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The Brown Animal Sanatory Institution

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Chapter 8. RESEARCH WORK AT THE INSTITUTION

2. SYSTEMS OF THE BODY

The 10 or 11 years between 1884 and 1895 during which Victor Horsley and Charles Sherrington in succession superintended the Brown Institution constituted probably the most fruitful period of its existence. As Stephen Paget wrote (1919) it was 'a place of great importance, not only as a veterinary hospital, but as the chief centre in London of advanced research in pathology and physiology. It was crippled by lack of funds, but it did admirable work.' The Institution, small and out of the way though it was, had great influence and authority; it set the standard of research; and to be working at it was of itself a notable privilege.

In the 6-year period 1884 to 1890 of his superintendentship Victor Horsley (later Sir Victor) did most of his best research work, including that on the nervous system, the thyroid gland, and rabies; and in the following 4-year period Charles Sherrington completed his pathological studies and started, or rather more than started, his notable work in the field of neurology.

The Nervous System

Among Horsley's early investigations was that into canine chorea, a sequela of distemper. He found the disorder of mechanism to be in the spinal cord. The lesion appeared to be inflammatory; later it passed on to sclerosis, identical with disseminated sclerosis in man.

The discovery by Fritsch & Hitzig (1870) that the cerebral cortex could be stimulated by an electric current opened up a wide field of inquiry into which several investigators entered. In 1884 with Edward Schăfer (later Sir Edward Sharpey-Schăfer), who was Jodrell Professor of Physiology at University College, London, Horsley began his study of the functions of the cerebral cortex, and more particularly the character of muscular contractions evoked by excitation of various parts of the motor tracts. Later, with Dr D. E. Beevor (Beevor & Horsley, 1889), he concentrated on the localization of motor function in the brain and spinal cord. Together they made a minute analysis of the representation of movements in the so-called motor region of the cortex cerebri. The centre for any particular movement was defined by the weakest faradic current that evoked a response (primary movement). By increasing the length of application of the current further movements of a secondary nature were observed, obeying the laws

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of spread of the effect of a stimulus, referred to in Hughlings Jackson's term – the 'march' of the spasm. There was no abrupt passage from the representation of one movement to that of another, though each movement was most represented in one definite and constant spot. Thus the movements of the various segments of the upper limb were represented chiefly in the cortex in order from above downwards, i.e. shoulder, elbow, wrist, fingers, and thumb. Likewise the arrangement of fibres in the internal capsule followed the same relative order and position as the centres projected on the cortex cerebri of the same hemisphere (Beevor & Horsley, 1889). In this way Horsley and Beevor charted the areas responsible for motor excitation of the muscles of the upper and lower limbs and the face.

Together with Dr Felix Semon, Horsley studied experimentally the innervation of the laryngeal muscles in order to explain the paralysis of the recurrent nerve which leads to 'roaring' in horses and distressing results in man. This subject was taken up by other workers at the Brown, mainly with a view to correcting it by surgical means (see p. 514). Horsley & Semon also studied the phonatory centre in dogs described by Krause, and demonstrated the existence of an area – the anterior half of the foot of the ascending frontal gyrus – in which adduction of the vocal cords, as in phonation, is bilaterally represented.

Horsley and Beevor continued their researches on the motor region of the cerebral cortex. In particular, they studied the synchronous turning of the head and eyes to the opposite side, analysed further the facial region, and incidentally showed that the xith nerve, and not the viith, was the motor nerve to the soft palate. (For a short account of Horsley and Beevor's work at the Brown, see Burgen, 1976).

Horsley was very interested in the causation of so-called ideopathic epilepsy. Working with Dr Hughlings Jackson, he divided the spinal cord above the atlas vertebra and injected 1 or 2 minims of absinthe intravenously. This drug had been shown by Magnan in France not only to render an animal insensitive to pain, but also to be capable of evoking an epileptic fit. Horsley noted that convulsions were limited to muscles innervated from parts above the section. Using the absinthe method again, he found that in epilepsy the efferent or motor discharge started in the cortex cerebri, and not in one of the lower motor centres.

Turning from the motor nerves to the sensory, Horsley studied with Dr H. H. Tooth the course of afferent fibres in the spinal cord by following the upward degeneration that occurred after section at any one point. Dr F. W. Mott (later Sir Frederick) had already used this method when he destroyed in monkeys some of the roots of the cauda equina and followed the direct course of the fibres ascending the cord from the posterior roots. Finally, Mr Walter Spencer and Victor Horsley (1890) studied the effect of an increase in intracranial pressure on the circulation and respiration in the dog and the monkey. To increase the pressure, a small rubber bag was inserted through a trephine hole in the skull. Distension of the bag by means of a column of mercury served to show not only the pressure used, but also the extent to which the bag was distended. When the pressure was increased on any part of the brain, the heart, blood pressure and respiration were all affected in varying degrees; but when the bag was passed into the cavity of the

4th ventricle it was found possible to separate the effect on the heart, blood pressure, and respiration. Under these latter conditions the heart was slowed and finally arrested, but only after a considerable increase in intracranial pressure was exerted. Section of the vagus nerves restored the cardiac contractions. The blood pressure, after an initial rise, fell apparently independent of the heart; though, when the heart started again, it rose. The effect on respiration was one of impairment and arrest. This reacted on the heart so that, after the rise of blood pressure, respiration occurred again. By the application of pressure in the upper part of the 4th ventricle, the heart slowed down, the blood pressure rose, and respiration became so rapid as to be nearly three times the rate of the heart. Pressure below the calamus scriptorius stopped the respiration without influencing the heart; and pressure still lower down impeded the respiration and to a lesser extent the heart, and brought about a fall in the blood pressure.

Finally, it may be noted that in 1884, when he was only 27 years old, he made an important contribution to knowledge by demonstrating the existence of *nervi nervorum*.

Charles Sherrington (later Sir Charles), when he replaced Victor Horsley as Superintendent in 1891, studied the distribution of the spinal nerves to the muscles of the limbs in order to throw light on the phenomena of paralysis and spasm, and to define the exact localization of the seat of lesions inducing symptoms of that class. Then, taking up again a subject on which he had previously made some observations, namely the knee-jerk, he showed that its localization was in the vastus internus muscle and depended for its existence on the integrity of the reflex arc. On the correlation of antagonistic muscles he wrote: 'Thus the degree of tension in one muscle of an antagonistic couple intimately affects the degree of "tonus" in its opponent, not only mechanically, but also reflexly, through afferent and efferent channels and the spinal cord.'

