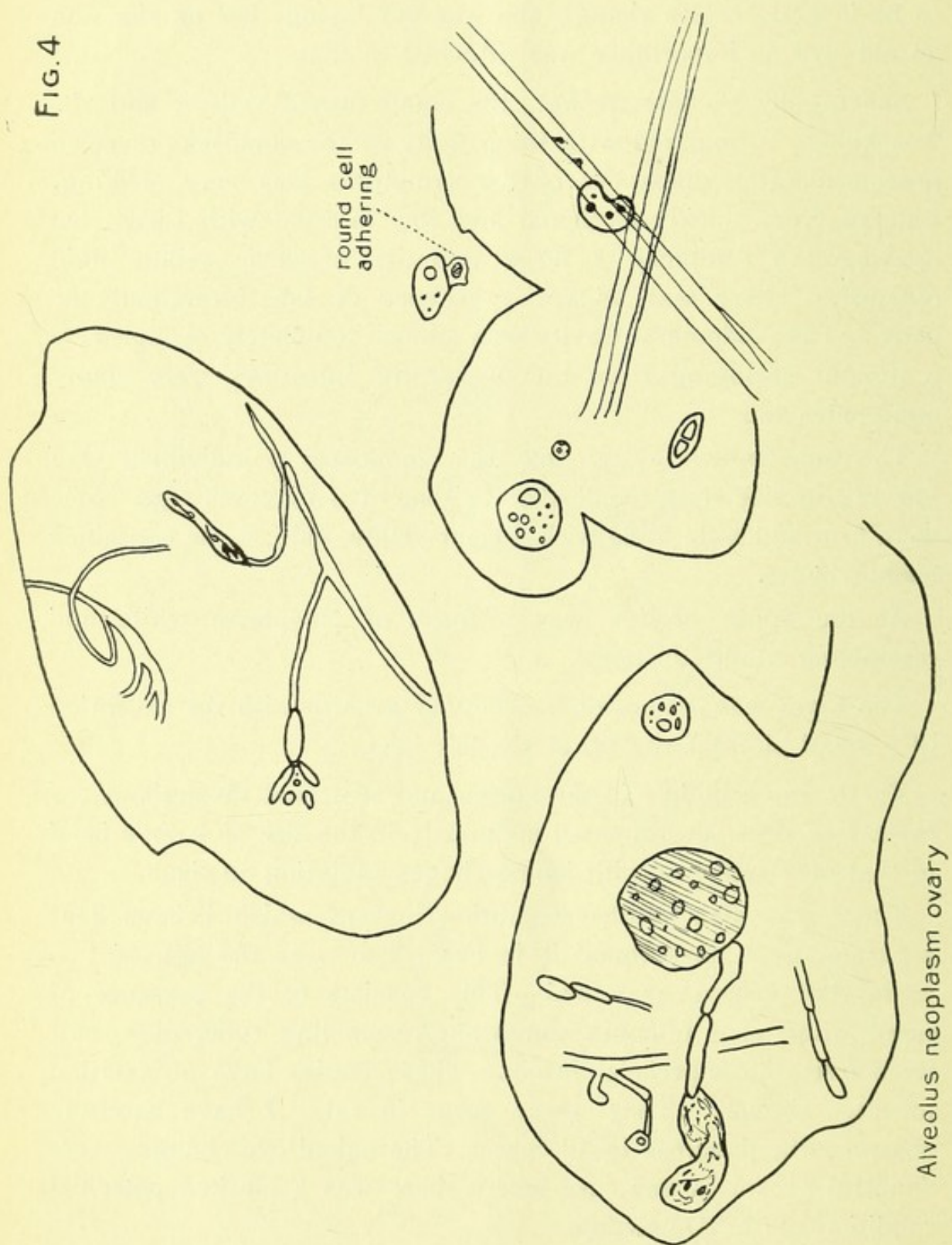
The Liver was replaced by secondary growth with the exception of a small piece at the tip of the left lobe.

There was a nodule in the spleen and scattered throughout the mesentery were several small nodules from the size of a pin's head to that of a split pea with hæmorrhages radiating to them.

There was also another condition present which I have kept separate, as I have found it in every hen over the age of two years that I have examined. This consists of the presence of small white opal tumours somewhat resembling tubercles scattered over the superficial fascia. These bodies have no relation to fatty tissues. They never occur in fat. I have carefully observed the pancreas in all cases. The naked eye changes were doubtful except in one case where there was a marked petechial condition of the Duodenum.

These small tumours stain green with copper sulphate solution and break down on maceration in saliva. Microscopically they present a very similar appearance to that observed in Molluscum

FIG. 4



contagiosum. On being kept under suitable conditions they develop the characteristic rim of white feathery hyphae.

A section through the Neoplasm shewed a fibrous stroma enclosing alveoli containing the usual large round cells. In the stroma aggregated into definite clumps was a small ovoid cell which stained very readily with methylene blue.

They were of a faintly granular appearance and in some cases shewed concentric markings in the same fashion as the starch grains of the potato. These bodies stain blue with Iodine and are the hyphal bodies of a hyphomycete.

They appear to be able to germinate (fig. 5) and also to break into fragments when each fragment seems capable of starting an independent existence. This latter condition seems to be occasioned by the drying of the organism.

