measured $14\frac{1}{2}$ in., and a systolic murmur was audible all over a smallish throbbing goitre. She complained of frequent faint feelings, had very marked palpitation, and an irregular pulse of 144 ; her face was flushed, and her skin beaded with perspiration; she had four to eight loose stools daily; she was much too weak to do any household work, her hands continually trembling; she had ceased menstruating six months previously. During the first three months she improved greatly under digitalis and quinine, the pulse being sometimes under 100 , the skin often dry, there being less trembling and palpitation, and two or three formed stools daily; she could cook and do other household work, and even walk a mile. During the next three months she swallowed 400 5-grain thymus tabloids, and ate numerous lightly-cooked lambs' thymus glands, besides continuing digitalis most of the time; but while the pulse was commonly between 150 and 180 , and occasionally 200 , she kept looking better and feeling stronger, passing two formed stools daily, the neck measuring $13\frac{1}{2}$ in. instead of $14\frac{1}{2}$, and doing all her household work, and occasionally walking two miles easily. During the next three months, while medicinal treatment was almost abandoned, the neck still appeared to lessen, palpitation was much less, nervousness and tremblings stopped, the eyes looked normal, she was on her feet all day, doing all her household work and walking long distances, yet the pulse remained about 150 . During the next three or four months, in only one of which thymus was administered, she continued to look and feel perfectly well, with a pulse of about 140 , rarely having palpitation and never tremblings, there being no ocular signs, but still some thyroid enlargement.

Case III.

This patient, originally severely and dangerously ill, became practically quite well; but the improvement began long before the administration of thymus, and seemed to continue independently of it; moreover, thymus was taken in comparatively small doses of four to six tabloids daily. Digitalis at first seemed beneficial but subsequently did apparently more harm than good. The photograph, taken at the beginning of the treatment, can with difficulty be distinguished from another taken at the end.

CASE IV.—Mrs. D., aged 47, born of a goitrous stock in a goitrous district, had noticed her goitre for three or four years, and had recently observed that, as she sat reading or sewing, she could feel her chin resting upon a throbbing swelling; she had lately been troubled with palpitation, heats, and flushings (which she attributed to the possibly commencing change of life), and occasional tremblings and cramps. Her neck measured about $15\frac{1}{2}$ inches, and by frequent mere blisterings during eighteen months it was reduced to $14\frac{1}{2}$ inches. She was then photographed at the age of 49, the upper eyelids being then slightly retracted so that nearly the entire corneae were ordinarily visible, and blinking was infrequent, so that she had a staring look, but no obvious lagging or jerkiness was noticeable in lowering the upper lids; throbbing was no longer obviously felt in the goitre, though a systolic murmur was audible all over it; the pulse-rate was 100 and regular; and she was occasionally troubled with palpitation; there was no looseness of the bowels or aptitude to perspire except near a fire. For six weeks thyroid 5-grain tabloids were tried very tentatively, usually only one daily, occasionally two; but the pulse-rate ran up to 140 , palpitation became most annoying, and a systolic murmur was heard at the base; she felt more nervous, heated, weak and liable to tremblings and cramps; even slight exoph-

thalmos seemed to develop, and certainly the upper lids seemed more retracted, so that the sclerotic became ordinarily visible above the cornea of the right eye, and the staring look seemed more pronounced; nevertheless the neck seemed to be reduced by another inch during the six weeks. During the next twelve months she swallowed 700 5-grain thymus

tabloids, usually six or eight daily for periods of several weeks at a time, under which treatment the pulse returned to 100 , palpitation and nervousness vanished, ocular signs disappeared, but the neck was no further reduced. During three consecutive months of this period she took no thymus, yet the pulse was found at 110 , palpitation very rare and slight, nervousness a thing of the past, and no ocular signs discernible.

In this case, while thyroid extract produced most unpleasant effects, no certain benefit could be traced to the use of thymus. Nevertheless the patient was found a year and three-quarters subsequently perfectly free from all discoverable symptoms except a pulse of 96 , and a very slightly enlarged thyroid, having throughout that period treasured up her last stock of thymus tabloids, convinced that they cured her of her troublesome symptoms and might therefore be needed at some future time.

EXPERIMENTAL NOTE ON THE FERMENTS OF THE RINGWORM FUNGI.