Sherrington, whose reports to the Committee of the Brown Institution were much shorter than those of his predecessor, continued the work carried out earlier by Mott and by Horsley on secondary degenerations in the spinal cord. He explored the sensory root distribution, and charted a series of segmented skin fields. From this work he concluded that each bunch of many sensory nerve trunks in the limb consisted of fibres which entered the cord by two or three distinct posterior nerve roots. Each root, however, possessed a single field of cutaneous distribution, not one of separated patches as had been previously supposed. Thus he introduced the conception of overlapping skin areas which, as Liddell (1952) says, was soon to seed itself in clinical fields.

Sherrington published an account of his work at the Brown in a seeies of 32 papers, most of which were on the nervous system (for a list see Liddell, 1952). It was a highly productive period, and was the forerunner of a long series of researches, the description of which was embodied in over 250 papers, articles and books during the next 55 years.

After Sherrington's departure in 1895, little further work on the nervous system was carried out at the Brown. Dr Ballance (later Sir Charles) and Dr Purves Stuart (later Sir James) investigated the regeneration of nerves after injury; and

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Dr Alexander Morrison innervation of the viscera. The golden era had passed, and was to be replaced by studies on other systems of the body.

Blood and Circulatory System

Numerous workers carried out investigations under this head, but the results they obtained deserve but passing notice.

Dr L. C. Wooldridge studied the albumen of the blood, and the vexed subject of coagulation. Unlike the current belief that it involved active participation of the corpuscles, he found that it was the plasma which was essential. He thought that coagulation resulted from the combined action of two substances, provisionally named Fibrinogen A and B, which led, with the help of lecithin, to the formation of fibrin.

He also isolated from fresh animal tissues – particularly the testes and thymus of the calf – a substance that caused instant death from intravenous coagulation when injected into the blood of an animal. At *post mortem* the whole vascular system was completely thrombosed, and the clotting in the portal vein led to haemorrhagic infarction of the liver. The substance responsible appeared to be a combination of protein and lecithin. Unfortunately Dr Wooldridge, whom Victor Horsley regarded as one of the most constant, original, and successful of the visiting workers, died before he was able to follow up these observations further.

Charles Sherrington interested himself in the behaviour of leucocytes in normal and inflammatory blood; Dr Batty Shaw in leucocytosis; Dr Walter Edmunds in the lymphatic system; and Dr C. C. Twort in infection of the lymph glands after intraperitoneal inoculation, and in the destruction of bacteria within them. Mr Harold Barnard investigated the function of the pericardium, and the pathology of pleural effusion; and Dr T. G. Brodie and Dr Winifred Cullis the exchange of gases between the blood and the alveolar air.

Liver and Genito-urinary System

Starting with Dr J. Rose Bradford's (later Sir John) work on the innervation of the renal blood vessels, a number of investigations were made during the years 1895 to 1908 on uraemia and chronic nephritis. In 1889 at University College, London, Rose Bradford had studied the spinal distribution of the nerves controlling the kidneys in dogs, and found that the vasoconstrictor nerves originated from the 4th thoracic to the 4th lumbar roots of the cord. At the Brown he went on to study the origin of uraemia. By removal of increasing amounts of the kidneys in dogs he showed that renal function remained intact till the total kidney volume had been reduced from the normal 6·7 g/kilo of body weight to 2 g/kilo. Below this amount the dog became emaciated, passed urine profusely, and suffered from a great accumulation of urea in all its tissues. Polyuria was of special interest in explaining the prominence of this symptom in chronic nephritis when much of the kidney had been destroyed by inflammation. Rose Bradford went on to study the reasons for renal hypertrophy and atrophy. He also, along with Dr Hugh Smith, investigated cirrhosis of the liver in cats.

The subject of chronic nephritis was taken up again by Dr T. G. Brodie in the early years of the 20th century. The occurrence of haemorrhagic infarction of the liver was observed by Dr Wooldridge (p. 504). In 1925–6 Dr Stanford Cade (later Sir Stanford) investigated the experimental production of gall-stones in dogs. In 1908 Dr Brodie and Professor S. G. Shattock carried out a series of cocaine injections into the bladder to see what effect was produced upon micturition when the mucosa was rendered anaesthetic; and in 1904 Mr C. S. Wallace (later Sir Cuthbert) removed the testes in order to observe what effect this had on the nutrition of the prostate. Dr A. G. Auld worked on the suprarenals.

The Ductless Glands

At the time, 1884, at which Victor Horsley became Superintendent of the Brown Institution little was known of the function of the thyroid gland; and no one had realized its great importance in maintaining homeostasis in the mammalian body. Two to 3 years earlier Kocher and Reverdin in Switzerland had found that operations on the thyroid gland for goitre were followed by myxoedema. Horsley took up the study of the thyroid at the request of the Clinical Society. Working on monkeys, cats and dogs, he made such rapid progress that within a year he was able to give two lectures embodying his results entitled 'The Thyroid Gland and its Relation to the Pathology of Myxoedema and Cretinism; to the Question of the Surgical Treatment of Goitre, and to the General Nutrition of the Body' (Horsley, 1885, 1886).

Removal of the thyroid in young cats and dogs led to the rapid appearance of violent nervous symptoms and to death in a few days. In older animals the symptoms were less violent and later in their appearance, and death did not occur for two or three weeks. In very old animals removal of the gland simply hastened the torpor of old age. Adult monkeys survived thyroidectomy for six or seven weeks, and died of myxoedema. Horsley pointed out that the gland was of extreme importance when tissue metabolism was most active and diminished in importance as the senile state advanced. He drew attention to the fact that the symptoms of old age, i.e. wasting of the actively functional parenchymatous tissues, atrophy and falling out of the hair, decay of the teeth, dryness and harshness of the skin, tremors and so on were likewise the most prominent features of the myxoedematous state, whether it occurred naturally, prematurely as in cretinism, or artificially as after operation in monkeys. The changes in the experimental animal were delayed by maintaining it at a higher temperature, e.g. 90 °F, and occurred in three stages. In the first and second stages – the neurotic and the mucinoid – the symptoms were subdued, but in the third or atrophic stage there was great emaciation, functional paresis and paralysis, imbecility, falling blood pressure and temperature, and death in coma. The failing nutrition was manifested by a weakened tetanoid response to cortical stimulation succeeding a heightened response a day or so after thyroidectomy. Ultimately the nerve centres became so depressed that stimulation induced practically no reaction.