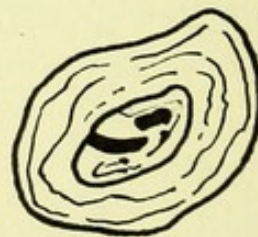
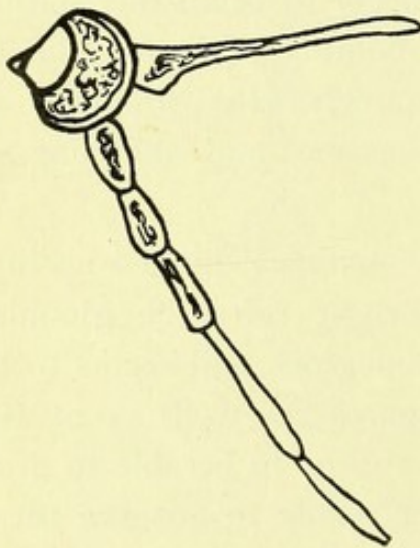
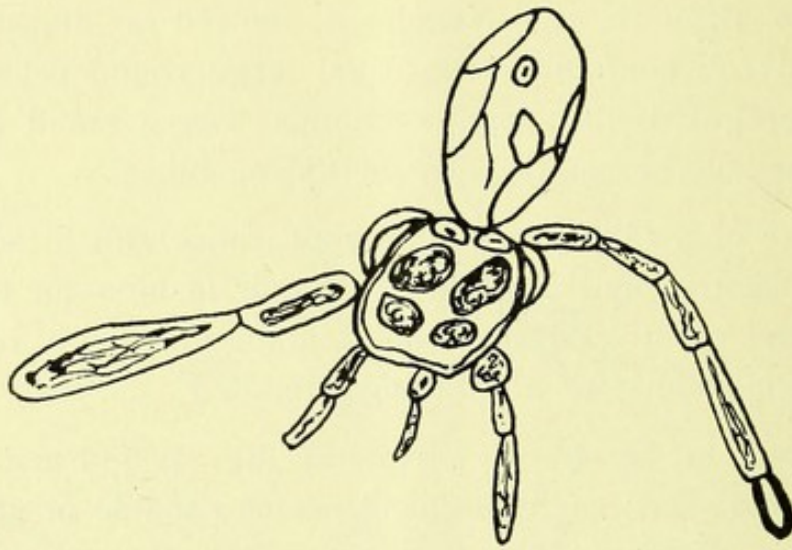
In the space surrounding the section were found large ovoid bodies of a highly refractile nature.

In addition to these are found circular discs which contain small highly refractile globules. These discs seem to be of oily nature as they are distorted if they come into contact with any chance fibre lying on the slide. They also possess the property of extracting the surplus stain from a section and diffusing it throughout their substance.

Besides these may be found a hyaline substance divided up into irregular areas and dotted over with bright refractile globules (fig. 3). This is a ground substance, or zoogloea and seems to be the product of the conidia or other spores as well as of the mycelium. The globules contained in it appear to be able to drop out and presumably germinate, as it is possible to observe these irregular areas perforated with clear cut circular holes and the globules lying round about them.

These bodies are also characteristic of the development of moulds and the vacuolated bodies of malarial blood are probably of similar origin.

In the empty alveoli of the section were found hyphae skirting the boundary wall, bridging across it, or projecting into the cavity, in some cases there were indications of the formation of



from mesentery.

conidia. In other alveoli were found zygosporos some of which were seen to be germinating.

HYPHAE.

There appear to be two varieties of Hyphae.

1. Large septate with well marked cell wall. In the young state each segment is filled with dense protoplasm which stains readily. Contrasting with the transparent lightly refractile cell wall this gives the organism a characteristic stencilled appearance. This protoplasm develops brightly refractile granules, which stain blue with Iodine during certain stages of their development. On drying the cell wall breaks up into small fragments resembling bacteria, and it is possible that these fragments may possess the power of growth. As they grow older they lose their power of staining and become quite transparent.