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Among the recent additions to our knowledge of the ringworm fungi is the fact that they are zymogenic or ferment-producing organisms. The steps by which this information has been gained may be briefly recapitulated. In the year 1892 I began the method of feeding artificially-reared trichophyta with human and animal hairs, and then observed, for the first time, that the fungus penetrated and disintegrated the hair when removed from the body, just as it does in the natural process of ringworm.

I can well remember the particular species which impressed my mind for the first time that the process of disintegration was essentially one of digestion. It was a Chinese variety of trichophyton, and the original affected hair had been taken from the head of a Chinese boy in the clinic of my brother, the late Dr. Frederic Roberts, of Tientsin. Never before or since have I seen any variety of trichophyton which could match this Chinese specimen in its remarkable power of diges-

tion. It belonged to that group now known as the trichophyta megalospora. And what to me was still more astonishing was the fact that a commensal of this Chinese fungus had likewise remarkable power of digestion; and this observation acquired peculiar significance when I discovered it to be not a trichophyton, strictly speaking, but an aspergillus, an order of fungi which are universally distributed over temperate climes as saprophytic moulds.

In a thesis entitled the *Introduction to the Mould-Fungi Parasitic on Man* (1893) I illustrated the artificial origin of ringworm. The method was again briefly described in the BRITISH MEDICAL JOURNAL of September 29th, 1894. In 1895 Dr. Allan Macfadyen¹ brought forward evidence to prove that "the ringworm fungus" produced a proteolytic enzyme capable of digesting gelatine. Macfadyen, who worked with fresh specimens of a trichophyton (variety not mentioned), based his conclusions upon the examination of the soil in which the fungus had grown. He found that a solution of gelatine in which the trichophyton had grown had active proteolytic powers, and was capable of digesting fresh gelatine apart from the fungus. He further showed that the active agent was destroyed by heating for two minutes at 100° C. He found that acids retarded, while alkalis favoured the action of the enzyme. Macfadyen could find no evidence of a sugar-inverting ferment. He was not able to satisfy himself that the proteolytic ferment had any action on fibrin or on hair; but he made the further observation that his specimens of trichophyta could grow on soils composed almost entirely of keratin.

Four months later I published² the evidence which led me to conclude that the keratolytic function, that is, the power to digest keratin and corneous structures, was more extensively possessed by fungi than had been previously suspected. I proposed to call these hair-digesting organisms the keratolytic fungi, a group which included not only the trichophyta proper, but favus, and some species of aspergillus. In 1896 my observations were confirmed by Pelagatti³ in Parma.

My own observations on the proteolytic ferment of the trichophyta, which I will now briefly record, were made on different lines to those of Macfadyen. This observer dealt with fresh specimens of the fungus in question, and, as I have said, his conclusions in regard to the ferment were based on examination of the soil in which the fungus had grown. On the other hand, the specimens which I examined were all aged, some of them 6 years old, and from which all traces of the original nutrient medium had disappeared. They were in fact simply dry museum specimens, which had long since lost the power of reproduction. The fungi which I tested were trichophyton microsporum (homo), T. megalosporum (homo), T. equinum, T. caninum, and T. achorion.

Observation 1. Trichophyton Microsporum.—The specimen was 6 years old (less 39 days), and in a perfectly dry state. On the surface of this dried specimen I poured 4 c.cm. of a 5 per cent. solution of gelatine in distilled water, and placed it in the incubator (32° C.). After fourteen hours it was removed, when the gelatine was found to have lost the power of resolidifying at low temperatures.

Observation 2. Trichophyton Megalosporum.—This completely dry specimen, 5 years and 10 months old, was covered with 4 c.cm. of a 10 per cent. gelatine solution, and maintained for nineteen hours in the incubator at the temperature of 32° C. When removed and allowed to cool down to the temperature of the room (16° C.) the gelatine, which was clear, remained perfectly limpid, and refused to set even when surrounded by cold water.

These observations show:

1. That the active agent in the liquefaction of the gelatine is contained in the mycelium itself, and not formed outside the body of the fungus by secondary changes in the soil.

2. That the active agent can retain its activity in a dormant state for a period of six years, when the fungus has been preserved in a perfectly dry state.

3. That the activity of the agent is independent of the life of the trichophyton.

What is this agent which can retain its functional activity and integrity over so long a period, and can resist the common tendency to disintegration?

Observation 3.—A small quantity (0.6 c.cm.) of a previously digested 5 per cent. gelatine solution (Observation 1) was added to 4 c.cm. of a 10 per cent. fresh gelatine solution. After maintaining this for twenty-one hours in the incubator at 32° C., the gelatine was found to have lost the power of resolidifying at low temperatures.