Besides having a profound effect on metabolism, Horsley concluded that the thyroid gland regulated the formation of mucin in the body and aided the manufacture of the blood corpuscles. This last conclusion was based on the observation that blood corpuscles were more numerous in the thyroid vein than in the artery. Whether this observation has ever been confirmed, I do not know; but considering the very primitive nature of the technical apparatus available in Horsley's day, it is probable that the difference in the counts, which was not more than 10 per cent, was due to experimental error.

Horsley's further researches on the function of the thyroid gland were interrupted by an investigation into the etiology of rabies and its prophylactic treatment by M. Pasteur, begun in May 1886 at the instance of a committee appointed by the House of Commons of which he was made Secretary. Dr Walter Edmunds, however, continued his work, concentrating at first on Graves's disease. He remained as a visitor at the Brown for many years. In 1900 he summarized his work on the physiology and pathology of the thyroid body in lectures delivered at the Royal College of Surgeons, and in 1905 was studying the effect of removal of the thyroid and parathyroid glands.

Horsley's results clearly showed that the treatment of goitre and cachexia strumipriva by thyroidectomy was wrong in both principle and practice. He proposed instead, as Schiff had before him, to transplant the thyroid gland of a sheep to the human patient. This treatment was, of course, later replaced by oral administration of the thyroid, as introduced by Dr George Murray, and later still by the active principle itself, namely thyroxin, after it had been synthesized by Sir Charles Harington at University College Hospital Medical School.

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Chapter 9. RESEARCH WORK AT THE INSTITUTION

3. Diseases of animals

The diseases among animals brought to the Institution for treatment have been summarized in the section in Chapter 6 describing the work of the Animal Dispensary. The present chapter is concerned with experimental work on animal diseases carried out mainly on animals bought in specially for the purpose. Apart from Victor Horsley's work on rabies, and Greenfield's development of a vaccine against anthrax (see Chapter 7), few investigations of note, comparable for example with those on the nervous and endocrine systems (see Chapter 8), were performed. In view of the fact that the superintendents of the Institution were all medical men, and that the numerous visitors there included very few veterinarians, this is perhaps not surprising. Though the Institution was intended primarily for the prevention and treatment of animal diseases, the truth is that at the time it was founded in 1871 and for many years afterwards research workers in the veterinary profession were practically non-existent. Towards the end of the century McFadyean (later Sir John), who held both a veterinary and a medical qualification, approached the study of animal disease from the research angle; but apart from two or three disciples who were closely associated with him, he left no one to copy his example. He was a lone worker and founded no school of veterinary research. It was not till the Agricultural Research Council in the thirties of the present century promoted the development of veterinary research into diseases such as tuberculosis, contagious abortion of cattle, mastitis, and Johne's disease, that a field for veterinary graduates was opened up, and rapidly exploited by whole-time employees of the Council.

Another reason why much of the research on animal diseases at the Brown Institution proved comparatively fruitless was that the time was not yet ripe for the solution of the problems attacked. With the exception of rabies, against which Pasteur empirically prepared a vaccine, the technique for investigating the virus diseases had not been developed. This failure was not an isolated or even uncommon experience. In various branches of science, research in certain subjects has been brought temporarily to a halt, because neither the knowledge nor the technique that were necessary for success, and that often had to come from other fields of inquiry, were sufficiently advanced at the time. Any investigations, therefore, on the subjects in question were bound to be premature. One of the distinguishing characters of great men is their ability to select intuitively problems that are capable of solution by the current means available – using 'intuition' to mean, broadly speaking, the imagination playing on previous experience, much of it unconsciously remembered.

Rabies

Besides his study of the nervous system and the function of the thyroid gland (see Chapter 8), Victor Horsley devoted much of his time at the Brown to the diagnosis, prevention, and control of rabies. Most of this work was a confirmation of Pasteur's findings; but the struggle for the extirpation of the disease by the universal imposition of a muzzling order on dogs, coupled with the destruction of stray animals and restriction on importation, was his own, and possibly his greatest contribution to the public welfare (See Horsley, 1889).

As mentioned earlier, Horsley took up the study of rabies as the result of his appointment as Secretary to a committee appointed by the House of Commons. He first of all repeated Pasteur's experiments on laboratory animals and confirmed them in every detail. Turning to human beings, he concluded that in young children bitten on the face by rabid dogs the incubation period might be as short as 6 days, so that treatment unless started at once might be too late. On the other hand, in some cases 2 years might elapse before symptoms of the disease appeared. He calculated that Pasteur's method of treatment reduced the incidence of the disease in persons bitten by rabid or supposedly rabid animals from an average of about 15 to one of 1·36 per hundred.

The laboratory diagnosis of the disease then occupied his attention; and after a number of experiments he finally recommended the following method, based again on Pasteur's findings. The spinal cord of the suspected animal should be preserved in 10 per cent glycerolated water, crushed in broth in a mortar, and injected through a small trephine opening into the subdural space of rabbits. Rabbits were the animals of choice, since the disease, which appeared after the incubation period of 14 days, was paralytic from the start. Death occurred after 4 days. By applying this method to material from deer that were suffering from an epidemic illness of doubtful origin in Richmond Park during the years 1886 and 1887, he showed that the outbreak was not one of poisoning, as was at first thought, but one of true rabies – of the furious form. Again, by applying the same method to material of human or animal origin, he was able to give figures year by year of the number of genuine cases of rabies in Great Britain, as judged by tests made on specimens sent to the Institution for diagnosis.