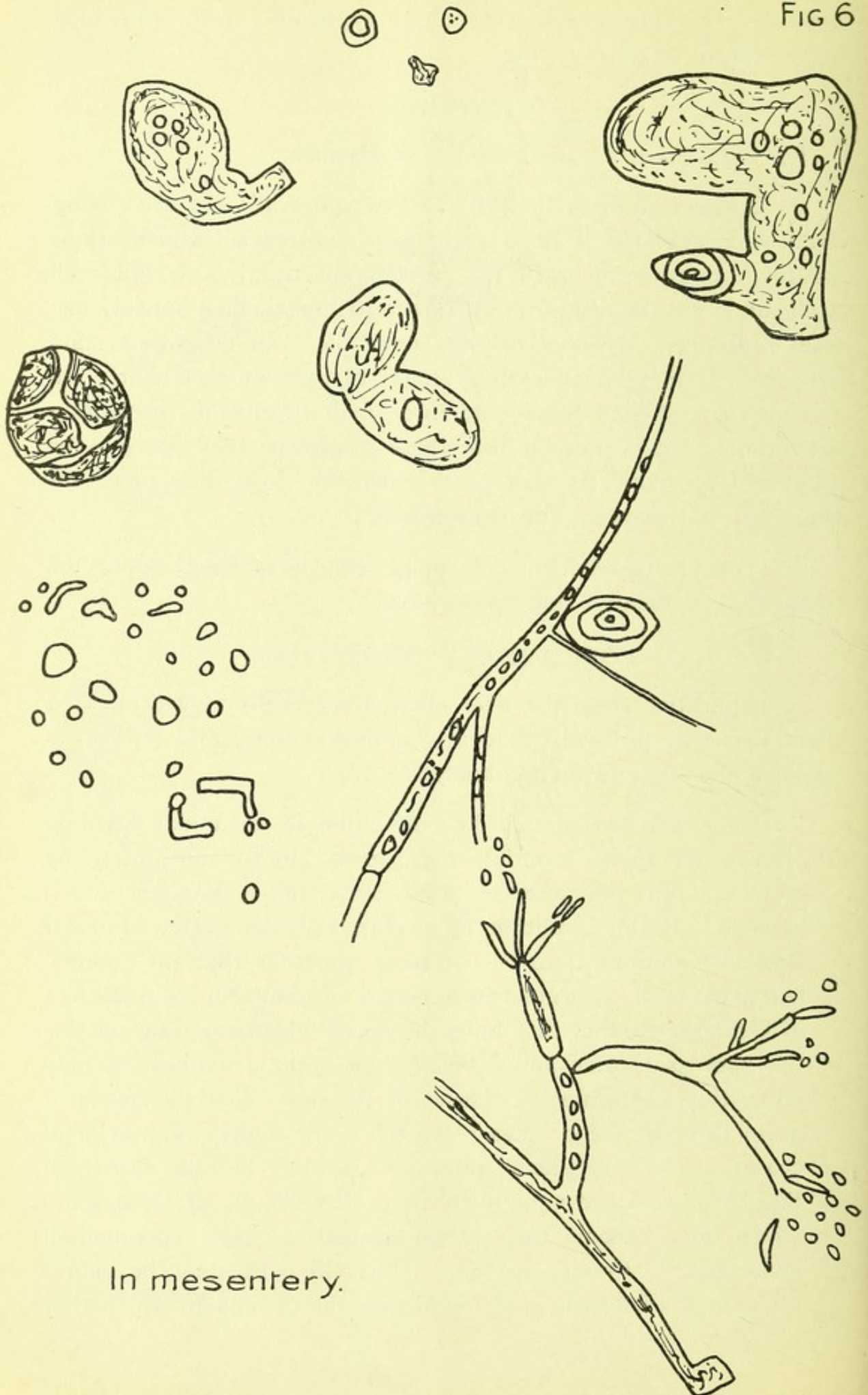
2. Thin transparent hyphae, these seem to be solely connected with the fructification and do not stain.

SECONDARY GROWTHS.

A preparation from the liver shewed the entire replacement of liver tissue by an oval cell which stained readily, and represents the conidial stage of the hyphomycete.

“ It has been shewn that by cultivation in a suitable medium
 “ promycelial spores multiply themselves almost indefinitely by
 “ budding, but the nutrient fluid must be maintained unex-
 “ hausted. In this condition the growth is similar to that of yeast.
 “ Brefeld maintains it to be extremely probable that the conidial
 “ fructification in a toruloid form occurs in nature in many species
 “ of Ustilagineae that they have the power of propagating outside
 “ the host as torulae and develop their spore fructification only
 “ when they penetrate the tissues of the host plant by means of
 “ germ threads which takes place when the supply of nutriment
 “ ceases. The extreme assumption is that certain forms of
 “ *Saccharomyces* are aquatic forms of the conidia of Ustilagines
 “ which have become toruloid on account of their surrounding
 “ conditions.” Cooke, op. cit. “ Brefeld cultivated the spores
 “ of many Ustilagineae and found that the conidia to which they

FIG 6



“gave rise were in form and dimensions similar to those of various species of yeast Fungi—those of one being ovate, of another oblong ovate, of another fusiform, of another cylindrical, of another small roundish, of another filiform, and so on.” (W. B. Grove quoted in Cooke, op. cit.)

From this point of view the round cell of the round cell infiltration is comparable to a yeast cell: the spores of a trichophyton, the cell infiltrations of malignant disease, and rodent ulcer, and the perivascular infiltration of trypanosomiasis all belong to the same category.

In the Entomorphthoreae which include the fly mould *Empusa Muscae*, infection results from contact of one of the conidia which adheres to the surface of the host, germinates there and the germ thread enters the body. After entering, growth proceeds rapidly and forms hyphal bodies which are short thick fragments of variable size and shape continually reproduced by budding. Having absorbed the contents of the body these hyphal bodies germinate each one producing one or more threads which proceed directly into the outer air and bear conidia. The discharged conidium germinates alone but failing to reach a suitable host a secondary conidium is formed resembling that from which it was derived. Should this fail a third is formed from the 2nd in the same manner. The other form of reproduction is by means of resting spores which may be sexual or asexual and proceeds also from the hyphal bodies.

