qualities, seems theoretically the most rational type to employ, but it soon loses its effect owing to an inherent compensatory ability of the skin to assume a permanent alkaline reaction. On the other hand, the use of hydrochloric, lactic, tartaric, carbolic, and other acids, the acid effect of which is due rather to their molecules than to their hydrogen-ion content, tends later to become irritating. In view of these facts, and after reading an article by Armstrong in the *British Medical Journal* which described the relief obtained by the use of lemon juice in vesicular dermatoses of external irritant origin, I decided to try its effect on those of mycotic origin.

For the last four months I have compared the results of therapeutic concentrations of some of the aforementioned acids with those obtained by the use of lemon juice, which were definitely superior. Although I have not treated a sufficient number of cases to draw any accurate conclusions it would seem that the vitamin content in fresh lemon juice might play some minor part in addition to the citric acid content. This acid has the added advantages of possessing buffer qualities, as well as being endowed with a greater number of hydrogen ions than boric acid.

It is my practice to advise the patients to bathe the affected parts in a pint of hot water to which is added a drachm of liquor plumbi subacetatis fort. night and morning. This serves to increase the vascular supply, and is shortly followed by a sedative effect. An application is then made of 1 per cent. of ammoniated mercury in lanolin to prevent possible pyococcal superinfection. In addition, the patients are instructed to rupture the vesicles with a sterilized needle, and to rub the affected parts four or five times daily with half a lemon from which the peel has been removed. Where irritation is a marked feature the relief is dramatic, even though a temporary sensation of smarting may be experienced. The vesicular stage of the disease resolves under this treatment more quickly than with any other I have used.

In the later stages, when a certain amount of eczematization has supervened, the lemon juice is diluted, or dispensed with, and weak tar or ichthyol applications to which salicylic acid may be added are then employed. These applications may be supplemented if necessary by the use of x rays. However, the use of lemon juice materially lessens the duration of the condition: assisted by an acid powder it is particularly beneficial in the intractable toe infections.

The other applications which I have found most beneficial are one part in four thousand aqueous perchloride of mercury baths in the acute stages, associated with the weak mercurial ointment previously mentioned. This is followed later by a weak salicylic acid and tar or ichthyol ointment, assisted by fractional doses of x rays preferably delivered as one-quarter of an erythema dose weekly for four or more doses. I have found x rays to be almost infallible in the temporary alleviation of the condition. Sometimes a permanent cure will result, although the great majority of cases recur, occasionally within several weeks, but more commonly when the next summer approaches.

If an infected focus remains between the toes or in one or more nails this must be eliminated to prevent recurrence. As far as the nails are concerned the difficulty is known to all, since surgical removal, radiation, and other means may have to be employed. Curettage of the toe interspaces twice weekly, and the application of 2 per cent. of cignolin in benzol night and morning, followed by the application of a powder containing salicylic acid 8 parts, boric acid, thymol di-iodide, and zinc oleate—of each ten parts—in prepared talc, has produced the most satisfactory results in my hands, until recently, when lemon juice was substituted for the cignolin lotion.

In those cases where the fungus element has died out, and eczematization or sensitization to external irritation remains, the removal of toxic foci, such as infected teeth roots or tonsils, will sometimes help to eradicate the condition. This is often assisted by the administration of an autogenous vaccine made from the organisms present in the toxic focus, and will sometimes produce a cure in chronic lesions in which fungus is still present. Intravenous injections of calcium either as the chloride (afenil), the gluconate (Sandoz), or the combination of gluconate and thiosulphate (ifah) in doses of 10 c.cm. thrice weekly in conjunction with fractional doses of x rays, will often produce excellent results. One further treatment, with which I have had complete success in four very chronic eczematized cases, is high colon lavage three times a week for several weeks with two pints of normal saline solution, followed by one pint of normal saline solution containing one drachm of ichthyol, which is left in the colon. This routine is accompanied by a restricted but nutritious diet and copious fluids.