The muzzling Orders

Victor Horsley had not been long at the Brown Institution before he was impressed by the importance of rabies and the risk the population suffered from bites by stray dogs. In 1885 there were 26 deaths in human subjects from the disease in London alone. His practical sense showed him the way in which such deaths could be prevented; and impelled by his pioneering spirit he determined to take action. To quote from his obituary notice by one of his colleagues, Dr Mott (1920), in the Proceedings of the Royal Society: 'The scientific acumen, courage, strength of will and determination of the man was shown in a remarkable manner in his successful efforts to stamp out rabies by muzzling of all dogs. Fortunately, Mr Walter Long was, at the time, President of the Local Government Board, and to these two men, who had the courage of their convictions, the nation owes a deep debt of gratitude for resisting the clamorous attempts made by the public to relax or abolish the Acts until it seemed safe to do so.'

A Muzzling Order was introduced for London in November 1885, and rabies was later scheduled by the Privy Council. By 1887, after this Order, combined with the destruction of stray dogs, was enforced in London, not a single rabid animal was brought to the Institution. In the rest of the country, however, rabies still remained prevalent. Lancashire was the worst centre; in the first ten months of 1887, 75 cases in dogs and 37 human cases were reported in this county alone. In July 1889 the muzzling regulations were applied to all centres of infection and to the surrounding districts. Before, however, these were confirmed rabies had re-invaded the metropolitan area where the Order had been suspended; but after the Order had been re-imposed in London and extended to the country as a whole, only one further case occurred in the metropolitan area, affecting a boy who had been bitten by a dog 2 years previously. A few cases occurred outside London, but for all practical purposes the disease became extinct. Few other examples are extant of the almost immediate eradication of a disease by the application of scientific methods of control; and few other workers could claim such a triumph as Horsley was able to do.

Diseases of Cattle

Among the diseases of cattle that occasionally assumed epidemic proportions, cattle plague, pleuropneumonia, foot-and-mouth disease, and splenic fever occupied a prominent place at the time the Brown Institution was established in 1871. There had been a major epidemic of *cattle plague* (Rinderpest) in England in 1865 in which the disease, imported from Russia via the Baltic, killed off 500 000 cattle. Burdon-Sanderson, the first superintendent of the Brown, had established the infectivity of the blood and mucous discharges. Prevention lay in a complete embargo on the importation of cattle from infected areas. Control of an outbreak consisted in the slaughter of all ruminants and pigs that had been exposed to infection, together with suitable disposal of their carcasses, disinfection of the premises, strict quarantine for several miles around, and the keeping of susceptible stock away from the infective focus (Burdon-Sanderson, 1866). A smaller outbreak occurred in 1877. This was investigated by Mr Duguid, the veterinary assistant at the Brown, in collaboration with the Veterinary Department of the Privy Council. It was rapidly dealt with and caused no serious loss. It may be noted that the preventive and control measures recommended by Burdon-Sanderson for cattle plague in the 1870s had already been laid down by Monsieur Turgot in France 100 years before (see Condorçet, 1787). Substantially, they are those current at the present day (see Henning, 1956).

Pleuropneumonia and Foot-and-Mouth Disease

In 1874 an arrangement was entered into between the Committee of the Brown Institution and the Council of the Royal Agricultural Society for investigating pleuropneumonia and foot-and-mouth disease; and in 1875 the Society presented the Institution with £500 for this purpose. In a preliminary report Burdon-Sanderson (1876) says that the Committee had purchased 2 milk cows, 2 calves, and 4 other animals. All had been kept in quarantine for 3 months and had remained healthy. Experiments were then carried out to discover whether infection

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with pleuropneumonia could occur in any other way than by direct contact. In a concluding report in 1879 it was stated that the experiments started in 1876 had had to be brought to an end in consequence partly of the legislative difficulties that stood in the way, and partly of the absence of suitable cases of pleuropneumonia in the neighbourhood with which to carry out experiments on the prevention of infection. The few experiments that had been possible had failed to demonstrate the occurrence of infection by indirect transmission.

In an attempt to immunize animals by preventive inoculation, exudate from the lungs of infected animals was injected into the shoulder or the side of the neck of cattle. These sites were chosen because the current practice of injection into the tail often resulted in gross inflammation; the tail sloughed off and the animal died – presumably owing to secondary infection, though little was known about the nature of this at the time. The shoulder and neck, however, proved likewise unsatisfactory, and it was decided to inject the exudate directly into the blood stream (Burdon-Sanderson, 1879). Quantities of 1 to 3 drachms (2–6 ml) were injected into an ear vein; and the process was repeated after some weeks. Only one out of seven animals injected suffered from serious ill effects; this was a cow with old lung disease. The six other animals were exposed to infection but remained well over a period lasting up to 6 months. Another six animals were injected intravenously, but, as there were no infected animals in the neighbourhood to which to expose them, they were got rid of, and the experiments, as already mentioned, abandoned.

On account of the small number of animals used, conclusions had necessarily to be tentative. Pleuropneumonia was considered to be a virus disease with a long incubation period, often some months. It was spread mainly by direct contact; and it appeared to be prevented by the intravenous injection of infected exudate. Insufficient observations, however, had been made to determine the duration of immunity. For purposes of control, infected animals and apparently healthy animals that had been in direct contact with them should be slaughtered, and the usual disinfection measures carried out.

The pathological anatomy of pleuropneumonia was studied by Dr Yeo, Professor of Physiology at King's College, London, who made a valuable and comprehensive report to the Royal Society of Agriculture (Yeo, 1878).

No mention is made of the other subject to be investigated, namely foot-and-mouth disease. One can only surmise that legislative difficulties, as with pleuropneumonia, interfering with the movement of infected cattle from one area to another, were at least partly responsible. Some years later, Dr Klein (1886) reported the finding of a micrococcus that he considered to be responsible for the disease; but not till 1898 was the real causative agent shown by Loeffler and Frosch (1898*a*, *b*) in Germany to be a filtrable virus.

Anthrax

Both Dr Burdon-Sanderson, the first Superintendent, and Mr Duguid, the Veterinary Assistant, were concerned in the investigation of splenic fever (anthrax). In 1878 Mr Duguid visited the scene of two outbreaks, one of them at a farm at

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Rigsby in Lincolnshire, where upwards of 50 animals died in a few days. In connexion with this, Dr Burdon-Sanderson (1880) carried out experiments which showed (1) that the disease could be transmitted to small rodents and that, when transferred back to cattle, the infection gave rise to a much milder disease than the original; and (2) that the poison of anthrax could be readily communicated by various food materials for cattle, and particularly by brewers' 'grains', in which the poison multiplied indefinitely so that the whole bulk became poisonous.

