with considerable pain, the ulcer, which had hard, raised edges, slowly grew, till it nearly encircled the distal joint of the finger." Sufficient material from the edge of the ulcer was curetted away to demonstrate clearly in sections the epitheliomatous nature of the lesion. The epitrochlear and axillary glands were not enlarged. After nine short X ray exposures the ulcer underwent distinct involution, its size being reduced by about one-third and the pain being entirely removed. Unfortunately, the patient died at this time from sepsis following an operation on the genito-urinary tract.

CASE 28.—*Multiple epitheliomata of the trunk, developing after keratosis, in a man who had taken arsenic for years*: Jay F. Schamberg. (Private letter: case thought to have been reported at a meeting of the Philadelphia Dermatological Society.)—The patient, a physician aged about 43, who had taken large quantities of Fowler's solution as a tonic over a period of years, became covered over the trunk with scores of small keratoses, with telangiectases, and numerous epitheliomatous growths. One growth, involving the right nipple, was so pronounced that its removal was advised, but the patient did not return, and the subsequent history of the case is not known.

CASE 29. "*Epithelioma of neck, due to arsenical irritation*": Frederic S. Eve. (Unpublished communication.)—The patient, a man aged 40, employed for 20 years in the preparation of material for sheep-dipping (viz., sulphur, soda, and arsenic), who had for two years noticed a small and nearly painless growth above his left collar-bone, was admitted, on July 3rd, 1910, into the London Hospital under the care of Sir Frederic Eve, to whom he had been sent by Dr. C. R. Porter, of Berkhamsted. There was marked pigmentation of the entire skin, with mottled brown areas, extreme keratosis of the palms (which last, however, the patient stated to have been present before he began the work), but not of the soles, a large number of warts on the back of both hands, and an epitheliomatous growth a little above the middle of the left clavicle. This was an inch in diameter, raised and ulcerated, with hard and somewhat everted edge. It was not deeply fixed, and no enlarged glands were detected. Two small areas of desquamating skin were present below the left clavicle. On August 8th the growth was excised by Mr. R. Warren, together with the glands of the left suprascapular triangle and one of the warts on each hand. Sections showed squamous-celled carcinoma; no keratinization; large nuclei to the cells, with relatively little protoplasm, the cells resembling those of a rodent ulcer. The patient was discharged well a fortnight later and returned to work. He continued well when seen by Dr. Porter in February, 1913.

CASE 30. *Epithelioma of shoulder and chest wall in a man employed in an arsenicated sheep-dip factory*: Charles R. Porter. (Unpublished communication.)—The patient, a man aged 35, employed for 20 years in carrying tins of sheep-dip (a powder containing sulphur, soda, and arsenic), consulted Dr. Charles R. Porter in February, 1910, for an ulcerating epithelioma on the left shoulder, which had begun as a wart eight months previously. There was marked pigmentation of the skin all over the body. He was sent into the West Herts Hospital, where the growth was excised, and on microscopical examination it proved to be an epithelioma. Recurrences soon occurred in the skin of the chest wall below the scar, and were removed two months and again seven months after the first operation. As growths still returned and spread he was treated with radium and with X rays at the London Hospital, where he was under the care of Dr. J. H. Sequeira, further operation being considered useless. He suffered great pain, and for a long time he took morphia in large doses. The growths ulcerated and appeared to involve the ribs on the left side both anteriorly and posteriorly. He had continued cough and repeated profuse hæmoptysis. After being confined to bed for six months with increasing weakness he died in December, 1911.

Addendum.—The foregoing cases comprise all that I have been able to find with histories sufficiently conclusive and complete to warrant their being placed in the list. Among them have been included three cases of psoriasis (Nos. 1, 2, and 5) in which, indeed, the history of arsenic is not conclusive; but it has been considered justifiable to include them, because at the time of their occurrence no suspicion rested on arsenic as a contributory cause of cancer, so that its administration, which was so usual for that disease, especially in England and France,⁴ during the latter half of last century, may easily have escaped being mentioned, and also because they all exhibited a warty condition of the skin, which is no part of psoriasis, but is frequently seen in arsenicism. They find a place also in the lists of Nielson⁵ (8 cases), Hartzell⁶ (11 cases), Dubreuilh⁷ (20 cases), and Wile⁸ (18 cases).