Observation 4.—The same quantity (0.6 c.cm.) of digestive gelatine was placed in a clean watchglass and subjected over a waterbath to a temperature of 85° C. for exactly two minutes. It was then mixed with 4 c.cm. of fresh gelatine solution and allowed to stand for twenty-one hours in the incubator (32° C.). After this period of incubation it was permitted to

cool down to the temperature of the room. The gelatine resolidified; there had been no digestion.

The following conclusions can be drawn from these two observations:

1. That very minute quantities of the active agent can digest comparatively large quantities of gelatine.

2. That the activity of the agent is completely destroyed by an exposure of two minutes to the temperature of 85° C.

3. That the active agent is of the nature of enzyme or soluble ferment.

Observation 5.—A small quantity of the enzymed gelatine from the last experiment was evaporated over a water bath at 65° C., and the residue extracted with absolute alcohol. This alcoholic solution was allowed to evaporate slowly at the temperature of the room (20° C.). A whitish opalescent residue was left, which had the faint odour of a trichophytic vegetation. This residue from the alcoholic extract was now rubbed up with a small quantity of distilled water; but only a small portion appeared to dissolve, most of the residue being held in a state of suspension. This watery mixture of the alcoholic extract residue was then poured on the surface of 4 c.cm. of 10 per cent. fresh gelatine, and maintained for twenty-one hours in the incubator at a temperature of 32° C. After removal, when allowed to cool down to the ordinary room temperature, the gelatine was found to have been unaffected, and resolidified equally as well as the control gelatine.

We may conclude, therefore, that the absolute alcohol is not capable of extracting the enzyme from the mycelium.

Observation 6. Trichophyton Equinum.—The specimen, which was perfectly dry and of a deep brown colour, was covered with 4 c.cm. of distilled water, and made to stand for twelve hours in the incubator (32° C.). This watery extract of trichophyton was then poured over the surface of a 10 per cent. gelatine solution, and maintained for twelve hours in the incubator (32° C.). When removed the gelatine was found to be digested, and to have lost the power of resolidifying at low temperatures. The same specimen (T. equinum) which had already been extracted with the distilled water, was now covered with 4 c.cm. of a 10 per cent. solution of gelatine, and made to stand twelve hours in the incubator at 32° C. When it was removed, and allowed to cool down to the ordinary temperature of the room, the gelatine was found to be undigested, and resolidified like ordinary gelatine.

The conclusion of this observation is obvious, namely, that pure water has the power of extracting the proteolytic ferment from the mycelium, which by such treatment ceases in a few hours to be enzymophorous.

In respect of an amylolytic ferment, my observations, so far as they go, point to the conclusion that this does not exist in the trichophyta. I have examined many specimens of British and foreign trichophyta, also T. equinum and T. caninum, and have never been able to detect the slightest evidence of the presence of a starch-digesting ferment. Its absence, however, does not surprise me, for the trichophyta can assimilate starch as such without any saccharine transformation.

It may be asked, What is the relation of this proteolytic ferment to the keratolytic ferment? I think there can be no doubt that the two are perfectly distinct and different ferments. The proteolytic ferment, as we have seen, is soluble in pure water, and may excite active fermentations, apart from the life of the fungus. It is simply an enzyme or soluble ferment. On the other hand, the keratolytic or keratine-digesting agent is an organic ferment, whose operations are purely vital, depending not only on the life of the organisms, but varying in intensity and in kind from one species to another.

Another point of much interest is that the keratolytic action of the T. megalosporum in scalp ringworm is directed against the interior substance of the hair, leaving, when this is digested, a hollow shell of cuticle. T. microsporum, on the other hand, directs its keratolytic powers against the cuticle, digesting this first and subsequently attacking the interior cortical matter.

REFERENCES.

- ¹ *Journal of Pathology and Bacteriology*, vol. iii, p. 176, 1895. ² *Ibid.*, vol. iii, p. 300. ³ *Transactions of Third International Dermatological Congress*, London, p. 590.

ON TONSILLAR CALCULI.

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THE occurrence of large calculi in the tonsils is a condition so relatively rare that it merits a description of the following case.

The patient is a healthy man, aged 50. About six years ago he began to suffer from repeated attacks of tonsillitis, which often ended in suppura-