SOME TOXAEMIAS OF ANIMALS DUE TO ANAEROBIC ORGANISMS

A COMPARATIVE PATHOLOGICAL STUDY OF RECENT
WORK WITH PARTICULAR REFERENCE TO
THE TOXAEMIA OF INTESTINAL
OBSTRUCTION IN MAN*

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The conditions in which these organisms are of material importance in human infections fall into three main groups: (1) wound infection with gas gangrene, (2) puerperal infection, and (3) toxæmia in intestinal obstruction and peritonitis.

Of the first I shall say little. The circumstances or accessory factors favouring infection of wounds with the anaerobic sporing bacilli are well known, and this type of infection presents no particular problem. It is nevertheless desirable to keep in mind the fact that there are such essential accessory factors when considering other types of anaerobic infection. Of the second group—puerperal infections—it may at once be said that they are in the main complications or sequelae of abortion, and not of normal labour. They are therefore very closely allied to the first group of wound infections. Attention cannot fail to be attracted to them because of the very high mortality associated with them, and the difficulty of devising any very successful treatment.

The third type of anaerobic infection—namely, that alleged to cause the toxæmia associated with intestinal obstruction and general peritonitis—is easily the most interesting group, and despite a very considerable amount of experimental work and clinical observation there are many points relating to it which are obscure. At present it may safely be said that there is no agreement with regard to the pathogeny of the toxæmia associated with intestinal obstruction. The most noteworthy contribution to the subject of recent years was that by B. W. Williams (1926), in which he pointed out, in the first place, the striking resemblance of these cases to the toxæmia of gas gangrene; secondly, the frequent presence of many species of anaerobe in the alimentary tract; and thirdly,

* Abstract of a paper read in opening a discussion in the Section of Pathology and Bacteriology at the Annual Meeting of the British Medical Association, Melbourne, 1935.

that the obstructed small intestine provided ideal conditions for the germination and proliferation of anaerobic spores reaching it from the stomach. Since the publication of Williams's paper many fresh investigations have been attempted, and in quite a number his findings, and in particular his success with the use of anti-gas-gangrene serum, have been doubted. One of the most recent pieces of work is recounted in a paper by R. L. Holt (1934), who, after examining the same question, comes to the conclusion that the effect of the exotoxin produced by *B. welchii* is negligible, and that the use of antitoxin—that is, anti-*B. welchii* serum—is not warranted. To us as bacteriologists this is an important question. Are these anaerobic intestinal organisms the chief or main cause of the toxæmia, and can suitable antitoxins be of great use, or is the presence of numbers of anaerobes incidental and comparatively unimportant?

My object is not to attempt an answer to these questions, but to bring to notice some experimental work with regard to a number of animal infections of somewhat similar nature, and to suggest that, in the light of the investigations to be described, much of the work and many of the papers relating to human infections might well be revised. If any excuse be needed for the bringing before you of this work by one not directly engaged in it, my apology must be that I have taken a very great interest in the Australian work, have had some share in initiating it, have followed closely its progress at the hands of old students of my own, and have formed a high opinion of the quality of the work itself and of its scientific and economic value.

"Black Disease" (Infectious Necrotic Hepatitis) of Sheep

This is a disease of sheep widely prevalent in New South Wales, Victoria, and Tasmania, and involved losses, a few years ago, probably exceeding £1,000,000 per annum in value. It attacks sheep of all ages and breeds, and generally those animals which are in the best condition. Affected animals are rarely seen alive, and when so seen usually die within one or at most a few hours. The most thoroughgoing and ultimately successful investigation of the disease was made by A. W. Turner (1930), beginning as a research scholar in my laboratory and continuing his work at the Pasteur Institute, at the Institute for Animal Pathology in Cambridge, and finally as a research officer of the Council for Scientific and Industrial Research here in Melbourne. Many other workers, however, contributed something to the story, notably Gilruth, Albiston, and Dodd.

