remains so for a considerable time. Scrub the penny with emery powder, and it loses its radio-activity. Test the emery powder used, and behold it has become radio-active. Wash the penny with nitric acid and it loses its radio-activity; evaporate the nitric acid and the residue left is radio-active. In brief, there comes off from radium an emanation, or if you like a vapour, which has the power of rendering any body it touches radio-active. There is no method of inducing radio-activity except by the emanation, and it is evident that this emanation leaves on any surface it touches an active deposit—a deposit which you can take off and remove.

It is probable that much of the future of radium as regards surgery lies with the emanation. This active deposit forms on any surface exposed to the emanation. By increasing the surface so exposed you increase the amount of radio-activity.

As I have been very careful not to mention any fact other than what I have myself seen, I wish to state the following as a thing told me: An eminent scientist in London has used a solution of this active deposit as an injection into the tissues of the body, for it is easy to get a solution of that deposit. This solution was injected into a mouse which was the subject of an abdominal cancer produced artificially, and the growth vanished. It is scarcely fair to mention this case, because I can add no further details. Such an experiment needs to be verified and supplemented by many other data. I have noted the local effects of subcutaneous injections of the solution of the emanation in the human subject. I will not give you details of the case, because the issues are misleading, and open up a wide subject into which I need not now go. Each injection performed in this patient with an ordinary hypodermic syringe produced a scar and pigmentation of the skin such as I have never met with in my whole surgical experience. The appearance at the site of each puncture was entirely new to me, and led me to think that I was viewing a condition of scar which had hitherto been unknown.

I will now conclude by pointing out the lines upon which the future investigation of this subject will probably extend. First of all, it is very essential to ascertain the action of the radium rays and of the emanation upon bacteria and their products. In the next place, the selective action of the radium on certain tissues must be studied. This selective action is one of the most astonishing things about radium as illustrated by the manner in which it picks out vascular tissue for destruction. Under its influence this tissue, as met with in the angioma, vanishes. What is radium likely to do for other conditions associated with vascular growth? What is it likely to do for Graves's disease? Has it any kind of selective effect upon embryonic tissue, which is allied to that of certain growths? All that has yet to be ascertained. Then comes the effect of radium in large amount. On this question of the amount great possibilities appear to hang. Little has yet been done, except by Dr. Dominici, to ascertain the effect of introducing radium into the substance of a growth in a tube permeable to its rays, such as a tube of thin aluminium. So far as he has investigated the matter the results have been encouraging.

Then come the questions of the effect of the emanation if inhaled, the effect of injection into the diseased parts of a solution of the emanation, the utility (if any) of radio-active water and other substances rendered potent by radium.

Finally, let me once more warn you against raising false hopes in discussing the potentialities of a little-known remedy.

A PETITION promoted by the Betterment of London Association to the Prime Minister requesting early legislation to check unnecessary and objectionable street noises has been signed by a large number of medical men residing in the West End of London.

THE second international course of legal psychology and psychiatry will be held at Giessen, April 13th to 18th, 1909. The course will be under the direction of Professor Sommer, who will have the co-operation of Professors Mittermaier and Dannemann of Giessen, and Professor Aschaffenburg of Cologne. All communications on the subject should be addressed to Professor Dr. Sommer, University of Giessen.

Observations
ON
HUMAN GLANDERS:
WITH A STUDY OF SIX CASES AND A DISCUSSION OF THE METHODS OF DIAGNOSIS.

BY

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WITHIN the last few years five cases of glanders have been admitted to the wards of the Westminster Hospital. The disease, in its different types and stages, presents such diverse clinical pictures, and diagnosis is so often difficult, that there is warrant for recording these cases at some length.

This article was almost complete in 1905, but after making a study of 134 cases reported in the literature, an exhaustive treatise by Robin of Montreal appeared with an analytical report of 156 cases, including most of ours. Hence we did not feel justified in burdening the literature with a repetition of what had been so well done in Robin's thesis, but preferred to await further cases to enable us to investigate several points that had occurred to us. So far no other case has come into our hands, but many have been diagnosed recently in London, and we are firmly convinced that with a better knowledge of the protean symptomatology many will be revealed which otherwise would be overlooked. There can be no doubt that the Registrar-General's statistics, which show glanders as a rare disease, are misleading, and considerably underestimate the incidence of this disease.

CASE I.

H. A. L., aged 25, horsekeeper. Admitted November 12th, 1904, under the care of Mr. Spencer.

On October 31st fell in the stable and hurt his ribs; for this he was strapped. Two days later went to a dentist with an "alveolar abscess"; "cellulitis" developed, and for this he was treated at various places; no incision was made. On November 9th nodules appeared on the limbs, more or less in the neighbourhood of the joints, the knees more especially. Next day, 10th, a pustular eruption broke out on the neck, trunk, and limbs; the buccal mucosa sloughed, and a nasal discharge appeared; the upper part of the face became swollen. On admission temperature 103.4° F.; respirations 38. Restless, low delirium; no expectoration, no diarrhoea. The glandrous lesions were of three types: (1) A diffuse, brawny, dark-purplish swelling of the face and neck, (L.) involving the temporal portion of the left conjunctival sac; the advancing edge erysipelatoid. (2) A pustular eruption, distributed without special reference to aspect, upon face, neck, trunk, and limbs; the lesions consisted of a clear yellowish-white mattery head upon an angry red areola. Upon the left cheek these pustules ultimately became confluent, and, breaking down, left a large honeycombed, ulcerating surface. (3) Multiple subcutaneous and intramuscular nodules apparently in the course of the lymphatics; these nodules reddened superficially and broke down; but in no case did the skin actually give way over them. One or two were incised for diagnostic purposes; the pus was thick, yellow, curdy.

Abdomen normal. Splenic dullness increased, but edge impalpable.

Breath sounds altered chiefly in respect of prolonged expiration; there was no sign of consolidation; no gross added signs; the sounds might be described as "wheezing."

There was some articular pain, but the joints were not distended. There was no enlargement of the axillary, inguinal, or cervical lymphatic glands. The tongue was not furred, but the mucosa of the cheeks was extensively ulcerated. Muco-purulent discharge from the right nostril. Sensation, general and special, undisturbed.

The temperature kept above the 103° line until a few hours before death, which occurred on November 14th, at 6 a.m.

Thirty-two horses became glandrous, and it is worth noting that seven days elapsed after the first appearance of symptoms in the man before a diagnosis of glanders in the horses was made.