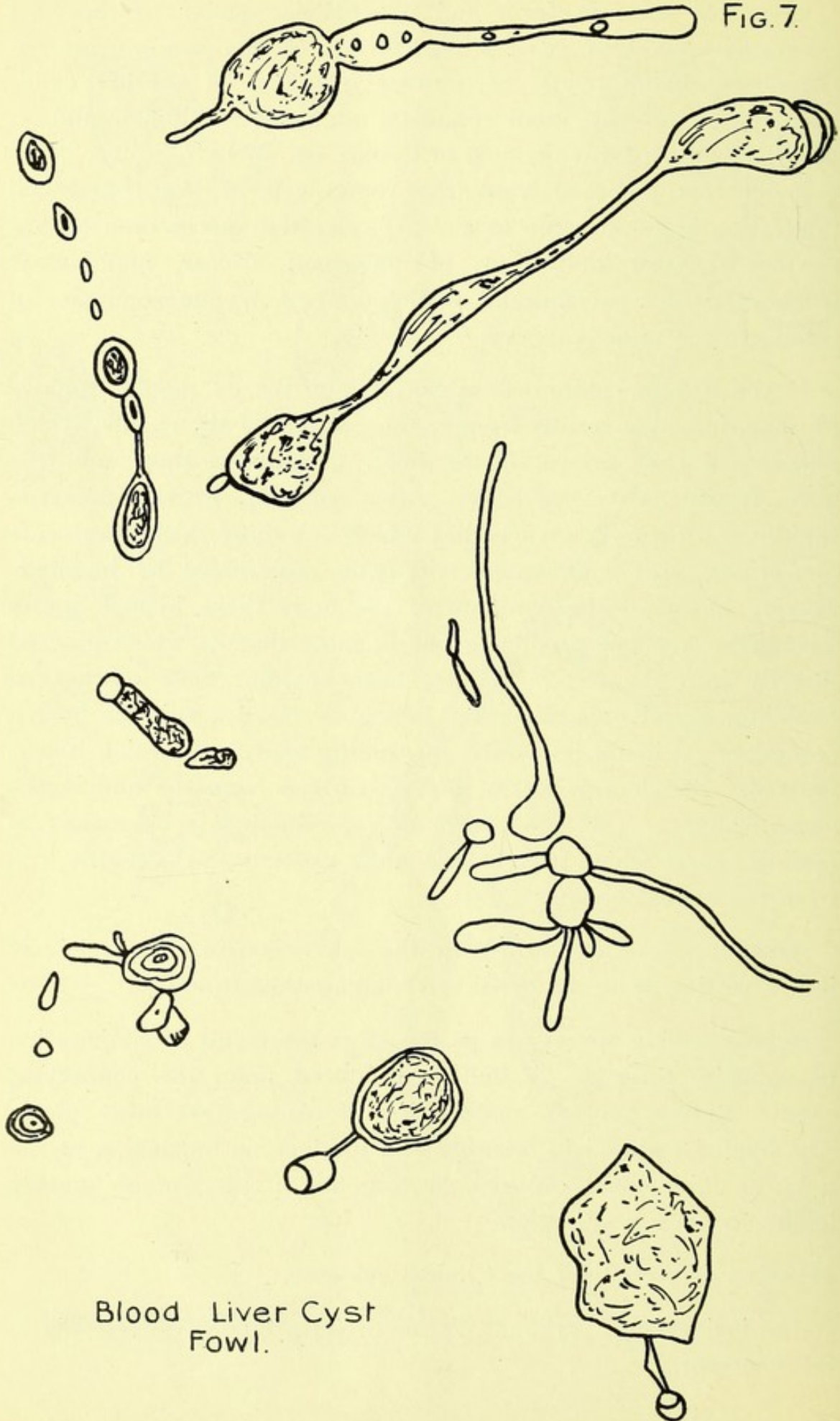
Asexual spores are formed by the conversion of a hyphal body into a resting spore or by direct budding therefrom.

Sexual resting spores are produced as the result of conjugation of opposite threads. A bud is produced upon the connecting canal. Rarely another modification of conjugation takes place. The hyphal bodies join laterally and produce an expansion at the point of union which absorbs the contents of the two conjugating bodies forming a zygospore.

Let us now consider the Clinical evidence.

The incidence of malignant disease is (1) primary, (2) secondary, (3) recurrent.

FIG. 7.



Blood Liver Cyst
Fowl.

PRIMARY INCIDENCE—SKIN.

No part is exempt but parts exposed to abrasion, continued, or repeated pressure, are peculiarly liable.

The palm of the hand and sole of the foot are exceptions, possibly because they contain no hair follicles. Workers in paraffin and soot seem specially susceptible. Moles, scars, warts, and old standing sebaceous cysts have a tendency to become malignant.

The possibility of inoculation by means of parasites must not be overlooked.

The natural orifices are especially prone. They are richly supplied with glands and are specially liable to fissures and cutaneous eruptions. They provide the necessary moist surfaces for the passage of zoospores.

The *Achorion Schonleini*, the organism of favus is a hyphomycete. Ringworm is nearly allied. Rodent ulcer is clinically a malignant Ringworm and bears the same relation to it as Epithelioma does to a wart.

The Eyelids are subject to *Molluscum contagiosum*.

They afford a means of ingress to the Lachrymal apparatus and also to the nasal cavity.

The anterior nares are the main openings to this latter Squamous Epithelioma occurs here and also less frequently Sarcoma.