As is the case with all these anaerobic diseases of sheep, putrefactive changes in the carcass are extremely rapid, and post-mortem invasion of the blood and tissues with anaerobic sporing bacilli of various kinds is common within a short time after death. Dodd emphasized the necessity of confining bacteriological investigation to those affected animals detected whilst still alive and examined immediately after death. All the subsequent workers have taken great trouble to observe this rule. Time forbids my dealing with anything but the salient features of the disease, following the description by Turner. When deaths are occurring among sheep on a property where black disease is prevalent, it is possible by dint of early rising and close observation to pick out from time to time sheep which, on disturbing the flock, are seen to lag behind the rest. These, on continued closer inspection, are found to be dull, have a desire to lie down, soon become comatose, and die in a short time—from a few minutes to a few hours—with little if any rise of temperature.

FINDINGS

Turner was able to examine fifteen cases taken at the moment of death, and to follow up each with a carefully planned pathological and bacteriological examination. The outstanding observation in all these cases, and confirmed in numerous subsequent ones, was the presence of one or more necrotic areas in the liver, usually only one or two,

roughly circular, and from 2 to 3 cm. in diameter—sharply defined, yellowish white, and with a zone of venous congestion several centimetres wide round them. Further, in all these livers there were definite signs of fascioliasis (infestation with the liver-fluke), and quite often one or more fluke burrows were closely adjacent to the necrotic areas previously mentioned. These necrotic liver areas in cases of black disease were first observed by Gilruth (1911), and also by Cleland (1913). Dodd noticed their constant presence, and it was he who first insisted that in all cases they were associated with recent invasion of the liver by migrating flukes. Turner rapidly came to the conclusion that fluke infestation was an essential factor in producing the necrotic foci in the liver, and many of his sections show young flukes—3 to 5 mm. long—in early necrotic lesions.

Microscopical examination of the necrotic liver areas at early stages revealed a marked infiltration with eosinophil leucocytes, and among these wandering cells were to be seen a few Gram-positive large bacilli in the vegetative stage. In older lesions the bacteria had proliferated, and could be found throughout the necrotic area, and notably at its periphery, but if the material for section was taken at the moment of death no bacilli were to be found in the living parenchyma in the great majority of cases. If carcasses were left for a few hours and then examined, bacilli were found throughout the liver tissue. No bacilli were to be seen in sections of kidneys, spleen, or lymph glands.

BACTERIOLOGY

A number of investigators have each added something to the elucidation of this problem of bacteriology. Gilruth undoubtedly saw the bacillus in sections. Dodd emphasized the importance of the necrotic areas, and secured cultures of an organism. Albiston (1927) isolated the organism in pure culture, and expressed the opinion that it resembled *B. oedematiens*, and it was with a culture supplied by Albiston that Turner and Davesne, working in Weinberg's laboratory, determined its identity as a strain of *B. oedematiens*. Subsequently, from fresh post-mortem examinations conducted under the conditions described, it was found possible to secure pure cultures quite readily by means of material collected in sterile Pasteur pipettes from the necrotic foci in affected livers.

The toxin was thermolabile, and heating to 60° C. for one hour destroyed it; it was largely absorbed by Seitz filter pads, but readily came through a Pasteur-Chamberland L₂ filter. It was found toxic for a number of different animals, and after either subcutaneous or intramuscular injection of a dose of approximately 1 m.l.d. in a sheep the animal died with post-mortem appearances similar to those produced by injection of a live culture, even to the characteristic congestion in the stomach and small intestine. All the evidence thus suggests that the pathogenic effects of *B. oedematiens* are due to its production of exotoxin.

Complete proof of the identity of the organism was forthcoming as the result of the neutralization tests which Turner used. He states: "For the identification of pathogenic micro-organisms, particularly anaerobes, the most valuable test, and indeed the crucial one, is undoubtedly the cross-immunity reaction—that is, the neutralization of cultures and toxins by antisera made from known microbial species, always provided the purity of the organisms used is absolutely above suspicion." The organism from black disease cases was therefore tested against anti-*B. oedematiens*, anti-*B. welchii*, anti-*Vibrioseptica*, anti-*B. sporogenes*, and anti-*B. histolyticus* sera. The anti-*B. oedematiens* serum neutralized all the strains recovered, whereas all the rest were without effect.