Dr Roy, the third Superintendent, obtained 3 months' leave of absence to investigate an epidemic of undiagnosed disease in the Argentine. This he identified with splenic fever, and successfully protected mice against it by inoculation with anthrax material that had been passed through the vizcacha or prairie dog. The credit, however, for preparing an effective vaccine against anthrax, for use in cattle and sheep, must go to Dr Greenfield, the second Superintendent, whose discovery anticipated by a short time that of M. Pasteur (see Chapter 7).

Dr Plimmer, and Dr Rose Bradford, the sixth Superintendent, spent 2 or 3 years studying the pathology of *tse-tse fly disease* in cattle. Later, Dr Plimmer and Mr Ranken experimented with the use of antimony in protecting against trypanosomiasis; and Dr Plimmer, together with Captain Bateman and Captain Fry, studied the disease and its treatment in dogs.

Dr C. C. Twort, brother of the Superintendent F. W. Twort, worked during 1912 and 1913 as a Beit Memorial Fellow on immunity reactions in *Johne's disease.* He found that complement-fixation and agglutination tests were not specific enough to distinguish infection caused by Johne's bacillus from that caused by other acid-fast bacilli, such as the various types of tubercle bacilli. He likewise experimented with the production of Johne's disease in rodents. Dr F. W. Twort, with the Veterinary Assistant Mr Ingram, prepared vaccines against Johne's disease. This task was attempted by several subsequent workers. Only partial success was obtained; and it was not for many years, in fact not till after the closure of the Brown Institution, that Doyle (1964) at the Ministry of Agriculture's Veterinary Laboratory at Weybridge reported that during the past 20 years he had found that vaccination of calves 3–4 weeks old with a preparation of living non-virulent bacilli suspended in equal parts of olive oil and liquid paraffin to which pumice powder was added as an irritant, combined with the usual precautionary hygienic measures, afforded a high degree of protection against natural infection.

Dr Bernstein worked on vaccinia in calves; and Dr Monckton Copeman and Dr Blaxall experimented with *vaccinia* and *variola* in the lower animals.

Lord Pembroke provided a grant in 1881 for the investigation of distemper in dogs, with particular reference to finding out whether a method of protective inoculation could be devised. Here again, as with Johne's disease of cattle, the discovery of such a method had to wait for about 50 years before Laidlaw & Dunkin (1928, 1931) succeeded in immunizing dogs and ferrets with formolized vaccines prepared from infected ferret spleen or from the liver, spleen, and lymph nodes of infected dogs.

Other subjects that claimed attention were glanders and South African horse

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sickness. Melanosis in horses was studied by Charles Ballance (later Sir Charles) and Professor Shattock; swine fever by Dr T. Evans; an infectious disease of the Australian Diamond cock sparrow by F. W. Twort; swayback in sheep and ankylostomiasis in dogs by C. C. Twort; and an infectious disease of dogs leading to tumour formation by Dr Washbourn and Mr Smith.

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Chapter 10. RESEARCH WORK AT THE INSTITUTION

MISCELLANEOUS RESEARCHES

The opportunities provided by the Brown Institution attracted a great number of workers interested in a great number of different problems. In the three preceding chapters many of these have been described or referred to; but there remain a number of others that must be relegated to a miscellaneous collection. A few of these will now be recounted.

Surgical Procedures

After the introduction of anaesthesia towards the middle of last century it became possible to undertake operative procedures on the human and animal

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sickness. Melanosis in horses was studied by Charles Ballance (later Sir Charles) and Professor Shattock; swine fever by Dr T. Evans; an infectious disease of the Australian Diamond cock sparrow by F. W. Twort; swayback in sheep and ankylostomiasis in dogs by C. C. Twort; and an infectious disease of dogs leading to tumour formation by Dr Washbourn and Mr Smith.

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Surgical Procedures

After the introduction of anaesthesia towards the middle of last century it became possible to undertake operative procedures on the human and animal body that were almost inconceivable before. To attempt these directly on human patients would often have been too hazardous. An entirely new technique required to be worked out; and this could be learnt only by experimental research on animals. Even this approach was constantly being interfered with by the anti-vivisectionists, so that for some purposes the would-be experimenter had to carry out his investigations abroad where the opposition was less fierce. This was true even though every use was made of anaesthetics to prevent the animal suffering from any avoidable pain.

Intestinal Anastomosis

For the relief of intestinal obstruction – a by no means uncommon gastro-intestinal event – resection of a portion of gut was generally necessary. This presented the problem of how to unite the two ends, and so avoid the inconvenient solution of closing the distal end and bringing the proximal end to the surface of the abdomen where the contents could be discharged. In 1888 Nicholas Senn of Milwaukee described a method of gut anastomosis that cut down the usual time of 2 h for the suture operation to about 15 min. It consisted in using either a modification of Jobert's invagination method, in which a flexible rubber ring replaced the Czerny-Lembert suture; or circular or lateral anastomosis with perforated approximation plates, preferably made of decalcified bone.

At the Brown Institution Mr Walter Edmunds and Mr Charles Ballance (later Sir Charles) in 1896 studied three main methods of uniting two pieces of intestine, namely side-to-side by lateral openings, end-to-end, and end-to-side, this last being useful when the obstruction could not be removed. Working with dogs, they experimented with Senn's plates and other similar devices, such as Mayo Robson's bobbin and Murphy's button, comparing them with Halsted's method of suturing. They obtained their best results with Maunsell's method, which left the line of circular junction almost unrecognizable, in contrast to the ridge seen at the site of the longitudinal incision that had been closed by Czerny-Lembert sutures only. Incidentally, they found that, instead of intestinal clamps, a piece of rubber tubing, passed through a hole in the mesentery and tied with a single hitch, was a simple and effective method that avoided damage to the gut.