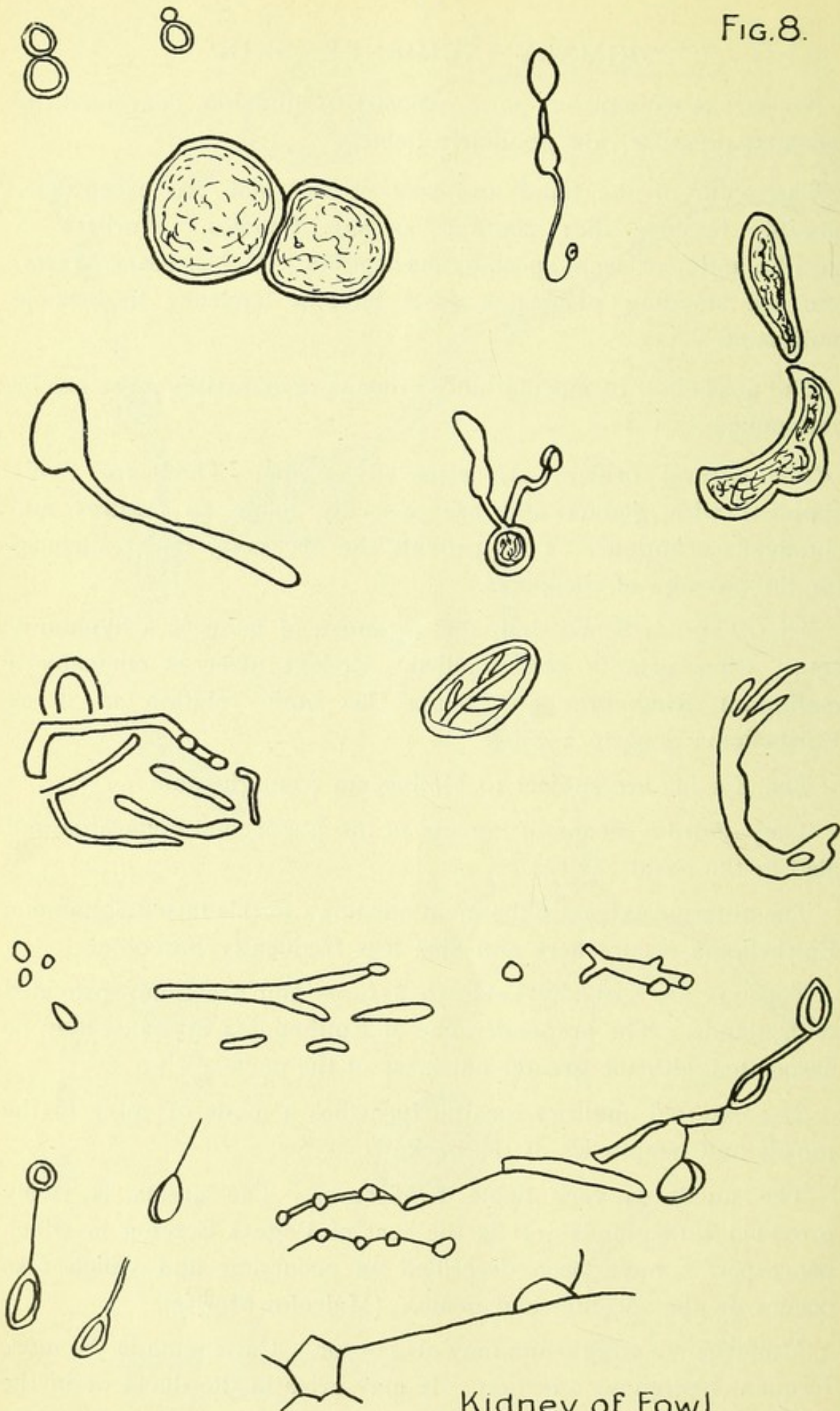
The lips are specially liable to fissures and are richly provided with glands. The preponderance of Epithelioma in males may be associated with the greater hairiness of the parts.

The external auditory meatus furnishes a mode of entry to the tonsils and lymphatics of the neck.

The nipple is very liable to fissures. The areola is richly provided with glands. It is the seat of Pagets Eczema in which psorosperms have been described as occurring and which also occurs on the scrotum and penis. (Malcolm Morris).

Molluscum contagiosum may also occur. Carcinoma is the more frequent malignant affection. It may arise in the ducts or in the acini.

FIG. 8.



Kidney of Fowl

Epithelioma occurs on the penis where it is associated with phimosis and retained secretion. It also occurs on the vulva and anus.

The scrotum is subject to *Molluscum contagiosum* and Paget's Eczema. It is also the seat of an Epithelioma which is almost confined to workers in soot, tar, or paraffin and which seems to be reappearing in colliers.

Sarcoma of the skin is nearly always secondary to lymphatic affection. (Malcolm Morris).

There are certain allied forms Xanthoma, Xanthelasma tuberosum, mycosis fungoides, whose pathology is obscure.

There is a form of Xanthoma connected with diabetes.

ALIMENTARY CANAL.

The organism of thrush *Oidium albicans* belongs to the hyphomycetes.

It is possible that dental Caries may be due to these organisms as spores are found in the saliva and on the gums. The tongue is a frequent site of Epithelioma, males being chiefly affected. There is often a previous condition of superficial glossitis or ulceration from carious teeth. The gums are very liable to Sarcoma, which is often associated with carious teeth.

