ASPERGILLOSIS—ASPERGILLAR MYCOSIS.

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ASPERGILLOSIS.—Infection by some form of aspergillus occurs both in man and animals, and particularly in birds. I have recently met with three cases at *post-mortem* examinations, and perhaps a short dissertation may prove not uninteresting.

Aspergillus.—The genus belongs to the family Perisporeaceæ, the sub-order corpoascees of the order Ascomycetes of Fungi, and numerous members of the genus have been encountered in pathological lesions. Castellani and Chalmers, in their very interesting and valuable work, “Manual of Tropical Medicine,” enumerates no fewer than thirteen which are parasitic in man. Many, of course, of these are found only in tropical countries. The fungi are found frequently in the ear, causing an otomycosis, but they may cause, in addition, lesions of the cornea and of the skin as well as the respiratory passages and lungs and other viscera.

In the lower animals (mammals) the first observation recorded was made by Revolta in 1857, who found the fungus in a pharyngeal abscess in the horse; and since then other infections have been recognised in the ear and in the lungs (seven animals were attacked in one stable

by mycotic pneumonia traceable to mouldy hay upon which the animals had been fed), in pulmonary abscesses, in lesions of the intestines, &c.

In birds infection by *aspergillus* has been recognised for nearly one hundred years. The first case was described in 1815 by Mayer and Emmert, who found the fungus in the lungs of a jay, and in the following year Jæger described the infection in a swan. Since then it has been described as present in the long bones of a white stork, in the lungs of a raven, in the bronchi and lungs of a flamingo, in bronchi and air sacs of an eider duck, along with tuberculosis in a paroquet (note the date, 1842), in the pigeon, fowl, hawk, in a tuberculous bullfinch (1842), in the abdominal air sacs of a plover, in the tuberculous lesions of a pheasant (1853), in the bustard, parrot, duck, goose, ostrich, turkey, &c., &c. The infection, therefore, has been recognised in a very large number of different kinds of birds, and, in addition to those mentioned above, I have seen the *aspergillus* in the black stork, rhea, and in a vulture. It appears, therefore, that infection occurs not only in the grain-eating birds, but also in flesh-eaters. The point is of interest because the mouldy corn is blamed as the cause of the condition; in support of which the case is recorded of a bird with a grain of corn in a bronchus around and from which an *aspergillus* infection had spread. Moreover, it is believed that some cases of aspergillosis in man are due to the method adopted of cramming pigeons, the birds being fed directly from the mouth of man filled with prepared grain. It is presumed that the grain carries the spores of *aspergillus*, which are inhaled whilst the grain is in the mouth. In man the first case of aspergillosis on record is by Hughes Bennett in 1842. Rayer found it in this year also in the pleural sac of a consumptive with pneumothorax, the fungus

being found in the sputum, cavities, and lesions of a tuberculous patient, and in 1847 Sluyter definitely demonstrated the fungus in the lungs of a patient. Virchow, in 1856, who referred to all known previous cases, described the presence of aspergillus in the bronchi and cavities of three tubercular subjects. The odourless gangrene he described as occurring in the lungs is believed by Saxer to be due to aspergillus. In 1879 Leber described a purulent keratitis due to aspergillus.

Dieulafoy, Chantemesse, and Widai in 1890 described their experience in Paris among the pigeon-feeders mentioned above. The lung lesions present in these persons were at first thought to be tubercle, but the presence of the mycelial threads in the expectorate revealed the true nature of the infection.

Boyce in 1892 and Nakel and Hinds in 1896 showed that the disease was in certain cases primary in man; but, as in Hughes Bennett's and other cases, the aspergillus infection is frequently secondary to some other prior infection, as tuberculosis.

Renon, who apparently closely studied the infection in man and animals, concluded that infection might arise among those handling grain or those engaged in operations where much dust, including spores of aspergillus, were liberated. He showed that animals and birds kept in rooms where hair was sorted and where rye flour was employed to assist in disentangling the matted hair became infected and died from aspergillosis of the lungs. The conclusions he arrived at may be given as follows. I quote from an article in the "Twentieth Report of the Bureau of Animal Industry," by Mohler and Buckley, to which I am indebted for many of the references above noted:—

- (1) That aspergillosis is a spontaneous disease affecting

the bronchi and lungs of birds and animals, and creating in the animals a generalised affection similar to hæmorrhagic septicæmia; that it develops in eggs in incubation, and may contaminate embryos contained therein.

(2) The disease may be transmitted experimentally. The botanical and cultural character of the fungus and the lesions it provokes are truly specific. In its pathogenic action it bears a strong resemblance to the tubercle bacillus.

(3) In man it develops on the cornea and skin, but has its particular evolution in the respiratory apparatus, creating pulmonary mycosis, resembling tuberculosis, and pulmonary gangrene, but without the fœtid odour. It may co-exist with tuberculosis. Occasionally it is fatal after the formation of cavities in the lungs. It may invade the bronchial apparatus alone, causing membranous bronchitis of special form and of long duration.

(4) In all its manifestations *aspergillus fumigatus* may play a primary or secondary rôle in both man and animals. It is not, therefore, a simple saprophyte, but a true parasite.