Pathological Findings.—Examination of the pus from a superficial abscess during life revealed polymorphonuclear leucocytes, and after prolonged search and careful staining a few typical *B. mallei* and no other organisms (Fig. 6);

some of the pustules, however, had become contaminated with staphylococci. From the deeper abscesses pure cultures were obtained on potato and glycerine-agar of an organism morphologically and culturally resembling *B. mallei* and these inoculated into guinea-pigs gave positive results, though the animals died too rapidly in thirty-six hours) to allow of "characteristic" changes suggesting that the organism was of exceptionally high virulence. Typical *B. mallei* were obtained from the bodies of the guinea-pigs.

Post-mortem Appearances (eighteen hours after death). — Body well nourished; great tumefaction of soft tissues of the face, especially of the left cheek and lips—the swelling is partly due to inflammatory oedema and exudation and partly to the presence of abscesses in the skin and muscles; numerous pustules of varying size (pin's head to pea) in the skin of the head, neck, trunk, and extremities (Fig. 1); some stand out, others are flat and depressed, whilst on the left side of the cheek and jaw many have broken down so as to produce a punched-out honeycombed appearance with a dusky purple hue; the muscles are the seat of numerous abscesses containing a thick sanious pus; joints normal; mucosa of nose and adjacent sinuses is much swollen and hyperaemic, that over the inferior turbinated bone resembling an aggregation of small papillomata (Fig. 2). The lungs are much engorged and oedematous and the seat of numerous small nodules with softened centre and hyperaemic periphery; pleurae covered with a thin layer of fibrinous lymph. Spleen, 12 oz., soft and homogeneous. Remaining viscera normal, save for engorgement of kidneys, adrenals, and brain.

Histological Appearances.—The abscesses in the skin, muscles, and lungs consisted of collections of round cells with indefinite nuclei, though some of these were undoubtedly polymorphonuclear cells; for the most part they could not be distinguished from monomorphonuclear cells by any method of staining. The blood vessels, of which some are in the centre of the cell collections, are congested, but it is not clear whether the virus has arrived by the veins or lymphatics. A characteristic feature of all these areas is the extensive central degeneration of a peculiar type, the *chromatotexis* of Unna, resulting in a deeply staining diffuse network of débris which obscures the detail of the sections. In the skin there is an epidermal and subepidermal collection of round cells, amongst which are some swollen and desquamating epithelial cells. In the muscles the cell collections spread along the interfibrillar tissue, and there is much surrounding oedema (see Fig. 3). In the lungs the small areas of consolidation consist of alveoli filled with cell and plasma exudation, and surrounded by a broad zone of hyperaemia in which the alveoli are choked with red blood corpuscles. Examination of the thickened, corrugated and hyperaemic mucosa of the nares showed merely oedema and congestion. There was no evidence of cell infiltration or proliferation, and no organism could be found.

Bacteriological Examination of Sections.—Careful search, after special staining (carbol-thionin blue after preliminary treatment with acid) revealed sparsely scattered typical beaded bacilli in the lungs, and skin and muscle abscesses, but the central degeneration, with its avidity for the same dyes, rendered their identification difficult (see Fig. 7). It must be stated that, with a modified Romanowski's stain, the bacteria were found just as readily, and the general appearance of the sections was more pleasing.

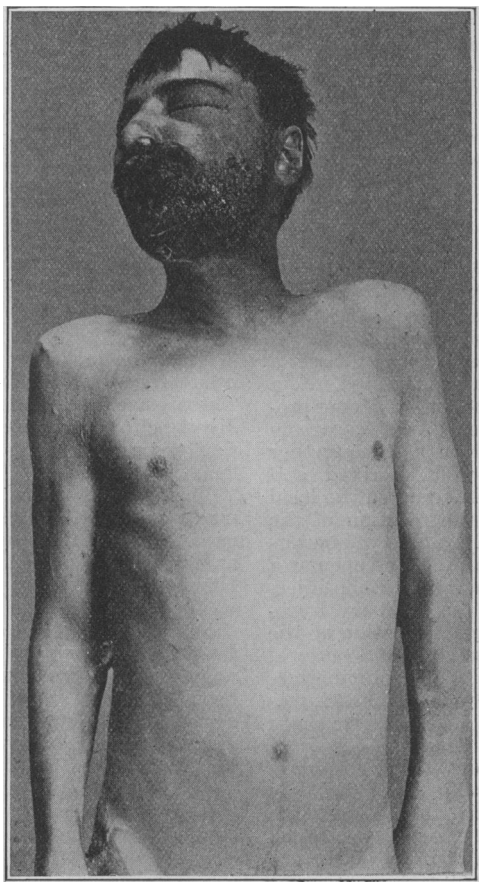


Fig. 1.—Photograph taken after death of Case I. The honeycombed appearance produced by the broken-down pustules on the cheek and jaw is well shown. Also some small pustules, discretely scattered over the left shoulder, and a few on the right and on the trunk.

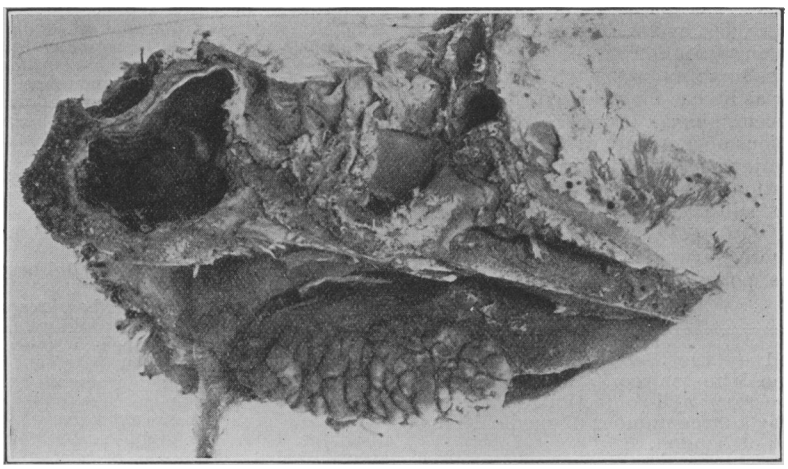


Fig. 2.—Wall of nasal cavity of Case I showing papillomatous condition of oedematous and engorged mucosa over inferior turbinated bone.

CASE II.