Ligature of Large Arteries

Before the introduction of salvarsan, late complications of syphilis were frequent. Among these were aneurysms of one of the large arteries. Subclavian aneurysm, which was a source of great suffering to the patient, and was almost invariably fatal, had been treated by ligature of the innominate artery. The attempt, however, had been a failure. Of 13 recorded cases, 12 proved fatal, usually within 6 weeks; and though the thirteenth patient survived, the aneurysm recurred after 10 years. The operation involved section of the sternal muscles. These retracted, leaving a cavity that filled with blood clot derived from the oozing ends. The escape of blood to the exterior led to the formation of a sinus

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up which infection passed to the ligature. The resulting suppuration caused haemorrhage from the artery and death of the patient.

At the Brown Institution Walter Spencer (1889) carried out experiments on monkeys in order to devise a method of ligaturing the innominate artery that avoided section of the muscles and the consequent infection of the wound. His results showed that for success three main requirements were: (1) a median incision that did not necessitate cutting through the muscles; (2) a ligature that was buried as deeply as possible, and drawn tight enough to divide the internal coats of the artery; and (3) simultaneous tying of the carotid artery so as to cause a thrombus in the subclavian artery and cut off all supply of blood to it.

Provided the wound was made with strict antisepsis and the silk ligature had been properly sterilized, no drainage was required and the wound healed by first intention.

Intestinal Peristalsis

Dr J. Theodore Cash (1886) studied peristalsis during intestinal rest and movement. By making a Weller's fistula in the jejunum of a dog, he isolated a portion of gut 18·5 cm long. Observation showed that, during hunger, periods of complete quiescence, lasting from two to 12 min occurred. At any time, however, regular rhythmical contractions might set in. Immediately after a full meal had been swallowed, the movements became much more active and persistent, falling to a minimum four to 5 h later. Contraction was often stimulated in other ways, such as by the swallowing of liquids, or the application of cold to the surface of the abdomen. Observations were also made on the rate of propulsion of solid bodies and of liquids through the intestine at various times after a meal. Exercise was found to be highly favourable to rapid and effective peristalsis.

Other Surgical Procedures

Numerous other surgical procedures were studied by workers at the Brown. For example, Mr Parker and Victor Horsley experimented on the union of cut tendons. They found that, in dogs, division of the tendo Achillis, followed by immobilization of the limb in complete flexion, resulted in perfect union of the two ends of the tendon.

Dr R. H. Clarke, working on the surgical relief of 'roaring' in horses, showed that, so far as this depended on obstruction of the glottis, it could be cured by complete excision of the arytenoid cartilage. A lateral operation enabled this to be done without opening the larynx or injuring the mucous membrane. Sometimes the obstruction extended beyond the glottis, and sometimes it was due to palatal paralysis; both of these gave rise to stertor.

Mr C. M. Page worked on the union of fractured bones; Mr S. G. Shattock and Victor Horsley on the healing of wounds by first intention; Mr F. B. Jessett on anastomosis of the gut; and Watson Cheyne (later Sir Watson) on the treatment of tuberculous joints. Mr G. J. Romanes, also, appears to have studied various experimental procedures.

Cancer

Several workers engaged in the study of cancer without, as can now be understood, recording any substantial progress. Dr Charles Creighton (1874), later the celebrated author of 'A History of Epidemics in Britain', concentrated on the histo-pathological examination of secondary growths in the liver of man and animals. Whether the primary lesion was a cancer of tubular structure, a spindle-celled sarcoma, a myxosarcoma, or a lymphoma, the secondary growth consisted of nodules of varying size. He formed the opinion that it was the parenchymatous and not the connective tissue cells in the liver that underwent transformation. Primary tumours, on the other hand, differed in that their elements were histologically equivalent to the cells proper to the tissue in which they developed. For example, he concluded that in the mammary gland the point of departure for the new growth was the epithelium.

Mr C. Leaf studied the effect of injury on cancer of the breast, and Dr H. Paine and Dr D. J. Morgan the infectivity of cancer. Mr H. G. Plimmer isolated a micro-organism that he suspected of playing a part in the development of cancer. Mr C. Ballance (later Sir Charles) and Professor S. G. Shattock also worked on cancer; and Dr J. A. Shaw-Mackenzie experimented on the immunization of sheep, and on the value of serum tests in diagnosis of the disease.

Of chief interest were the observations of Dr J. W. Washbourn and Mr W. R. Smith (1896) on a disease of dogs characterized by the formation of tumours. The disease, which was particularly prevalent in bulldogs, was found to be infectious, and transmissible by inoculation. This must have been one of the first accounts of the animal tumours now known to be caused by viruses.

Disinfectants

The history of the development and use of disinfectants is a fascinating one, but one that cannot be recorded here. The employment of aromatic vapours, and of smoking, salting and drying for the prevention of putrefaction goes back to the days of ancient Egypt and the Old Testament, and is not difficult to understand. But how chemical disinfectants for warding off infection came to be used – and rightly used – in the middle of last century, when their mode of action was unknown, is more of a problem. Their success in this respect must be regarded as one of the triumphs of empiricism. Yet in this land of the unknown Semmelweis in 1861 (see Sinclair, 1909) showed conclusively that chloride of lime was able to counteract the agent responsible for puerperal fever. Though, as already mentioned, the mode of action of the hypochlorites was not understood, they were employed probably in the belief that infectious diseases arose either from miasmata or from the smell of putrefying material. Substances, therefore, with a strong deodorant property that could cloak miasmata and prevent putrefaction were accepted as disinfectants. Hence, presumably, came the introduction of carbolic acid (phenol) and sulphur dioxide.

In the early days of the Brown Institution Dr Buchanan Baxter (1875), working for the Privy Council under the direction of Dr Burdon-Sanderson, took a some-what different view by saying: 'Up to the present time the ground on which disinfecting action has been attributed to certain drugs, has been rather that of inference from their chemical characters and properties, than that of observation and experiment.' He defined a disinfectant as 'any agent capable of so modifying the contagium of a communicable disease during its transit from a sick to a healthy individual, as to deprive it of its specific power of infecting the latter'.

Baxter was working at the beginning of the bacteriological era, and he carried out his experiments on vaccine lymph, the glanders bacillus and the virus of infective inflammation, using culture methods and animal inoculation to determine the comparative efficacy of the disinfectants he tested. The experiments need not be described, but the conclusions he reached on four of the commonly used disinfectants, namely chlorine, phenol, sulphur dioxide and potassium permanganate, were closely similar to those accepted today. One important observation he made was on the influence of organic matter in the substrate in diminishing the activity of disinfectants.