But further work was necessary for a complete understanding of the aetiology of black disease. What were the accessory factors—the special conditions—determining infection?

Turner's experiments with the spores of *B. oedematiens* in sheep showed definitely, in the first place, that toxin-free spores isolated from cases of black disease are innocuous (a) when injected either subcutaneously, intramuscularly, intraperitoneally, or intravenously in large

doses, and (b) when ingested; and that after ingestion they can be recovered from the liver in twenty-four hours; and secondly, that these spores remain latent, many having been consumed by phagocytes, but numbers of them remaining free, and that they persist in liver, spleen, and bone marrow for periods up to nine months after injection, and for at least five months after ingestion. They can be recovered in culture from these tissues, especially if, following Neisser's method, the whole organ or a large piece of not less than 50 grams is incubated. Further, Turner investigated the condition in forty-two healthy sheep from a property heavily infected with black disease, and by the means described was able to recover positive cultures of *B. oedematiens* from the livers of eighteen of them (43 per cent.). Thus it is quite evident that latent spores are present in a considerable proportion of healthy sheep which have been feeding on infected land.

BLACK DISEASE (EXPERIMENTAL) IN RABBITS

Toxin-free spores of *B. oedematiens* injected intravenously into the ear vein, together with an injection into the liver of 0.25 c.cm. of a 25 per cent. solution of calcium nitrate, caused the death of three rabbits—two on the second day and one on the third—with lesions resembling those of natural cases in sheep. In a similar manner infection was produced in rabbits by giving the spores intravenously to animals which had been fed with cysticerci, the larval phase of *Taenia serrata*, which larvae encyst in the liver. Even more applicable to the condition in sheep was the successful experiment with toxin-free spores together with cercariae of *Fasciola hepatica*, the liver-fluke.

Thus spores of *B. oedematiens* may be taken in by ingestion, may remain latent and innocuous in the liver and spleen for months, and may then be activated so as to germinate and multiply, by means of trauma or injury due to parasites, or to drugs.

The success of vaccination with anatoxin or anaculture against *B. oedematiens*, and of anti-fluke measures, in the control of black disease throughout the affected districts in Australia, is a sufficient proof of the soundness of the research.

Infectious Enterotoxaemia of Sheep

This condition is nearer still to the problem of infection in man. Attention was first called to the disease in 1915, owing to an outbreak in the Beverley district of West Australia, but the first thoroughgoing investigation was commenced in 1925 by H. W. Bennetts, veterinary pathologist to the Department of Agriculture of Western Australia. The disease had extended in the course of ten years, so that it was causing very serious economic loss to the sheep industry, often amounting to from 5 to 15 per cent. of sheep in infected districts. A special type of sheep husbandry is practised in this part of West Australia. There is practically no permanent pasture, but sheep are depastured on green crops, oats, wheat, rape, or on weedy fallows. The disease affects all ages and all breeds, but especially young adult sheep, the "pick of the flock" so far as condition goes.

BACTERIOLOGY

An anaerobic sporing organism closely resembling *B. welchii* was isolated without difficulty from mixed small intestine contents, and in seventeen out of the eighteen cases it was the only sporing anaerobe found. The toxin was found to be thermolabile, being destroyed by heating to 70° C. for half an hour. From the crude product a concentrated purified form was obtained by precipitating with 60 per cent. ammonium sulphate, drying the precipitate, and redissolving it in distilled water. This toxin would keep for months. Experimentally the toxin from culture filtrates produced the same fatal toxæmia as did the filtrates of intestinal contents, and both produced effects resembling very closely those produced by the toxin of *B. welchii*. Controls of bowel filtrates, prepared in the same way but from normal sheep, were innocuous when given intravenously or intramuscularly into mice and guinea-pigs in doses greatly exceeding the minimal lethal dose of pathological filtrates.