A. A., aged 45, horsekeeper. Admitted under the care of Mr. Spencer, July 14th, 1905.

Illness commenced seven weeks since with severe frontal headache, pains in the muscles of calf and forearm, and prostration. No history of infection could be obtained, and no initial lesion was discovered. Not till five weeks later did he notice any swellings; then in quick succession painful lumps appeared in the left leg and forearm. He stated that these lumps had to some extent decreased in size; he had no joint pain, no intestinal or respiratory disturbance, no ulceration of or discharge from the nasal or oral mucosae. Temperature, 102.2°.

Upon examination, some eight or ten subcutaneous and intermuscular abscesses were found and incised. All save one were upon the lower segments of the extremities. The urine at first was normal but subsequently became albuminous. Carboluria occurred after the first operation, at which pure phenol was applied to the abscess cavities. A few more abscesses formed and were opened. A fortnight after admission the right knee became swollen. It was aspirated, and, as the fluid contained *B. mallei*, subsequently opened and drained. From this time the condition was one of progressive intoxication with asthenia. Severe diarrhoea set in and respiration became embarrassed, though no pulmonary physical signs were detected. The temperature, which hitherto had run an irregular course, varying between normal and 104.8°, took a steady upward trend, and at death was 105.2°.

Pathological Findings.—On the day after admission pus from a cutaneous abscess revealed, after careful search, one or two bacilli only, and no other organisms; but characteristic cultures of *B. mallei* were obtained on glycerine-agar and potato (brownish slimy growth) in forty-eight hours, and these cultures, inoculated into guinea-pigs by Professor Hewlett, produced typical enlargement of the testicles. Fluid from the affected knee-joint, aspirated on August 8th, showed only two bacilli in the centrifuged deposit; but here, again, typical and luxuriant cultures were obtained.

Blood Examination.—On July 21st, when the general condition was fairly good, agglutination experiments were tried with the bacilli obtained, but the serum, even in 1 in 2 dilution, caused no clumping or loss of motility. About this time, also, cultures of the blood were made in large quantities of peptone broth and glycerine-peptone broth with negative results; but on August 10th — the day before death—the blood was again drawn direct from the vein, and in forty hours typical cultures were obtained.

Post-mortem Appearances (four hours after death). — Rigor mortis; body emaciated; numerous surgical incisions in skin and subcutaneous tissues of the extremities; one pustule on the left hand and another on the chest. Blood and muscles very dark in colour; the lungs alone showed evidence of secondary infection—the right, 17 oz.; the left, 14 oz.; no pleurisy; scattered throughout the lower lobes and felt superficially were numerous dark, haemorrhagic, firm areas of small size, con-

solidated so that they sank in water; in the centre of some of these areas was a little pus; the intervening lung tissue was apparently normal, as were the bronchi and trachea. Nothing of note in the heart (10 oz.), peritoneum, or abdominal viscera, save for slight congestion of the intestines; spleen (6 oz.), purple colour and firm; kidneys (15 oz.), febrile; brain (48 oz.), arteries and thoracic and abdominal glands all normal. The right knee-joint had been drained, and the cartilages were roughened.

Histological Appearances.—The lesions were similar to those in Case I—namely, inflammatory foci of a haemorrhagic type, but less active. In the lungs were patches of pneumonic consolidation, with much surrounding haemorrhage and great

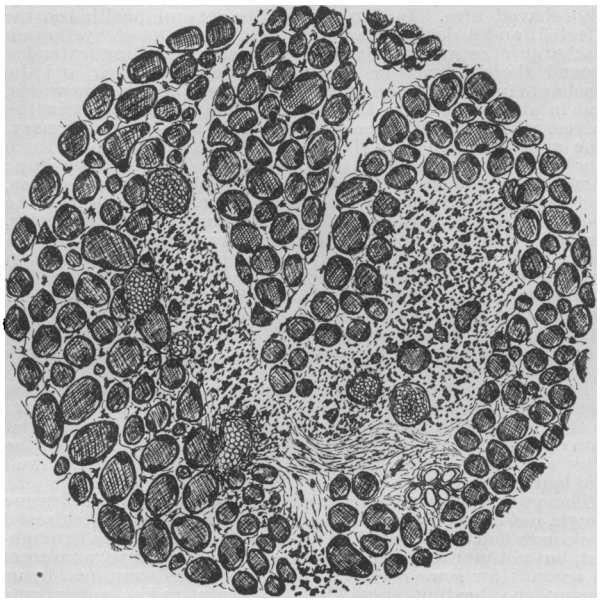


Fig. 3.—Section of muscular abscess from Case I showing purulent infiltration between the fibrils, congestion of vessels, chromatotexis of the infiltrating cells. (Semidiagrammatic drawing by Mr. J. Braxton Hicks.)

congestion of the capillaries. In these areas the central alveoli are filled with leucocytes, and the adjacent ones with leucocytes, blood, and fibrin in varying amount; in some the bronchi are occluded by a proliferative and exudative bronchitis, and in the centre of one is a vessel filled with leucocytes and débris (suppurative bronchitis), an appearance suggesting an infection via the pulmonary artery (Fig. 5). The affected bronchi are near to the inflamed vessels, so the condition may be described as septic bronchopneumonia. *B. mallei* were found in scanty numbers in the lungs in the pneumonic areas, but not in the spleen or kidneys, which showed little change histologically.

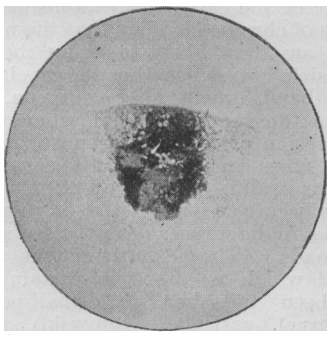


Fig. 4.—Patch of haemorrhagic bronchopneumonia. (About natural size.)

CASE III.

H. S., aged 25; horsekeeper. First seen in out-patient department by Dr. Hebb, who recommended him for admission with a tentative diagnosis of glanders.

Syphilis five years ago, but no sign for three years. The present illness began fourteen days ago, when he awoke to find swellings of right arm and leg; he thinks they have not increased in size since. On and off he has had severe nagging pains in both places. There have been no nasal or pulmonary signs or symptoms. The swellings were intramuscular abscesses, that on the arm being discrete, with little or no surrounding induration. The thigh lesion, on the other hand, showed a red area, saucer size, on the front of the thigh about the middle, and a wide area of brawny induration. Temperature on admission (December 18th, 1901) was 99°, rising to 103° at midnight.