There are other cases, however, to be found in medical literature where the details are too scanty for a satisfactory record, or where, though there may be a reasonable suspicion of its presence, no history of arsenic is given.

Dr. L. Geyer refers (49) to two further cases seen by Dr. Habel, who, however, had lost the notes, where cancer had developed in persons drinking the arsenicated water of Reichenstein.⁹

⁴ This is probably the explanation of the opinion of Bazin and of Hardy that they "had seen cancer develop frequently enough in those affected with psoriasis to believe in a certain connexion between the two maladies" (3, 11). Paget expressed the same opinion (27).

⁵ Melanosis et Keratosis Arsenicalis, translated by Dr. Elkind (10).

⁶ Epithelioma as a Sequel of Psoriasis and the Probability of its Arsenical Origin (3, 11).

⁷ Kératose Arsenicale et Cancer Arsenical (47).

⁸ Arsenical Cancer, with report of a case (39).

⁹ On the other hand, he erroneously credits Power with recording a case of arsenic cancer in a report to the Local Government Board. The cases described by Sir William Power (Report of the Medical Officer of the Local Government Board, 1878, No. 5, p. 31) in an epidemic among infants at Loughton, due to the use of a dusting powder containing arsenic, were not cancerous.

Dr. H. W. Stelwagon gives a plate (57) showing an epithelioma of the palm of the right hand which had "developed from a keratosis, in a case of psoriasis, after long-continued administration of arsenic. Possibly, however, this may represent Case 25.

M. Tillaux recorded a case (56) where a patch of psoriasis on the back of a middle-aged man had become the seat of an epithelioma, which, when removed by M. Tillaux, was "as large as the crown of a man's hat." The patient had consulted M. Hardy for psoriasis 11 years previously, but the medicinal treatment is not given.

Herr von Neumann (41) showed a man at the Vienna Society of Dermatology who had diffuse psoriasis and an epithelioma of the lower lip, but medicinal treatment is not mentioned.

Dr. C. W. Allen, in the discussion on Dr. Hartzell's first case (4), recalled a case so similar that he thought it was perhaps that of the same patient.

The late M. Du Castel recorded (46), under the title of "lichen corné," the case of a man aged 50, in whom epithelioma on the internal malleolus supervened after he had suffered for many years from well-marked hyperkeratosis of one of the upper and of both the lower limbs. Drug treatment is not mentioned.

Dr. G. W. Wende reported¹⁰ an interesting case of keratosis, resulting in multiple epitheliomata, in a man aged 37, in whom "no history of arsenic had been obtained," but who had "indulged in a few patent medicines." Dr. Hartzell, the late Dr. Nevins Hyde, and Dr. Schamberg, who took part in the discussion, all suspected that the keratosis was of arsenical origin.

Sir Jonathan Hutchinson also mentions in his *Archives of Surgery* and in notes of cases illustrated in the Museum of the Medical Graduates' College and Polyclinic (Case 1, drawer 13) several cases of cancer and rodent ulcer in which he had suspicions, but no proof, of arsenic having been concerned.

(To be continued.)

THE RAPIDITY WITH WHICH CONTAMINATION OF THE THORACIC CAVITY AND ITS CONTAINED GLANDS FOLLOWS INFECTION OF THE PERITONEAL CAVITY.

By C. C. TWORT, M.B., CH.B. ABERD.

(BEIT MEMORIAL FELLOW.)

(From the Laboratories of the Brown Institution.)