In the early stages of the work (1928-9) it was thought that the organism concerned was in fact *B. welchii*, and both toxin and bowel filtrates were tested against anti-*B. welchii* serum prepared by Burroughs Wellcome. Neutralization occurred, and this antiserum was an effective prophylactic against infective doses. All succeeding experiments, however, with later batches of anti-*B. welchii* serum of the same make, were invariably unsuccessful, whereas an antiserum prepared by the immunization of animals (sheep) with the organism recovered from affected sheep was an efficient protective. The organism was evidently not *B. welchii*, and Bennetts named it *B. ovitoxicus*. These neutralization experiments have been repeated many times with anti-*B. welchii* serum from different sources, and always with the same negative result. Anti-*B. ovitoxicus* serum, on the other hand, protects against the homologous toxin and against bowel filtrates from affected animals.

EXPERIMENTAL REPRODUCTION OF THE DISEASE

1. Inoculation of sheep with sterile culture filtrates of *B. ovitoxicus* intramuscularly caused death in twenty-four hours with symptoms and pathological findings resembling those of natural cases. A similar result was obtained in sheep by the intramuscular injection of bowel filtrates from natural cases, whereas control sheep which were injected with bowel filtrates from normal animals remained unaffected.

2. Ingestion of culture filtrates (50 c.cm. per day for many days on end) and of small intestine contents from natural cases produced no ill effects in sheep. Attempts were then made to secure infection by the administration of ox bile as an intestinal irritant some hours previous to drenching a sheep with an enormous dose of culture filtrate; similarly, by giving a large dose of sodium bicarbonate through a stomach tube, immediately followed by culture of *B. ovitoxicus*. In both cases repeated experiments gave negative results. Next, remembering the suggestion that bowel stasis might be the condition necessary, attempts were made to bring about stasis by means of large doses of opium, and finally with a combination of opium and belladonna given in milk. Three sheep so treated, and receiving two doses of *B. ovitoxicus* culture, became infected and died in nine, sixteen, and twenty-six hours respectively from the commencement of the experiment. Control sheep with the drugs but no culture, and others with culture but no drugs, were unaffected. Four out of six sheep so treated died with typical symptoms and characteristic bacterial smears from the jejunum. The other two showed symptoms of toxæmia, but recovered.

FACTORS PREDISPOSING TO INFECTION

Several possible factors have been suggested as affecting the vegetation and multiplication of *B. ovitoxicus* (or *B. welchii* in human cases) in the small intestine—namely, achlorhydria, dietary deficiencies, high protein intake, and more particularly bowel stasis—and the particular form of sheep husbandry in West Australia, with a diet deficient in fibre, and therefore not encouraging peristalsis, supports the suggestion that this last is a material factor. The habit of sheep to feed close to the ground, and the practice of depasturing them on cultivated land, allow of their taking up a high proportion of soil with their food, soil which is presumably contaminated with the organism in many cases.

From all the evidence it may fairly be said that this disease is a toxæmia due to the absorption of the toxin of *B. ovitoxicus* from the small intestine, and is quite independent of any tissue invasion with the organism. This view is strongly supported by the fact that vaccination of sheep with "anaculture" (whole culture of *B. ovitoxicus* treated with formalin and incubated) has given good results as a prophylactic measure. As an example, on one property, in 1930, 925 sheep were vaccinated and an equal number left unvaccinated. In the next disease season, of the vaccinated two died of enterotoxaemia (0.2 per cent.), and of the unvaccinated forty-two died (4.6 per cent.).

Conclusion

And now, having come to the end of my very summary account of these researches, there are a few points which appear of sufficient importance to deserve emphasis.

Experimental work to elucidate the matter of human infection has usually been done on the dog. Here in the diseases brought to your notice the affected animal is the sheep. The study of these conditions is of value because (1) they are natural infections, (2) the numbers concerned are large, (3) experiments can be controlled in many ways by normal sheep available at every abattoir, and (4) the experimental animal for a crucial test of the reproduction of the disease or its prevention is the same animal as is naturally attacked.

A point of great interest has been to discover the conditions allowing of infection. Williams wisely pointed out in his paper that it requires very particular conditions for the establishment of *B. welchii* infection in living human tissues, and our survey has provided ample justification for that remark, with a more general application.