Operation, December 23rd.—The swellings incised, contained curdy pus and gelatinous matter. The wound in the arm was sewn up and healed by first intention. In the thigh wound a sinus formed, but closed up rapidly; the superficial parts granulated and healed perfectly under a "leno" bandage.

On January 25th, 1902, there was pain in the left shoulder, which passed off, however, without anything definite developing. The notes state that "about half a dozen raised spots with vesicles are scattered over the left shoulder and neck under the chin." There is no evidence that these had anything to do with the disease. He was discharged well.

Pathological Findings.—From the pus typical cultures were obtained on glycerine-agar plates and subcultures on potato on December 24th, and these inoculated into guinea-pigs by

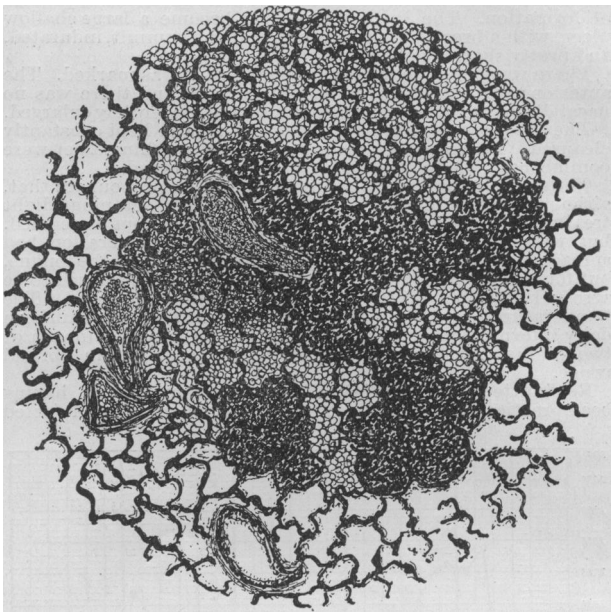


Fig. 5.—Section of a patch of pulmonary consolidation of Case II. In the centre is a branch of the pulmonary artery, which is filled with purulent clot; around this are alveoli filled with cell exudation and in a condition of advanced degeneration, while further afield are alveoli engorged with blood corpuscles; to the left and below this artery are a bronchiole and a vein, the former filled with cell-exudate the latter with corpuscles. (Semidiagrammatic drawing by Mr. J. Braxton Hicks.)

Mr. Shattock gave positive characteristic reactions, namely, "acute inflammation of tunicae vaginales, adherent testes, and intense engorgement."

On February 6th only *Staphylococcus pyogenes aureus* were cultivated from the wound.

CASE IV.

T. M., aged 26, carpenter, working in a stable where there were sick horses. First saw Mr. Turner in the out-patient department, where a diagnosis of glanders was suggested.

Admitted June 2nd, 1905, under the care of Mr. Stonham. Temperature on admission 101°. There had been general malaise for three weeks; pain and tenderness in lower third of the thigh and peroneal aspect of the right leg came on suddenly eight days ago, and confined him to bed.

At the operation intermuscular abscesses were found; there was no affection of bone or periosteum such as the clinical signs had led one to expect. Both wounds granulated well.

Pathological Findings.—On June 2nd, 1905, a blood examination showed a distinct leucocytosis, but no increase of polymorphonuclear cells. Red corpuscles, 4,920,000; haemoglobin, 55 per cent.; leucocytes, 19,400. On June 2nd in the fresh pus only one or two bacilli were found after long search, but characteristic cultures were obtained on various media, the growth being described as a Gram negative, relatively-thick bacillus, actively motile and non-beaded, and badly staining. Typical inoculation results were obtained in guinea-pigs in three days.

Seen again August 4th, 1906. Had no further trouble of any kind; his blood at this date possessed no agglutinating power for the *B. mallei*.

CASE V.

A. B., aged 22, carman. First seen by one of us in the out-patient department in May, 1904.

At that time the disease had existed for nine months. The patient stated that the earliest symptom was deafness, a sense of fullness in both ears; the nose became obstructed, and both nostrils discharged. His speech had become indistinct about a month after the onset of the trouble. When seen, the soft palate was entirely destroyed; the hard palate was perforated, and there was a widespread granular erosion of the oral and nasal pharynx. On the lateral aspect of the dorsum linguae was a soft discrete swelling, walnut size. There was no history or evidence elsewhere of acquired or congenital syphilis. The father and mother were healthy, but there was tuberculosis on both sides of the family. The condition was regarded as

syphilitic, an opinion concurred in by Mr. de Santi and most of those who saw the case subsequently. Mercury and iodides were prescribed.

In October, 1904, he was admitted under the care of Mr. Tubby, and remained under treatment at intervals until April, 1905.

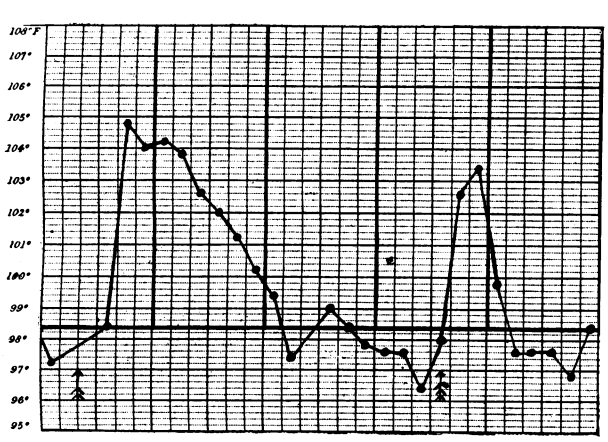
On admission, the oral surface of the hard palate, posteriorly, was tuberculated, and bathed in tenacious muco-pus; the tonsils were ulcerated, and the posterior wall of the pharynx, which had been the seat of extensive shallow ulceration, was now covered with crusts. When these were removed it was seen that many small ulcers had become confluent; the edge was circinate; in some places healing had occurred, with the formation of slightly depressed and puckered cicatrices; here and there yellow points indicated the sites of ulcers in process of formation. The lingual mass had become a large shallow ulcer, with a broad raised edge, pallid at the summit, indurated, and pretty sharply defined.

There was but little tenderness; salivation was marked. The anterior parts of the nose were not ulcerated, and there was no nasal discharge. The cervical glands were moderately enlarged.