AS is well known, if a small quantity of an emulsion of a *non-pathogenic* micro-organism is injected into the peritoneal cavity of an animal, one of the earliest signs of an active resistance to the micro-organism on the part of the animal is a leucocytic invasion into the peritoneal cavity and phagocytosis of the injected material. The bacteria are taken up not only by the wandering phagocytes, but also by the sessile phagocytes of the liver, &c. Smears made from the liver, spleen, mesenteric glands, and peritoneal fluid about 12 hours after the inoculation will usually show the presence of a large number of bacteria, and free bacteria in the peritoneal fluid may be no longer found. The majority of the bacteria in the invaded organs and in the peritoneal fluid appear to be destroyed *in situ*, but of those taken up by the liver many are excreted with the bile and leave the body with the fæces. There is no apparent influence on the animal's health, and we say that the animal is immune to the particular bacterium which is unable to grow and multiply on account of the destructive agents of the host. A somewhat different result will be obtained after an intravenous inoculation. In this case the majority of the bacilli become lodged in the lung, although here, also, the liver and spleen both play an important part in the defence of the body, and some of the bacilli are excreted by way of the intestinal tract. With this method of inoculation, however, the kidney is the chief excretory organ and it may be severely damaged as a consequence of the inoculation of too large a dose even if a saprophytic micro-organism is used. Numerous experiments bearing on this question have been performed at the Brown Institution.¹ On inoculation of a *pathogenic* bacterium the mechanism of defence appears to be more or less the same, but it is less efficient, the efficacy varying with the virulence of the bacillus for the particular animal used and the resistance of the animal to the bacillus; the survival or otherwise of the animal depends entirely on these factors.

In naturally acquired diseases one is justified in assuming that much the same mechanism of defence takes place. Such would be the case in a general infectious peritonitis,

¹⁰ Keratosis Follicularis Resulting in Multiple Epitheliomata, Dr. Grover W. Wende (6).

¹ Centralblatt für Bakteriologie, Band lxxviii, 1913.

or in a localised peritonitis where there is an invasion of leucocytes and the formation of an abscess.

It is well known, as regards the phagocytes, that the majority of micro-organisms are not killed immediately on being engulfed, and, indeed, among pathogenic bacteria a large number are capable of multiplying within these cells, while others are nearly always intracellular and appear to develop almost exclusively in this situation. Many pathogenic bacteria which on inoculation are able to multiply are ultimately killed out if the host does not succumb before it has had time to produce the necessary protective anticorps.

The important organs in the mechanism of defence and the prevention of the bacteria from becoming generalised and causing death of the animal from septicæmia, &c., are the lymphatic glands which act as filters to the lymph, and hold back foreign particles. The blood is thus kept more or less free from infection, and the vital organs of the animal economy are less likely to become infected. In the case of diseases affecting the peritoneum or the organs covered by a peritoneal membrane, it is generally considered that the abdominal lymphatic glands are the chief agents in preventing a generalised infection, while in diseases of the lung the bronchial glands are held to play a similar part. It is also held that in man tuberculous peritonitis is an infection through the intestinal tract, while on the other hand phthisis is an infection through the respiratory passages; a theory which is supported by the fact that a relatively large number of cases of tuberculous peritonitis have the bovine type of tubercle bacillus as causal agent (infection through milk), while tuberculous disease of the lung is nearly always due to the human tubercle bacillus. This theory is not free from objection, seeing that in many diseases the site of inoculation does not prevent the disease from being ultimately produced in its usual situation, although, of course, it influences markedly the severity of the subsequent infection.