The avoidance of any complication from post-mortem invading organisms has undoubtedly facilitated these researches. It is easy in the sheep, it is very difficult in man, and the confusion which may follow must be reckoned with and avoided if possible. The precise identification of an organism and the determination of a particular type of strain with its own specific toxin is an essential feature of any successful investigation. As with the pneumococcus so with *B. welchii*—typing is essential if serum therapy or prophylaxis is to be of use.

Lastly, the presence—potential or actual—of latent spores must be considered. Let us fully understand what are the possibilities of infection, and the conditions which make it actual, and we shall be well on the way to the discovery of means of prevention.

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The Minister of Health has addressed to the London County Council a letter arising out of his consideration of the report made by his officers following a survey of the L.C.C. public health services—a survey which is referred to at length in the annual report of the Ministry of Health published in August last. The Minister states that he has observed with appreciation the great work of organization and development of the medical and institutional services for the sick which has been carried out by the Council since the Act of 1929 came into operation. He draws attention to three points which afford him special satisfaction: the improvements in structure, equipment, and staffing of the hospitals which the Council inherited from the guardians; the separation from the Poor Law of services which could lawfully be provided under other powers; and the close interrelationship of the special services, such as those for tuberculosis and venereal diseases, for which the Council was responsible before the Act of 1929, the general hospital service, and the special hospital service. The Minister has also observed a number of interesting points of contact between the Council's services and those of the voluntary hospitals of London, especially the facilities afforded at Council hospitals for training medical students in obstetrics. He congratulates the Council both on its enlightened policy and on its efficient organization.

CHRONIC RHEUMATISM*

BY

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After a long period of stalemate a concerted effort against rheumatism is making good progress. Like the campaign against tropical diseases, it has widespread social, economic, and industrial purposes to serve in addition to its primary medical aim of prevention and healing. There are moments when those who are engaged in a long effort against disease should take stock of their position, of success and failure, of the ground won, of immediate objectives and those which are more remote, and of the best measures by which those objectives may be attained. It is ten years since the International League against Rheumatism had its small beginning. Two national organizations now represent the Anglo-Saxon countries: the Committee on Chronic Rheumatism of the Royal College of Physicians of London, which has just issued its first report, and the American Association for the Study and Control of Rheumatic Diseases. At the latter's recent annual meeting in Philadelphia much suggestive new matter was presented by good workers in rheumatology in the United States.

Causation

At such a moment it is well to consider, even at the risk of dogmatism, what new facts have been clearly ascertained, and, in default of facts, what guiding hypotheses or stepping-stones to facts may have emerged. It is the more desirable to arrange new facts and postulates in a country where rheumatism is so prevalent, for it is only as guiding principles emerge that it is possible to grapple with the great problem of rheumatism in its various aspects.

The reference of the College of Physicians committee was the chronic rheumatic diseases, and especially arthritis. It was agreed that chronic rheumatism forms a series of definite clinical pictures. Whatever anatomical or aetiological links may subsist between chronic rheumatism and "acute rheumatism," these two conditions differ widely in their evolution and clinical course, and present in practice two entirely separate problems. Incidentally, the acute disease, to which the name of cardiac fever might well be applied, appears to be diminishing in our country, at all events in the form in which we knew it forty years ago; this can hardly be said of the chronic and disabling maladies now under review.

There is good histological evidence that the connective tissues are the seat of chronic rheumatism. What are regarded as the typical abnormalities of the rheumatic state are found in these tissues of the mesenchyma. It is also generally accepted that the causation of rheumatism, like that of other chronic diseases, is complex. Some years ago the International League formulated four possible causal factors, internal or external to the body. It is impossible to state them in order of importance, since sometimes one, sometimes another, seems to be dominant. They are: (1) constitutional anomaly; (2) abnormalities in the circulation of the skin; (3) external factors, such as cold, damp, trauma, and occupation; and (4) focal or other infection.

A diagnosis of causes may well be made in the first instance. This will discover, so far as is possible, what in each case is the dominating, and what the contributory or accessory, causal factors. Only then can a scheme of treatment be framed which will counteract the combined forces of causation. The dominating factor may well be

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