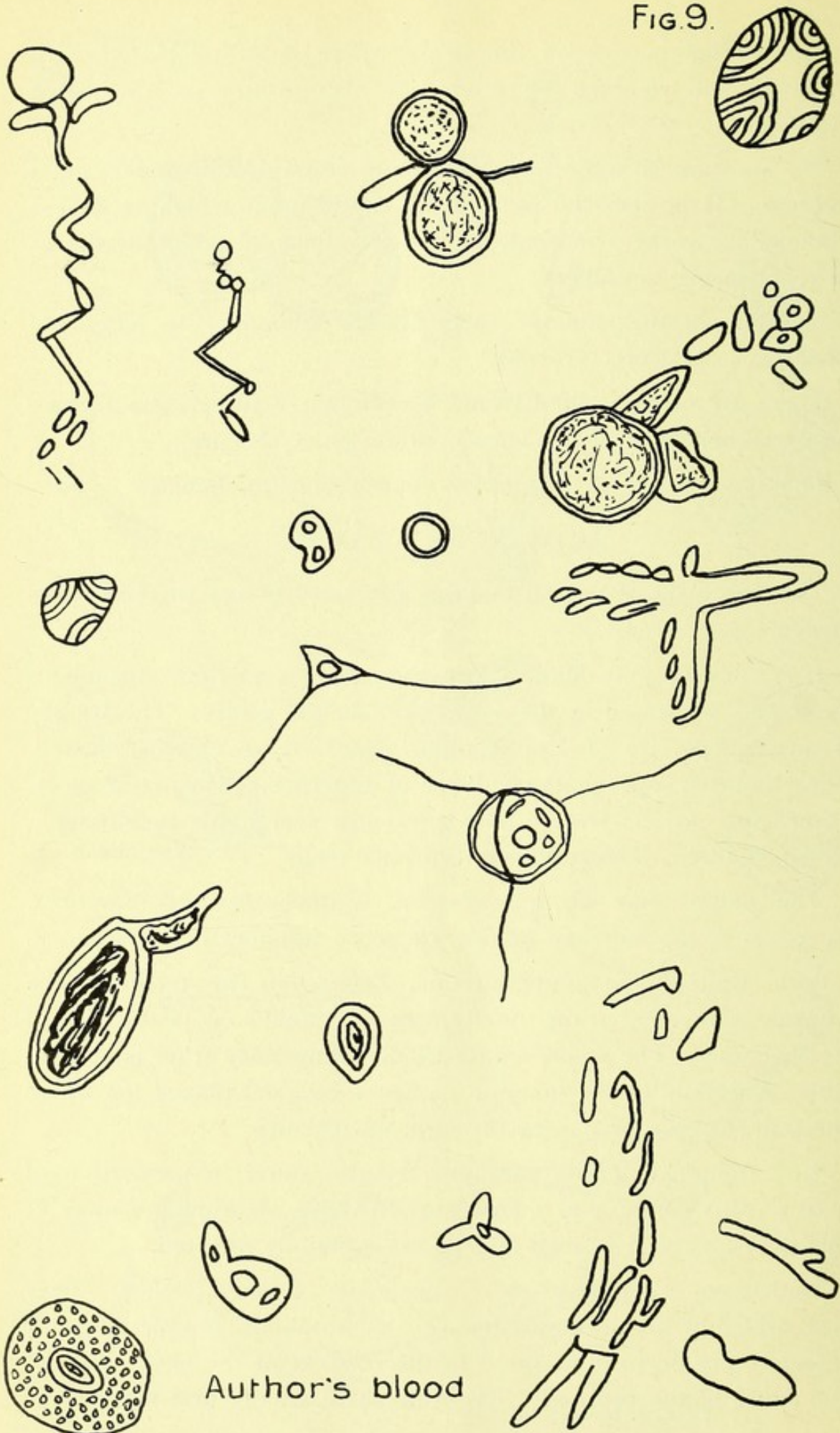
The palate may be the seat of Epithelioma and Sarcoma. Tumours of the salivary glands are more frequently sarcomatous.

Both Epithelioma and Sarcoma occur on the tonsils. The Larynx is invaded from the Alimentary Canal and is the site of Epithelioma. The whole length of the Alimentary tract is susceptible, especially at the junction of Embryological planes, or where the gut narrows or passes through an aperture.

In Carcinoma of bile passages females suffer in proportion of 3 to 1 (Musser) or 4 to 1 (Ames). In cases of primary cancer of bile duct men and women appear to be equally affected.

Gallstones occur in 90 to 100 per cent. of cases (Osler). They are probably an accumulation of the katabolic products of the infective organism, and stand in the relation of the effect and not the cause of the process. The Fundus is usually first involved in

FIG. 9.



the gall bladder, and in the ducts, the ductus communis chole-dochus. Primary disease in the bile ducts is less common. A very interesting form is that which involves the Ampulla of Vater (Osler, Practice of Medicine).

Cancer of liver is third in order of frequency of internal cancer. It is rarely primary ; women are attacked less frequently than men. It is stated by some authors that secondary cancer is more common in women owing to frequency of cancer of the uterus.

Heredity is believed to have an influence in 15 to 20 per cent. In many cases trauma is an antecedent. It is stated to be less common in the tropics.

The following forms of primary cancer may be recognised :—

1. Massive.
2. Nodular. Usually in one region a larger, older looking mass can be recognised, which indicates the primary seat and numerous nodules secondary to it.
3. Cancer with cirrhosis. On section cancerous nodules are seen scattered throughout the entire organ, surrounded by fibrous tissue.

Histologically the primary cancers are Epitheliomata, Alveolar and Trabecular. The character of the cells varies greatly. In some varieties they are polymorphous, in other small polyhedral, in others again giant cells are found. In rare instances, as in one described by Greenfield, the cells are cylindrical. Of primary Sarcoma of liver very few cases have been reported (Osler).

Of new growths of the Pancreas, Carcinoma is most frequent. Sarcoma and Lymphoma have been occasionally found.

GENITO-URINARY SYSTEM.

In the kidneys Sarcoma is more common. It is frequently found in young children and may contain muscle fibres. Calculi are frequent.

In the bladder Epithelioma is the usual type. Males are more frequently affected.

Carcinoma occurs in the prostate.

Both Carcinoma and Sarcoma occur in the testis.

Carcinoma of uterus starts :—

1. In the vaginal portion in the malpighian layer.
2. In the cervical portion in the glands of the cervical canal.
3. In the body, in the glands or epithelium.

Sarcoma may also occur.

The organism figured in Thoma's text book as *trichomonas vaginalis* would do equally well for a zoospore.

Carcinoma of the Fallopian tube is rare.

In the ovary Carcinoma is more common (Herman).

MUSCLE.

I can find no account of primary Carcinoma of muscle. Sarcoma of muscle and tendon occurs. It originates in the connective tissue.

Primary affection of the heart is exceedingly rare.

In the uterus Carcinoma of the cervix starts in the glands of the body in the Epithelium of the glands or of the surface (Herman).

NERVOUS SYSTEM.