Working at the Brown Institution for the Local Government Board, Dr Emanuel Klein (1885–6) made a careful study of the antiseptic or growth-inhibitory (bacteristatic) and the disinfectant or germ-destructive (bactericidal) powers of mercuric chloride, $HgCl_2$. Some years before, Robert Koch (1881) had been greatly impressed by the bactericidal power of mercury salts. Anthrax spores, he found, were killed by a 1/5000 dilution of $HgCl_2$, and their growth restrained by a dilution as high as 1/1 000 000. Klein worked with several different organisms, vegetative and sporing, using both cultural and guinea-pig inoculation methods to determine the death point. He concluded that Koch had overestimated the potency of $HgCl_2$, though not greatly. In this conclusion he was partly correct. It was left, however, to Geppert (1889) in Germany to show that Koch had in fact greatly overestimated its germicidal power. He pointed out that if, at the conclusion of the experiment when all the organisms appeared to have been killed, the mercury was removed by bubbling hydrogen sulphide through the solution, growth of the organisms often occurred on culture medium. A similar result could be obtained by inoculating the organisms into guinea-pigs, and finding not only that they were still alive but that they had retained their pathogenicity. Geppert showed that minute concentrations of $HgCl_2$ were enough to inhibit the growth of microorganisms, but that to kill them much greater concentrations were needed than stated by Koch. It may be added that Dr Gerland of Blackburn, at the Brown Institution, studied the antiseptic properties of thymol.

Nutritional Researches

Rickets

Dr Edward Mellanby (later Sir Edward), who was appointed in 1913 to a Chair of Physiology in the University of London held at King's College for Women (now Queen Elizabeth's College), appears to have been one of the very few workers at the Brown Institution who were interested in problems of nutrition. He was a visitor there during the First World War, and for two periods while Dr F. W. Twort, the Superintendent, was away on war service he held the post of Acting

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Superintendent. A grant from the Medical Research Committee for part-time work on experimental rickets enabled him, with an assistant supplied by the Committee, to make investigations on dogs. Some of these seem to have been undertaken at the Brown; some, on the histological and biochemical examination of the various dietaries employed and their effects, at Queen Elizabeth's College for Women; and some, probably most, of the dietary trials on dogs at the Field Laboratories at Cambridge.

The general plan of research was to feed puppies, usually about two months old, on a diet found to produce rickets; and then to add various substances to the diet and see whether they prevented the development of the disease in a fresh lot of puppies. On the diet used at first rickets took 3–4 months to appear; but later on, by employing a more stringent diet, this period was cut down to 6 weeks. His results showed that substances preventing rickets were meat, and watery extracts of meat free from protein, malt extract, commercial yeast extract, butter, margarine, cod-liver oil, and milk in an amount of 500 ml a day. Substances not preventing rickets were meat protein, casein, linseed oil, and 10 g of yeast daily. From these findings it seemed clear that fats, carbohydrates, and proteins were not causative factors in the disease. Rickets, Mellanby concluded, was a deficiency disease of the type of scurvy and beri-beri. The deficiency was caused by the lack of an accessory factor in the diet, present especially in animal fats, and closely associated with the vitamin A fat-soluble complex. That the accessory factor was not vitamin A itself appeared evident from the fact that lean meat, and extracts of meat and malt, though not strongly anti-rachitic, nevertheless had an inhibitory effect on the development of the disease; and the fact that the more rapid the growth of the dog, the more antirachitic factor was required to 'keep the growth straight'. The anti-rachitic factor seemed to be more essential for ensuring normal growth, vitamin A for preventing abnormal growth and keeping the tissues in good working order. It was some years before vitamin A was isolated as calciferol, and the anti-rachitic factor as vitamin D or ergosterol. This separation of the two factors was made easier by Professor Korenchevsky's production of rachitic changes in the bones of rats by diets deficient in both fat-soluble vitamin and calcium salts.

Mellanby's first two communications on the aetiology of rickets were made in the form of demonstrations to the Physiological Society in 1918. His detailed report to the Medical Research Council, as it had then become, did not appear till 1921, after he had left the Brown Institution. As Sir Henry Dale (1955) stressed in his obituary notice, Mellanby's work was the first really scientific attack on the problem of rickets, and cleared away a mass of conflicting arguments on the genesis of the disease. In his own words Dale says: 'I have always regarded this work of Mellanby's as one of the high peaks, one of the outstanding points of new departure, in the revolutionary advance of therapeutic knowledge and practice by research duing the present century – comparable in its direct success, and in its stimulating influence on further enterprise in research, to the earlier discovery of salvarsan, and like later ones of insulin and penicillin.' Unlike many other scientific discoveries, it had a direct effect on clinical practice, and was applied almost at once to the prevention of rickets in infants – with such success that before long rickets in this country had become a rare disease.

Alcohol

In 1917 and 1918 Professor Mellanby was partly engaged in studying the rate of absorption and disappearance of alcohol from the blood, and its effect on the phenomenon of intoxication. The chemical part of this work was apparently done at King's College for Women, whereas the experiments on dogs were presumably confined to the Brown Institution. This rather unusual investigation was carried out at the request of the Chairman, Lord d'Abernon, of the Central Control Board (Liquor Traffic), who wished for information that would enable him to formulate a policy for controlling the sale of liquor. The Medical Research Committee supported the inquiry, and the results of Mellanby's researches were published in one of their Special Report Series (Mellanby, 1919). Though the experiments were made on dogs, later observations on human volunteers indicated that the conclusions were applicable to man.

Briefly it was found that on an empty stomach the maximum amount of alcohol reached in a unit volume of blood was proportional to the amount consumed. Absorption from the stomach was rapid, the maximum concentration in the blood being attained in half to one hour. On the other hand, the rate at which it disappeared from the body was slow. For example, a dog of 13·5 kg took 20 h to get rid of 50 ml of alcohol This difference accounted for the fact that whether the intoxicating dose was drunk in one portion or in three portions at intervals of 1 or 2 h, it made practically no difference to the maximum concentration of alcohol in the blood. Dilution of the dose delayed the rate of absorption and resulted in a lower concentration of alcohol in the blood than the same amount of alcohol drunk neat. Food likewise delayed absorption, the degree depending on the type of food ingested. Milk was the most effective foodstuff for delaying absorption, and was almost equally so whether it was mixed with the alcohol or drunk 2 h beforehand. In contrast to milk, water had the opposite effect. It acted as the best stimulant to absorption so far discovered; and its effect was evident when it was taken even 4 h before the alcohol. The mode of action of the water was doubtful. According to Pavlov, water has a stimulating effect on the secretion of gastric juice, probably through liberation of gastric secretion from the pyloric end of the stomach; but Mellanby thought that, in addition to this effect, water had a specific stimulating action on the cells of the intestinal mucosa responsible for absorption.