The lesions were painted with lactic acid and kept constantly cleansed. In November mercurial injections (biniodide) were commenced; the tongue was several times scraped.

The failure of antisyphilitic remedies was so pronounced that, although no tubercle bacilli were found in the scrapings, light treatment (*x* rays) and high-frequency applications were tried, but without success. By December, 1904, the ulceration had spread considerably, involving the anterior parts of the tongue, but for a month or two the progress of the disease seemed to be arrested and the patient's general condition improved. The temperature curve for nine weeks showed an almost uniform daily intermission of 2 or 3 degrees, but for the last month or two of his first stay in hospital was almost within normal range.

Readmitted January 14th, 1905. The temperature having been practically normal for 48 hours, mallein mxvi was injected



Mallein reaction. Case v.

→→→ Injection of mallein, mxvi. →→→ Injection of mallein, mxvi.

and a definite reaction resulted. A second injection on the 17th produced a similar but less marked result. On the 26th an injection of tuberculin was given; there was no local reaction, and though on the 28th, 29th, and 30th there was some elevation of temperature there was nothing like a typical pyrexia.

Admitted for the third time, April, 1905. The disease had spread extensively, having destroyed the alveolar parts of the upper jaw anteriorly and to the left posteriorly. Almost the whole of the anterior third of the tongue was destroyed; the right antrum of Highmore was invaded.

Hypodermic injections of calomel were employed, thirteen doses of 5 grains each being given in six days, but without benefit.

By the courtesy of the medical superintendent of the Lambeth Infirmary, Dr. Quarry, we have learnt that death took place from "exhaustion" on August 19th, 1905. The lungs were clear; there was no generalized eruption, but he had had abscesses about the buttock, and at death there was a gangrenous patch on the palmar surface of the right hand. The lower jaw was extensively necrosed; there was ulceration of the nasal passages, with inflammation of the conjunctiva and lacrymal sac on the left side. The central two-thirds of the tongue had sloughed.

Pathological Findings.—A portion of the spreading edge of the ulcer was examined histologically several times during his stay in hospital. The tissue, consisting of mucosa and submucosa, showed the appearances of intense inflammation with superficial ulceration and subjacent inflammatory exudation and oedema; superficially there were fungi and bacteria of various kinds, but none characteristic; no tubercle bacilli could be found on special examination. A diagnosis was ultimately arrived at by inoculating a piece of the ulcer into a guinea-pig, subcutaneously, and obtaining a positive Strauss reaction. A more recent examination in the light of the diagnosis is of interest; a few beaded bacilli, sometimes in clumps, resembling *B. mallei*, can be found in the deeper parts amongst the cell collection, and no other organisms but these in the depths. The cells are of all kinds, leucocytes and connective tissue cells, with numerous blood vessels scattered amongst them. A striking feature is the presence of comparatively large areas of cell degeneration (chromatotexis) with a marked affinity for blue dyes. No giant cells were seen. The tissue is for the most part of the nature of granulation tissue.

CASE VI.

(Under the care of Mr. C. C. Choyce, Assistant Surgeon to the Seamen's Hospital, who kindly allowed us to make use of his notes and to see the case.)

A horse-bus driver in November, 1906, noticed two "boils" in the neck just below the left side of the jaw; these increased in size for a week, when they were accidentally cut by a barber who shaved him. In two weeks his general health became affected, and a doctor lanced the boils and a lot of "yellowish discharge" escaped. Gradually a large swelling extended around these boils over the whole side of the neck, and the discharge increased in amount. His general health grew worse, and in six weeks from the onset he had severe pains in the calves, which lasted three weeks, and he went to an infirmary. The swelling then spread on to the chest, and two or three small lumps appeared on the chest below the main swelling; these spread and coalesced, perforated the skin in several places, and ultimately fused into one large ulcer, extending from the second left intercostal space to the jaw, 3 in. to 4 in. in diameter, irregular floor and edges, with pus undermining them and discharging dirty-yellow foul pus; in the neighbouring bluish skin were several small, round, ragged ulcers discharging pus. In this state he was admitted to the Seamen's Hospital fourteen weeks after the onset. *B. mallei* were obtained in almost pure culture from the discharge, and corroborated by Professor Hewlett after animal inoculation, the guinea-pig dying in two days with swollen testicles.

Progress.—Active surgical treatment was adopted with a view to removing the entire area of disease, followed by skin grafting; in the course of this the ulcer perforated into the trachea and into one of the larger veins. He was discharged nine months after admission, cured, and a year later he was perfectly well and had resumed work.

The sputum was several times examined as he had a troublesome cough, but no bacilli were found, and on his reporting himself the cough had disappeared. There was a little pyrexia throughout, but not marked, and there were superadded pyogenic cocci to account for some of this. The serum was examined by us during the healing stage, but no agglutinative action was found.

About three weeks before the onset two of his horses were removed from the stables suffering from some trouble "involving the air passages," though the L.C.C. inspector denied any cases of glanders in the stables.

A study of these cases will reveal the remarkable circumstance that there is but one factor common to all six cases. This is an occupation bringing the individual into more or less direct connexion with horses. In all but Case v there was, in addition, a degree of prostration quite out of all proportion to the clinical signs. In Cases iii and iv it was entirely upon these two observations that even a tentative diagnosis was made, and it was not until bacteriological and inoculation evidence was forthcoming that the nature of the cases was established. So various are the lesions of chronic glanders that the mere fact of an occupation in any way likely to bring the patient into contact with sick horses, whether as coachman, carman, groom, stable hand, or veterinary surgeon, should bring the disease to the surgeon's mind whenever a chronic inflammatory lesion of the oral or nasal mucosae, or an inflammatory mass in the subcutaneous or muscular tissues, presents itself in such a patient.

Acute and subacute cases do not, as a rule, present such great difficulties in diagnosis; nevertheless, many mistakes have been made. The exanthematous eruption, the appearance of which is almost a certain precursor of death, has been mistaken for small-pox (Bosellini, Stewart, Wherry), varicella (Gutowski), impetigo contagiosa (Post), herpes zoster necrotica (Bosellini), erythema nodosum (Hartge), and anthrax (Bonomé). The general febrile state has been mistaken for typhoid (Buscke, Stewart, Goodall, Collie, Ehrlich, Rémy), influenza (Anderson, Hartge, Gutowski), pyaemia or septicaemia (Post, Bell, Goodall, Parker, Tedeschi, Ehrlich, and Wherry), acute rheumatism (Goodall, Ehrlich, and Wherry), pneumonia (Post, Collie), typhus (Rémy).