Primary Carcinoma is a rare condition.

Sarcoma arises in the membranes and is not common.

Glioma and Psammoma are probably allied conditions.

In the last named Corpora Amylacea occur.

VASCULAR SYSTEM.

Some of the primary Anaemias may be related. The association of Chlorosis with Gastric Ulcer should be noted. Atheroma, Arterio Sclerosis, and Varicose Veins, present many points of resemblance with tumour formation.

Sarcoma is disseminated chiefly by the blood stream.

In Carcinoma the lymphatics are the channels of secondary infection.

The Lymph Glands act as filters and are subject to Lympho-Sarcoma.

REMOTE ORGANS.

Certain organs not in direct communication with the external world may be infected through the agency of the blood.

The Liver, Spleen, Brain, Eye, Bone, are examples; the ductless glands do not seem to be specially liable, with the exception of the Thymus and its remnants.

EMBRYONIC RUDIMENTS

are specially liable. This may be owing to the lower tissue resistance following Disuse Atrophy or to the presence of some substance specially favourable to the development of the organism.

Moles, the junctions of embryonic planes which are in fact embryonic scars, the Jaws which are crowded with epithelial remnants and the Branchial Clefts, the remains of the Thymus, and Retained Testicle are commonly affected.

LUNGS.

Primary growths are rare.

Osler states that it is found in the Cobalt miners of Schneeberg and that a considerable proportion of all deaths in persons over forty is due to this cause.

The Mediastinal Glands are frequently affected and this is connected with the remains of the Thymus Gland found in this situation.

SECONDARY GROWTHS.

These may be in anatomical relation to the primary focus or they may be the result of a general infection through the blood stream.

RECURRENCE.

This seems to be due to the formation of resting spores.

There are many analogies in the vegetable world.

“The leaves of the ground ivy through the autumn will present the white blotches of *Ramularia Calcea* sometimes every leaf more or less affected, and during the winter most of these leaves will die and decay. With the spring there will be a carpet of green leaves again without a spot of *Ramularia*, but as summer

advances the pest appears as profusely as ever." (W. A. Smith quoted in Cooke op cit.)

Reducing this to its lowest terms

Carcinoma arises in the skin or mucous membrane, i.e., on the surface.

Sarcoma in the connective tissues.

The most commonly occurring lesions are grouped round the natural orifices and the progress of the disease is from without inwards.

The infective agent gains entrance either through some breach of the surface or travels up some duct until it reaches a gland cell.

In those cases in which we find a long and devious route from the surface we find that Carcinoma may occur, though rarely, e.g., the liver, where secondary Carcinoma is amongst the most common of secondary affections. Again in the kidney, though Carcinoma may occur, Sarcoma is the more common, and the great frequency of such tumours in early life opens the question of infection in utero.

In the vegetable kingdom some species of *Peronospora* bear Sporangia which contain numerous active Zoospores. These float away into a position favourable for development, where they project a thin germ tube which enters a neighbouring stoma in the foster plant and originates a new mycelium. (Cooke op cit.)

There is a marked antagonism in the sites selected by malignant disease and tubercle. The breast, tongue, oesophagus, stomach, larynx, lungs and uterus are familiar examples. There is as marked a correspondence in the regions selected by innocent tumours. This is one of the gravest difficulties of differential diagnosis.

It is a good working rule to consider every morbid process to be caused by a parasite, unless it can be conclusively shown to be due to something else.

Grouping together the other various possible causes of disease we may include :—

1. Errors of development.
2. Trauma.
3. Poisons.
4. Errors in the adjustment of the machine, e.g., myxoedoma, though even here the primary cause, i.e., disturbance of secretion of thyroid gland, may itself be due to an infection.
5. Animal parasites.

These act mainly by abstracting nutriment from the host or as foreign bodies. The formation of toxins is not marked except in the protozoa.

6. Vegetable parasites.

The bacteria act mainly by the formation of toxins.

7. Senility.

This is possibly the result of some form of the degradation of energy. The process of metabolism does not seem to be capable of indefinite continuance but gradually tends to come to a standstill. This would seem to indicate something corresponding to an intermolecular friction; and that some such condition obtains we have the strongest confirmation in the phenomena of rejuvenescence and the differentiation of sex.

In the fungi the sexual function degenerates as a consequence of parasitism.

“What happens first is the degeneration of the male organs. The male function is the first to go, but the form remains after the reality has ceased. After a while, that is in related species, the form goes too. Parthenogenesis is thus reached. In many cases the female organ follows suit and asexual reproduction remains.

“The more intimate the parasitism the more degenerate the sexual reproduction, and all trace of it is often lost. The fungus

fertilises itself from its host. In the coffee plant, for example, the stimulus of fertilisation is replaced as it were by an essence of coffee." (Geddes & Thomson, *Evolution of Sex*.)

Here also we may look for a physiological basis for the universal craving for stimulants. It is not without significance that the most widely employed of these should be the product of the yeast fungus.

MODE OF INFECTION.

There are two obvious elements of the environment which are common to both the systems affected. These are water and flies. Both of these are dependent on an antecedent factor, sewage contamination.

It is admitted by the water engineers that drinking water is merely dilute sewage, and efforts are being made to sterilise it by means of chloride of lime or ultra violet light. These methods are merely palliative, and the evil should be attacked at its source.

Sewage is specially suitable material for the cultivation of fungi. There are whole natural orders which are confined to this material. In some of the higher fungi, of which it is probable that many of the parasitic moulds are but the conidial forms, viz., in the Ustilagines, out of a total of about 300 known species upwards of one hundred affect the grasses. The danger of the system of broad irrigation and of using the sewage sludge for manuring purposes is obvious. It is possible also that farmyard manure is a fertile source of disease in cultivated plants.