Bostrum observed the fungus *Aspergillus fumigatus* in the sloughs and discharges from a fistulous tract of a case of chronic typhlitis. Olsen found a related organism *Sterigmatocystis antacustica* infecting the skin of an amputation stump. The cotton wool employed in the bandaging contained the organism which contaminated the skin, which became red, swollen, weeping, and studded with pustules as large as a lentil. The mycelium had penetrated the epidermis and was present in the pustules. The infection yielded to treatment after repeated application of carbolised water. Delépine records a similar case following treatment of a fractured thigh. This fungus had grown under the splint and had caused ulceration of the skin in two places.

Onychomycosis may be due to aspergillus as we know it may be due to favus. The superficial layers of the nail exfoliate, the fungus gains entrance, and at length attacks the root of the nail. It may then grow under the nail. The nail thickens, and yellowish-white patches develop under the whole extent of the nail or along its anterior and lateral borders.

Leber's case of purulent keratitis with ulceration developed after an injury by the husk of an oatseed.

In Upthoff and Berliner's case the patient, shaking a pear-tree, had received a blow on the eyeball from a falling pear. A fortnight later he had conjunctivitis followed by ulceration of the cornea. The ulceration increased in extent and then healed spontaneously after six weeks; a scab 1.5 mm. in thickness had formed over it. The superficial part of the scab was formed of a mycelium, the deeper parts of necrosed corneal tissue and some few mycelial threads. Fuchs records a similar case due to aspergillus fumigatus, and the fungus transplanted on the eye of a rabbit produced an ulceration of the cornea, the course of which was more rapid than in man.

Infection of the external auditory meatus appears to have been frequently observed, the aspergillus developing in and on the ear-wax. Several different varieties of the mould have been met with. The infection may or not be benign; on the other hand, there may be a discharge from the ear, which may become purulent and even foetid. Hearing becomes less acute, and deafness may result.

Aspergillus has also been found in different portions of the respiratory tract from the nasal fossæ to the pulmonary parenchyma. The mould may grow upon the mucous membrane of the bronchi and particularly occlude the lumen, or it may be present growing upon the walls of cavities in the lungs, or, having gained the alveoli, it may

give rise to lesions not unlike tubercles, sometimes miliary, sometimes of the nodular broncho-pneumonic type. The latter lesion is the form the infection assumes often in the ox, and is said to resemble the lesions of actinomycosis in that organ. Khan describes in man an infection by the *aspergillus fumigatus* in which the mycelium grew in the smaller bronchi, and that certain of the filaments traversed the walls of the blood vessels and entered the blood stream. As previously mentioned, Dieulafoy, Chantemesse and Widal have described cases in men employed in cramming or feeding pigeons, the food being directly passed from man's mouth to pigeon. The food consists of vetch seed and millet seed mixed with water. They have shown that the *aspergillus* is saprophytic upon the grain, and that from the grain both man and pigeon became infected.

Apparently the infection is not very fatal, but clinically up to a certain point resembles tuberculosis. There is, however, less fever and less loss of condition and wasting in aspergillosis. It is much more serious when the aspergillosis complicates another pulmonary infection, as is often the case, and not rarely this other infection is tuberculosis. Cases have been accidentally encountered or diagnosed by the discovery, on examining the sputum for the tubercle bacillus, of the *aspergillus* mycelium.

If there is any doubt animal experiment is suggested, a pigeon, in preference, being used. The pigeon is peculiarly susceptible to the *aspergillus*, and dies in three or four days. One may also attempt to isolate the mould, and as it grows readily on ordinary media—potato, bread, &c., for preference—there is little difficulty in arriving at a positive diagnosis.

In experimental aspergillosis, when spores are injected into the blood stream, as, say, into the auricular vein of a

rabbit, the spores are arrested in the capillaries of the lung, liver, kidney, and other organs. The mycelium soon develops and nodules arise, which in appearance resemble miliary tubercles. If the number of spores be small, then phagocytosis may prevent any infection at all. It is not the rule that many fruit-bearing hyphæ form in the lesions, only occasionally and apparently exceptionally.

I have no time to refer to cutaneous aspergillosis further than to point out that in Central America pinta may be due to aspergillus and related fungi. The black, blue, violet, and red pinta has been shown to be due to aspergillus.

It is generally held that the commonest variety of aspergillus found in lesions is the *Aspergillus fumigatus*, but others are found.

The *Aspergillus glaucus* is commonly found on organic substances in damp places. It has been found in the air sacs of a goshawk, in the lungs of a paroquet, in the eggs of fowl, in the nasal passages of man, in cocoons of the silk-worm, in the vomit of a man.

Aspergillus repens observed in the lungs of an owl and in the ear-wax of man.

Aspergillus liquiersi found in the lungs of a penguin, and pathogenic for rabbit and fowl.

A. aviarius found in a canary's lung.

A. malignus in the ear, pathogenic for rabbit.

A. virido-griseus, pathogenic for rabbit, not for fowl.

A. bronchialis, found in the bronchi of a diabetic.

A. tokelau, cause of tokelau, a dermatomycosis of the Malay Archipelago.

A. niger, *Sterigmatocystis nigra*, found in different lesions and in different animals and contaminating dressings as in Delépine's case above.