It is to be noted that in the literature there has been a failure to distinguish in description between the lymphatic nodes and the true exanthematous eruptions. Many cases of recovery after the occurrence of "lymphatic abscesses" are recorded, but of survival after the appearance of a generalized cutaneous eruption, few, if any. The cutaneous lesions appear as pink papules, which become vesicular and then pustular. In Case i there was never any

close resemblance to small-pox; but it is obvious, apart from the fact that good observers have made the mistake, that confusion might arise.

All authors are agreed as to the difficulty of distinguishing the lesions of chronic glanders from those of the other granulomata, especially syphilis and tubercle, including lupus. As a distinction between glanders and tubercle, both Besnier and Hallopeau mention the rapid progress of the ulceration, and the tendency to spontaneous healing, which characterize the former. Besnier further states that there is no analogy between the profuse suppuration of glanders and the secretion of lupus. For discrimination between chronic glanders and syphilis we have no criteria, since even the fallible evidence often to be derived from therapeutics is in this case ruled out by the fact that of all the drugs vaunted in the treatment of glanders, mercury is the only one for which success can be claimed with any show of reason.

Whilst these remarks apply to chronic lesions of the mucosae, there is still less to be said of cases such as Nos. III and IV. In very many reports mention is made of some peculiar character of the pus. It may be pink, red, grey, or merely a gelatinous material, quite unlike true pus. To find such contents in an abscess occurring in a patient whose occupation and illness had already aroused a suspicion of glanders would, of course, be so far confirmatory, but in itself the phenomenon cannot be regarded as of high importance.

If we appear to lay too much stress upon these points it is because a common termination of a chronic case is, in an acute outburst, fatal from its inception. The interval of quiescence may be a month or two, or ten years. Here, too, we may point out that, judging from the clinical course of Cases III and IV, it would be extremely easy to overlook their nature altogether.

Some authors have referred to "the typical chancre of glanders"; the term is misleading, and is, indeed, not often met with in the most modern reports. In some cases evidence that a given lesion is the infection point is complete; in many presumptive; but in a very great many it is impossible to do more than hazard a guess as to the means of entry of the virus. In some cases of wounds infected direct from an affected animal the initial site has been considered "characteristic" in appearance, but there is no general consensus of opinion as to the characters.

A case very similar to our No. v, in which for a long time extension took place by continuity only, has been described and figured by Besnier in the *Atlas of Rare Skin Diseases;* Hallopeau and Jeanselme, Bonomé, and others have described cases of long duration very similar, but in most of them there have been other lesions to afford some clue to the nature of the malady. Upon this fact—the multiplicity of the lesions—Gabrielides and Remlinger lay great stress as diagnostic, but we think this feature is only reliable in the case of the more acute forms.

The Mallein Test.

In three of our cases diagnostic injections of mallein were given. Of these, only five out of six injections were under proper conditions, but in all a typical reaction followed. The constitutional disturbance was not much more than could be accounted for by the pyrexia. Pain at the point of injection and at the site of the lesion was noticed; in three instances there was vomiting, and in one the malaise and restlessness were such that a hypodermic injection of morphine was given. In one instance there was a definite rigor. In one case the temperature rose in five hours to 104.8°, and fell to normal in another thirty-six hours; an injection given the next day led to an immediate rise to 103.4°, with return to normal in eighteen hours. In the other 3 cases the maximum rise—103.8°, 103.8°, and 103.2° respectively—was attained in ten, fifteen, and eighteen hours, and in all three the return to normal was delayed beyond forty-eight hours. In two instances injections of tuberculin were given as controls, but in neither was there any response. In is noteworthy that all 3 cases were "chronic," and that the most typical reaction was obtained from that of longest duration. In several other cases which turned out not to be glanders the mallein test produced no reaction, including 1 case of generalized tuberculous subcutaneous abscesses, which did give a typical "tuberculin reaction."

The dose we have used in all cases is 10 to 15 minims, and this, though the usual dose for a horse, has not produced any untoward results in non-glandrous cases.

Animal Inoculation.

For practical purposes this is perhaps the most reliable diagnostic procedure. In four of our cases it was tried with positive results, and in one the diagnosis was not arrived at until this was done, it being impossible to isolate any characteristic organism from amongst so many contaminating bacteria that occupied the ulcerated surface (Case v). In these contaminating cases it is better to inoculate an emulsion of the suspected tissue subcutaneously into the abdomen of an adult male guinea-pig; if inoculated intraperitoneally the contaminating germs may cause death from peritonitis before the characteristic enlargement of the testes with acute inflammation and engorgement of the tunicae vaginales is produced. The reaction is noticeable in seven to ten days as a rule, but in some few cases it has been delayed for several weeks (seven in one case reported), and in others it has not been obtained at all, and it must be remembered that the bacilli may be present in too scanty numbers to infect.

Liénaux suggests, with good cause, that the *B. mallei* are not always of equal virulence, and hence a certain number are destroyed in the guinea-pig, whilst others of more active character are capable of producing a positive reaction. In one of his experiments with an attenuated culture a positive Strauss reaction was only obtained after ten days, but a typical growth appeared on potato in three days, and so it is advisable to make cultures on potato simultaneously with the animal inoculations.

Bullock and Twort have also found that the virulence of *B. mallei* obtained from human cases, of which they had five, including two acute, is much greater than that from equines, and they got a rapid positive reaction in two or three days. In our Case v, however, a definite reaction was not obtained until the twelfth day, though in the acute cases the response was more rapid.

Valuable results of experimental inoculation with cultures of *B. mallei* have been worked out by Nicolle, who details the various types of lesions following inoculations into guinea-pigs of different ages and sex. He proved the marked vulnerability of the tunica vaginalis of the adult male, the greater resistance of the female, and the still greater resistance of the young male guinea-pig.* From this it seems feasible to conclude that several animals should be used, and these adult males only, and that varying doses should be inoculated. Further, he showed that the testicular lesion is not the only one of importance, though in the later stages it is a striking one.

Bacteriological Diagnosis.