As a food, alcohol was peculiar in behaving differently from other non-nitrogenous substances. Thus, though it was able to supply up to 30 to 40% of the total energy lost by the body, its rate of combustion was independent within fairly wide limits of the amount circulating in the blood. Moreover, it had no specific dynamic action on metabolism, but simply replaced other foodstuffs without stimulating the total combustion processes. Again, the rate of combustion was apparently independent of the types of other foodstuffs being metabolized.

Of particular interest was the effect of exercise on the rate of combustion of alcohol. When present in low concentration in the blood, alcohol was oxidized more rapidly during exercise than when the dog was at rest; but at higher concentrations exercise made practically no difference to the rate of combustion. In other words, the greater the toxic action of alcohol, the more limited was the increase in its rate of combustion by exercise, and the closer did the rates of combustion in the active and the resting states approximate. At high concentrations alcohol appeared to have not only this self-limiting effect on its own oxidative process, but to extend its baneful influence to limiting the oxidation of other combustible material. As a result, intermediate oxidation products accumulated, and rapid fatigue set in. The evidence suggested that, though the combustion of alcohol supplied heat to the body, it could not serve as a source of energy for muscular contraction.

As one of the duties of the Superintendent of the Brown, Professor Mellanby in 1918 delivered the official lectures, taking as their title 'Alcohol, Rickets, and Vitamins'.

Other Miscellaneous Researches

Dr Wakelin Barratt studied the common skin diseases of animals; Dr Hillier the laws determining sex; Mr W. R. Smith the relation of water to disease; Mr Barnard the pathology of pleural effusion; and Mr Wright the causation of glycosuria.

Mr Ballance (later Sir Charles) and Professor S. G. Shattock removed aseptically various tissues from healthy animals and studied their maintenance *in vitro*. They found that on gelatin media in an incubator at 100 °F some tissues survived for 1 to 3 weeks without any noticeable change. Experiments with liver tissue were less successful, suggesting that the liver *in vivo* was not always sterile.

Mr Lingard investigated gangrenous stomatitis or noma in man, and showed that a similar disease occurred in monkeys and calves, and in the form of gangrenous pneumonia in the lungs of horses. By the inoculation of calves he reproduced a disease closely resembling the noma of human beings.

It may be of interest to mention some of the visitors who worked at the Brown Institution. The following list is by no means inclusive, nor does it indicate how long they spent there – weeks, months or years. The number of visitors in any 1 year was greatest in the early stages of its existence. Later, when other clinics, institutions and university departments gradually became established, the number dwindled, till during the First World War, when Dr F. W. Twort was away on military service, Professor Mellanby was the only scientific worker left in the building. After the war, apparently not more than four visitors made use of the laboratories. The list does not include the names of the Superintendents; these are given in the next chapter. Pen sketches of many of the visitors who worked at the Brown in the last quarter of the nineteenth century will be found in Sharpey-Schäfer's History of the Physiological Society (1927).

List of visiting workers

Dr T. D. Acland
Mr Anderson
Dr F. W. Andrewes (later Sir Frederick)
Dr H. G. Auld
Dr W. Bain
Mr C. Ballance (later Sir Charles)
Mr Harold Barnard
Dr Wakelin Barratt
Captain Bateman
Dr Buchanan Baxter
Dr C. E. Beevor
Dr Bernstein
Mr Blandford
Dr F. H. Blaxall
Sir Farquhar Buzzard
Dr Stanford Cade (later Sir Stanford)
Dr J. Theodore Cash
Mr Watson Cheyne (later Sir Watson)
Mr R. H. Clarke
Mr M. P. H. Collier
Dr Monckton Copeman
Dr Charles Creighton
Dr Winifred Cullis
Mr G. F. Dowdeswell
Mr Durham
Mr Walter Edmunds
Surgeon Evans I. M. S.
Mr T. Evans
Professor J. W. H. Eyre
Mr A. G. R. Foulerton
Captain Fry
Dr Gerland of Blackburn
Dr G. F. F. Grünbaum
Dr Herman of Cape Town
Dr Tanner Hewlett
Dr Hillier
Dr William Hunter
Sir Jonathan Hutchinson (Junior)
Professor Thomas Henry Huxley
Mr F. B. Jessett
Mr A. E. Jones
Dr A. A. Kanthack
Dr Emanuel Klein
Mr Latham
Mr C. Leaf
Mr A. Lingard
Dr Maas
Dr J. McFadyean (later Sir John)
Dr W. H. Manwaring
Dr Edward Mellanby (later Sir Edward)
Dr D. J. Morgan
Dr H. Morotti
Dr Alexander Morrison
Dr F. W. Mott (later Sir Frederick)
Dr G. W. de P. Nicholson
Dr W. Nicoll
Mr C. M. Page
Dr A. Paine
Mr R. W. Parker
Dr F. W. Pavy
Mr H. G. Plimmer
Lieutenant H. S. Ranken
Dr Nathan Raw
Dr Robertson
Mr G. J. Romanes
Dr A. Ruffer (later Sir Armand)
Dr Felix Semon (later Sir Felix)
Professor S. G. Shattock
Dr J. A. Shaw-Mackenzie
Dr Batty Shaw
Mr W. K. Sibley
Dr Hugh Smith
Mr William R. Smith
Mr Walter Spencer
Dr Purves Stewart (later Sir James)
Mr G. R. Symes
Dr H. H. Tooth
Dr C. C. Twort
Mr C. S. Wallace (later Sir Cuthbert)
Dr J. W. Washbourn
Dr L. C. Wooldridge
Sir Almroth Wright
Mr Wright
Professor G. F. Yeo

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