A. nidulans. Sterigmatocystis nidulans found in cases of human otomycosis.

Aspergillus fumigatus culture.—Aspergillus grows readily as an aërobe on most laboratory media, but for choice upon potato, bread, &c. Colonies develop in a few days at the temperature of the incubator as white, circular, downy points, which rapidly increase in diameter. Soon a green colour appears, and this deepens until in about a fortnight *A. fumigatus* is mouse-coloured or smoky. The colony is formed of a dense mycelium which is more or less colourless, the aërial hyphæ carrying the fruiting heads are coloured. The fruiting heads carry sterigmata which are enveloped with spores or conidia. The conidia are oval, having one diameter slightly in excess of the other, the greater being 3μ or so, the less slightly smaller. The transverse section of the conidiophore equals about 30μ ; the hyphæ has a diameter of about 15μ . The conidia stain by the Gram method, but the hyphæ and mycelium are readily decolourised.

In the bird the aspergillus is found growing in the air sacs, along the bronchial tubes, and invading the lung parenchyma; but lesions may be observed in the liver, kidneys and other viscera. The aspergillus forms a felted layer of a greenish colour, and in the lungs appears to interfere mechanically with respiration. In some cases the fungus appears in the air sacs as an isolated growth, circular with concentric ringing, pale yellow in colour, of an appearance and firmness like to horn. There may be little to suggest aspergillus, but if the horny mass be removed and broken down in sterilised water and cultures made, the fungus grows readily and profusely. Two of the specimens of culture shown were obtained from such growths from a rhea and from a vulture.

It is not uncommon to find that the aspergillosis is

associated with another infection—that of tuberculosis—and in the case of the black stork, of which a culture is shown, there was extensive tuberculosis of the lungs. Sections made from the lungs and stained showed aspergillus lining the bronchi and infiltrating the lung tissue, which also showed changes due to innumerable bacilli of tuberculosis.

It appears that aspergillus does not form a toxin, that it grows parasitically in the respiratory tract, and that its presence may be serious, as it encroaches in its growth upon the lumen of the tube. If it is able to pass through the walls of a vessel and reach the blood stream, then, of course, matters will be very different, as infection may become generalised by the blood stream and lesions occur in other organs. In other organs, however, the conidia as a rule do not form, only the mycelium develops and lesions resembling actinomycosis or tuberculosis develop. Professor McWeeney many years ago gave me a block of a piece of kidney from a rabbit which had developed an extraordinary kidney lesion following an injection of blood containing a mould. Sections showed a mycelium, but no fruiting heads, and a very remarkable development of enormous and numerous giant cells. So also in experimental work with aspergillus injection of spores a sufficient number must be injected—not less than 100,000,000. Lesions develop in kidney and liver where the mycelium may be found.

PROFESSOR E. J. M'WEENEY, referring to a specimen of aspergillar mycosis of his which Professor Mettam had mentioned, in which aspergillar nodules had developed in a rabbit, said this occurred at the commencement of their knowledge of the immunisation of animals against the blood of other species. Instead of injecting, as they now did, either serum

or the corpuscles separately, according to the particular kind of anti-serum they wished to obtain, he injected the defibrinated entire blood of the ox into the rabbit. It had been kept in the cold press in the refrigerator, and must have become infected; indeed, almost all his specimens of blood became infected with aspergillus after about a fortnight. One of the most remarkable histological features was the gigantic cells with which the films were surrounded. They were evidently foreign-body giant cells, and attained a very much larger size than tubercular cells. Had Professor Mettam grown the specimens from a pathogenic source from some infected animal? Had he tried the experiment of forcing those fungi to produce their secondary sexual form of fructification? It would be interesting if Professor Mettam would initiate some experiments on the artificial culture of tumour cells. They had been cultivated in purity outside the human body in hanging drops. The human pathologist had difficulty in such experiments, as he could not get the material in perfect freshness, but Professor Mettam, with the power he had over his subjects, was in a favourable position for carrying out such work.

DR. T. T. O'FARRELL asked if the aspergillus in tuberculosis retarded or encouraged the tubercular process. He had a case which died, and he considered it died of the mould. He found that the moulds did not grow so well in the incubator as in the sun. As to the osteo-chondroma, he had found one *post-mortem* recently which was growing under the scapula, and he remarked that it grew both from the pleural surface and from the outside.

PROFESSOR ARTHUR WHITE thought there were cases diagnosticated as tuberculosis which were really infections of the nature of aspergillus. He had known three such cases, in one of which the thing grew apparently from the lungs and appeared in the nostrils after death.

PROFESSOR METTAM, in reply, said he thought the aspergillus hastened the tubercular process. A section under the microscope showed the specimen practically swamped with the tuberculosis. It was doubtful, he thought, in most cases, whether aspergillus actually caused death, as there

were cases on record in human medicine of patients who had suffered from the infection and recovered. The specimens were all grown in the incubator. They had been inoculated only about a week, and later would get quite mouse-coloured. When his time was a little more his own he might try the culture of tumours.