The *B. mallei* in the lesions are generally very scanty, and even in the acute abscesses it is often impossible to find them, so that in apparently sterile pus it may be recommended to bear glanders infection in mind. The bacilli are difficult to stain, and are Gram negative, and where there is much cell degeneration the deeply-staining detritus masks the bacilli and increases the difficulty. In four of our cases it will be noticed that in films of the pus from the abscesses only one or two bacilli were found after prolonged search (Fig. 6). They stained well with weak carbol-fuchsin warmed for some time, but we found it much more satisfactory to stain with carbol-thionin blue or carbol-gentian violet after a preliminary treatment with acetic acid, and where the cell degeneration was most marked, as in sections, this latter method was most valuable (see Fig. 7); but in most cases equally good results were obtained with a modified Romanowski's stain. The size of the bacilli and the definite beading are fairly characteristic (see Figs. 6 and 7). With careful staining they were found in greater numbers in the lung tissue of our cases than at first appeared.

In contrast to the difficulties of bacterioscopic diagnosis the cultural characteristics are so definite and so constant as to render the diagnosis simple. Smears of pus,

* Since writing the above, one of us (J. M. B.) has met with an, as yet unclassified, streptothrix which caused a fatal suppurative pneumonitis in a man, and which, when inoculated intraperitoneally into guinea-pigs, causes a rapid and enormous enlargement of the testicles, with immobility, etc., and severe general symptoms. The details of this will be published at length later, but it is worthy of note here.

which is generally uncontaminated in the unopened abscesses or farcy buds, on glycerine-agar produce in twenty-four hours a gelatinous confluent growth, and on potato a brownish growth in forty-eight hours, which later darkens, and after some time may become of a chocolate tint. Compared with the brownish growth of *B. coli* it is darker, more gelatinous, and more luxuriant, yet in one of our cases the organism was at first described as coliform. The question of motility is of importance in this respect.

Note on B. mallei.

The *B. mallei* is by all authors said to be non-motile and often showing active Brownian movements. The strains obtained by us were to all appearances, however, actively motile, and many individual organisms were seen to move across the field of vision. Repeated observations strengthened our suspicion that the *B. mallei* is truly motile, despite the fact that no flagella could be demonstrated by any method of staining. Mr. E. N. Nelson has for long held that he can see flagella, and with him we are inclined to agree.

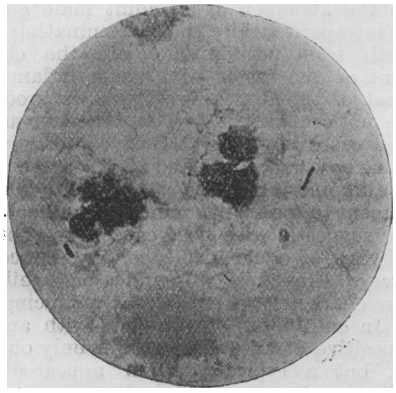


Fig. 6.—Two bacilli, the larger one showing beading, in the pus taken during life from a superficial abscess. (× 1,000.)

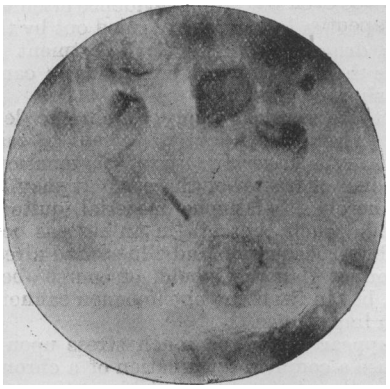


Fig. 7.—Single bacillus seen in focus and two out of focus in section of lung. (× 1,400.)

There is another point that we wish to note concerning the vitality of *B. mallei*. It appears to be generally taken for granted that the organism soon dies out on culture media and when grown for long as a saphrophyte loses its virulence. Our experience with our strains cannot confirm this. A potato subculture from the blood of Case II was kept in the cold incubator for twelve months from August, 1905, and then, even, subcultures from this grew slowly and proved virulent for a guinea-pig. From the organism, reobtained from the animal, subcultures were successively made in November, 1906, January, 1907, and in May, 1907, showing a capacity for remaining alive for months. It must be added, however, that a glycerine-bouillon flask inoculated in May, 1907, failed to give subcultures in August, 1907, the flask containing a prolific mass of organisms arranged in long chains and sometimes branching — a pleomorphism often described. Some of these long kept cultures on potato were inoculated into guinea-pigs in fairly large doses, but beyond raising the temperature and producing some malaise produced no fatal results.

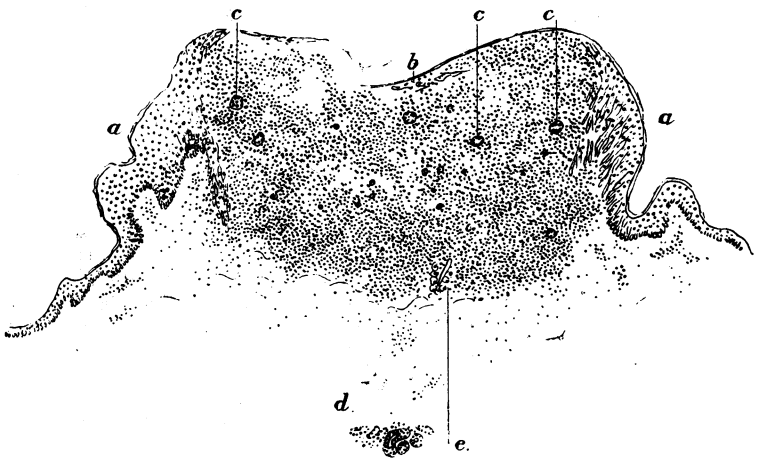


Fig. 8.—Drawing of section of pustule in skin of glanders (Case II). *a*, Thickened epidermis—acanthoric oedema. *b*, Horny layer of epidermis. *c*, Large round bodies containing many round deeply-stained masses probably balloon or swollen epidermal cells. *d*, Sweat gland. *e*, Hair or part of hair follicle from which epidermis has been torn away; cell infiltration consists of round cells (probably polynuclears for the most part). (From a drawing by Dr. H. G. Adamson.)

HISTOLOGICAL DIAGNOSIS.

There is only one feature that may perhaps be regarded as characteristic of glandrous lesions, namely, the peculiar nuclear degeneration known as *chromatotexis*. This, indeed, is found in some other necrotic lesions, but in glanders the process is very considerable and constant, beginning very early, so that in small foci the deeply-staining detritus resulting from this degeneration is a striking feature (Figs. 3 and 5).