FLIES.

There are 150 species of Mycetophilidae—Fungus Gnats—most of which appear to live solely on the fungi they infest. (Fred. V. Theobald, *Account of British Flies*, Buller *Researches on Fungi*.) In the mycelium of the fungus occurring on the Apricot, mentioned previously, I found an aphid in quantity, so that the aphides may play the same part in the vegetable kingdom that the flies do in the animal.

The association of the mosquito with tropical disease calls for no further comment.

I had occasion to prepare a mucilage from wheat flour, which I left on my desk in full sunlight for some considerable time without any mould developing. A blue bottle fly then fell in and within a few days moulds began to develop, starting from the nervules on the wings and also the back of the fly. There were also two other clumps apart from the fly. This mould grew on a hyaline and viscid base, which extended round the edges which were corrugated, the whole forming a dome shaped islet with short upstanding hyphae like the pile of white velvet. These later became green from development of conidia.

This method of growth is identical with that of the mould observed in the solution of Zinc chloride, in which the organs were preserved from the case of Carcinoma of ovary of the fowl. It seems probable that the complete life cycle of these parasitic moulds requires an alternation of generations on hosts of two distinct species. Whether the asexual mode of reproduction can induce infection is a question for future research.

TERMINATION.

This is not due so much to any inherent virulence on the part of the infective agent as to the persistence of its growth and the number and diversity of its methods of reproduction. The extreme similarity of the condition produced by old standing gastric ulcer where kinking of the gut had taken place and where the diagnosis is only established on the operating table, will occur to any surgeon of experience.

Thoma states : It seems that cancerous tissue can itself produce poisonous substances which give rise to cachexia. This is more especially true of the cases in which cachexia is produced by a non ulcerating tumour. Cancerous cachexia is however really a combination of the symptoms of chronic leucocytosis and oligocythaemia and of atrophic and degenerative disease of the liver, kidney and heart and other organs.

It is to be noted that the fatal issue of this disease is practically always due to the secondary effects. Tabulating :—

Primary. Abstraction of nutriment from host. Provision of tissue cells for protective mechanism. Intoxication.

Secondary. Absorption and erosion of vital organs.

Pressure Effects. These cause distress by preventing the ingestion and digestion of food by embarrassing the respiration, by obstructing the excretion of effete products, by obstructing flow of blood or lymph, or by causing pain and loss of sleep.

Thrombosis and Embolism. These are in the nature of accidents.

Mixed Infection. The intoxication of the septic process may be superadded.

REACTION TO THE ENVIRONMENT.

These moulds seem to prefer an acid medium. They flourish best in dark, damp, airless situations, and are particularly sensitive to slight variations in moisture. Malignant disease has long been associated with damp areas, such as the banks of rivers and low lying districts subject to floods. It has also been observed to exhibit an incidence on particular houses—Cancer houses—a fact which has a parallel in yellow fever.

The damping off of seedlings, which is also due to these organisms, is favoured by a damp and close stagnant atmosphere. The importance of free access of air and sunlight in dwelling houses cannot be overstated, and I would especially draw attention to the overcrowding, overheating and under ventilation in our public institutions and council schools, which latter may be defined as places where the health of the rising generation is undermined at the expense of the rate-payers. It is highly probable that such conditions as carious teeth and adenoids are dependent on a stomatitis in early life.

The chemical affinities of the fungi are of profoundest interest. Containing no chlorophyll they are dependent for their supply of carbohydrate material from preformed sources. In this their metabolism resembles that of the animal world. Amongst their constituents we find substances allied to sugar, mannite and trehalose, vegetable acids, acetic, citric, malic, fumaric, oxalic, oxalates of lime and potash. Trimethylamine *Amanita muscaria* yields muscarine and amanitine, which is identical with choline.

Glycogen is found in the asci of Ascomycetes.

It has also been found permeating the young hyphae and sporangia of mucors.

Errara contends that glycogen plays the same part in fungi that starch does in other plants. It is formed out of pre-existing organic carbon compounds, especially products of the decomposition of other food products. (Cooke op cit.) To this I would add that I have observed crystals of calcium oxalate, leucin balls and tyrosin sheaves in tumours occurring in fowls in association with and presumably as a consequence of the action of parasitic fungi. These organisms possess an intense avidity for the carbohydrates which they are obliged to obtain from organic sources, and so there is every gradation from saprophyte facultative saprophyte, parasite to a perfect symbiosis as exhibited in the lichens. From this point of view disease becomes a one-sided symbiosis—an ill-assorted union in which the extravagant demands and selfish conduct of one of the contracting parties brings the alliance to an untimely close.

The diseases associated with carbohydrates are dental caries, gout, diabetes, and rickets.

There is a group containing Pellagra and Beri-Beri which has been attributed to the ingestion of mouldy grains. This has a very striking similarity to alcoholic neuritis, and Manson suggests that Beri-Beri is due to chronic intoxication caused by inhaling the toxins of a germ living outside the body in the soil or surroundings.

In this connection it is interesting to note the part played by moulds in the production of chronic Arsenical poisoning.

“The investigations of Gosio, confirmed by Sanger, have shown that a Volatile compound is formed by the action on Arsenical organic matter in wall papers of several moulds, notably penicillium, mucor mucedo, etc. In moisture and at a temperature of 60° to 95° F. a volatile compound is set free, probably an organic derivative of Arsenic pentoxide.” (Osler, Practice of Medicine.)