The question as to whether the lesions are true abscesses or granulomata is still debated. According to McFadyean the former is the case in horses, whilst Unna describes the lesions in man as consisting of epithelioid cells derived from proliferative connective tissue cells. In our most acute case (I), though polymorphonuclear cells were found in films from the pustules in life, the sections *post mortem* showed cells for the most part with round, indefinite nuclei, which may, of course, have contracted after death. In the more recent lesions in the lungs, however, the polymorphonuclear cells predominated; hence we are inclined to consider the lesions as comparable with local abscesses, with rapid liquefaction and marked chromatotexis, with in the more chronic foci, an additional element in the form of connective tissue cells, due to the proliferative reparative process.*

No giant cells, such as described by others, were found in any of our sections, though the ballooned epidermal cells (Fig. 8) might at first glance be mistaken for giant cells. In Case V, in the light of our present knowledge, we think that the marked chromatotexis in the floor of the ulcer would prevent us overlooking the diagnosis in a similar condition.

BLOOD EXAMINATION.

McFadyean remarks, in discussing the *B. mallei*: "It is a tissue parasite, and in all cases of glanders and farcy in horses the bacilli are almost entirely confined to the lesions and discharges from them; no doubt they are transported by the blood as well as by the lymph, but in horses there is never a septicaemia." Considerable quantities of blood of affected animals have failed to transmit the disease after experimental inoculation, and it is almost impossible to find the bacilli in the blood of acute cases in horses.

Sections of lung in Case II bear out this view. In Case II, the only one in which blood cultures were made, the *B. mallei* were only obtained in the blood drawn shortly before death, and it is most probable that this was merely a terminal infection, such as seen in many other infections. Experimentally, also, the organisms after inoculation into the veins rapidly disappear from the blood and become localized; a somewhat analogous condition was seen in Case II, where the

* Duval and White working recently with experimental glanders support this view.

organisms set up an arthritis early in the course of the illness.

Leucocytosis does not seem to be a marked feature; in two acute cases (Pilcher) there was no leucocytosis, whilst in one of our chronic cases there was a slight increase (19,000), but no increase of the polymorphs; and in an acute case of Wherry's there were 21,000, but he does not mention a differential count.

Agglutination Test.—In horses McFadyean has obtained positive agglutination phenomena in very weak dilutions—1 in 1,600 as compared with 1 in 300 in healthy animals. Dr. Eyre tells us that in 3 cases recently admitted to Guy's Hospital the serums agglutinated *B. mallei* in dilutions of 1 in 100. In our Case II no definite results could be obtained, and various observers have obtained different results; so at present the value of this diagnostic procedure must be regarded as indefinite.

Mode of Infection.

In none of our cases was there definite evidence of the point of inoculation or path of infection, and the general evidence, clinical and experimental, on both these questions is so conflicting that the time is hardly ripe for the expression of decided opinions. The hypothetical paths are by direct inoculation through a wound or by the hair follicles, by inhalation or by ingestion.

Direct wound infection is conclusively proved by laboratory accidents; glanders has been assigned as the most frequent cause of accidental death amongst laboratory workers.

As to the hair follicles, Babes performed numerous experiments on guinea-pigs, rubbing in an emulsion of *B. mallei*, and succeeded in producing infection. Nocard, however, repeated the experiments with indefinite results.

Infection by ingestion has been definitely proved, in horses, by MacFadyen, but the comparative frequency of respiratory lesions and the infrequency of abdominal, in man, suggests that the problem will be as difficult of solution as that which has to be faced in the case of tuberculosis. Gutowski pointed out that ward infection does not occur, and in this connexion we may record that one of our acute cases on several occasions was allowed to breathe through an apparatus containing glycerinated broth, which however remained sterile. It is obvious that no stress can be laid on an experiment under such conditions. The fact remains, however, that contact, not only directly with infected sputum and discharges, but even with soiled fomites, may be dangerous.

Weichselbaum and Phillipowicz have recovered *B. mallei* from the urine, and Cao from the milk of sick mares. Cao also observes that the *B. mallei* remains virulent after passing through the alimentary canal of flies and other insects.

Although it is generally recognized that knackers and others dealing with glandrous carcasses are rarely infected, yet the case is different with man, because the disease is necessarily allowed to proceed to the bitter end; and it is only in the latest stages that the organism becomes generalized in the blood, which is then highly infectious.

Extension from a primary local lesion, if it occurs, does so in the first instance by the lymphatic vessels; and this, unlike the blood infection that may ensue, is not necessarily fatal.

Latency of the bacillus in the tissues is well recognized, for the records show many cases in which entire quiescence was observed for several years, yet admitting of a fatal outburst. Babes states that he found encapsuled glandrous nodules in the viscera—especially the lungs—of knackers and others dying of some other disease, and discusses the question of occult glanders.

The incubation period varies within wide limits. For instance, in the recent Czernowitz laboratory accident the disease broke out amongst several of the staff in a few days after the scattering of the bacilli by the breaking of a centrifuge tube; in Stewart's case, after the autopsy on a guinea-pig, the first symptom appeared in six days; in Pilcher's case, six weeks after a bite by a glandrous horse.

In conclusion, we must express our thanks to Dr. Hebb for much valued advice; to Dr. Colcott Fox for kindly having had made for us the photomicrographs (Figs. 6 and 7); and to the staff of the hospital and to Mr. C. C. Choyce, for permission to make use of their cases.

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ANAESTHESIA IN THE HUMAN SUBJECT WITH KNOWN PERCENTAGES OF CHLOROFORM VAPOUR.*

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INTRODUCTION.

THE theory and practice of anaesthesia are too often spoken of as distinct and even antagonistic entities. This view is founded on a misconception. Theory is based on practice, and on that alone; and if in practice by careful and accurate measurement any facts appear that are not accounted for by the theory, this must be due to some error in the latter.

There is, however, a suppressed premiss in the statement of the case that is often the unconscious basis of such ideas. It does not necessarily follow that the facts observed on healthy animals can be applied without correction to the pathological conditions often met with in the human subject. It is, therefore, by no means waste of time to examine as carefully and accurately as may be, details of anaesthesia in man that have already been carefully studied in the lower animals, and this is what has been attempted in the observations that are recorded in the present paper.

It is, perhaps, a truism to say that our knowledge of any subject is in direct proportion to the accuracy with which exact measurement can be applied to it. Yet this

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