A number of experiments bearing on the distribution of the bacilli in the lymphatic glands after the inoculation of an emulsion of bacilli into the peritoneal cavity of rabbits, rats, and mice, and the rapid escape of the bacilli from the peritoneal cavity, have recently been carried out at the Brown Institution. The experiments on the rapidity of escape of the bacilli from the peritoneal cavity were performed as follows. Emulsions of bacilli of the acid-fast group, such as the tubercle bacilli, *Johne's* bacillus, and *B. phlei*, and of various non-acid-fast micro-organisms, such as *B. pyocyaneus*, *B. subtilis*, *B. coli*, and several varieties of micrococci were inoculated into the peritoneal cavity of the above-mentioned animals, mice being used in most cases. The quantity of emulsion inoculated was 0.1 to 0.2 c.c. for mice, about double this amount for rats, and 1 to 2 c.c. for rabbits. The animals were killed at varying intervals of time after the inoculation, and a microscopical examination made of the different lymphatic glands, special attention being given to those of the thorax. Where living emulsions were used cultures were also made from the glands. The animals were killed by crushing the cord and medulla, care being taken not to cause any hæmorrhage which would interfere with the subsequent removal of the glands. To obtain the glands one proceeds thus: the skin is laid back and the pectoral muscles removed from the thorax, which is opened with great care so as not to disturb the contained organs; the anterior thoracic wall is thrown back without being completely severed from the rest of the thorax, as this would necessitate cutting the internal mammary arteries; the thymus, which in mice and rats is nearly always prominent, is smoothed down and one of the lobes is carefully raised, when the tiny lymphatic glands, about a pin's head or larger in size, at the apex of the thorax can be seen. One of these glands is snipped off with fine scissors, and after being cut into pieces in a sterile tube it is inoculated on to tubes of suitable medium. Another gland is then taken and a smear made for microscopical examination. Needless to say, the manipulations must be carried out under strict aseptic precautions. Emulsions of acid-fast bacilli proved to be the most suitable for these experiments, both on account of the acid-fastness of the bacilli and the relatively low degree of virulence of most varieties for the animals under consideration. For many reasons it has been found that an emulsion of *Johne's* bacillus is the most convenient. *Johne's* bacillus is an acid-fast micro-organism allied to the tubercle and lepra bacilli,

and is the causal agent of an intestinal disease of cattle, sheep, &c., called *Johne's* disease. It is impossible in this paper to discuss the special biological features of the bacillus, but details will be found in the monograph on *Johne's* disease by F. W. Twort and G. L. Y. Ingram. It need only be mentioned here that the bacillus is pathogenic for mice and rabbits, and possibly for rats, and that it is several months before the intestinal tract becomes infected.

The experiments that have been performed demonstrate that, although the peritoneal cavity is provided with an extensive protective mechanism, inoculated bacilli escape from this cavity and can be found living and virulent in the thoracic glands shortly after inoculation. The rapidity with which this transmission takes place is remarkable, the bacilli being found from two to five minutes later in the glands, and from these cultures may be easily obtained. The bacilli found at the end of five minutes are mostly free, but a few may be already within the cells, and as the interval of time between the inoculation and the death of the animal is extended the number of bacilli not only becomes progressively greater, but the proportion of intracellular to extracellular is relatively much higher than in the animals killed earlier. It is interesting to note that as early as five minutes after the inoculation of the animal cultures can also be obtained from the pleural fluid, but the possibility of contaminating the fluid during the manipulations by the severing of the lymphatic channels is evident. On examination soon after inoculation, of the cervical, submaxillary, axillary, and groin glands no bacilli can be found. No bacilli were found microscopically in specimens made from the thoracic glands and pleural fluid of animals that were killed before making the intraperitoneal inoculation and an examination made five minutes later. A sufficient number of experiments of this description have not yet been performed to allow of very definite conclusions being drawn from them, although positive cultures were obtained. It does not necessarily follow that the human subject would react in the same way as the animals used in these experiments, but there is no reason to suppose that the reaction would be different. If bacilli other than acid-fast bacilli are used they also rapidly invade the thoracic glands, and cultures can be obtained in the same manner. If a mixture of an acid-fast bacillus and some other micro-organisms such as one of the various cocci or bacillus coli is inoculated, the bacteria soon find their way to the thoracic glands, but if the animal survives the inoculation all the bacteria disappear within a few days with the exception of the acid-fast bacilli, which, although not multiplying perceptibly, remain alive for many months.

There does not appear to be much difference in the number of bacilli found in the mesenteric and thoracic glands in animals killed about two to five days after being inoculated, although even as early as this, where the quantity of emulsion inoculated has been small, bacilli are found in the thoracic glands more often than in the abdominal glands. At a later period—at any rate, in the case of mice and rabbits inoculated with *Johne's* bacillus or tubercle bacilli—the bacilli gradually become less in the mesenteric glands, while in the thoracic glands they remain numerous for several months, but ultimately disappear in an animal unsusceptible to the particular bacillus inoculated. Among 55 rats and mice inoculated intraperitoneally with acid-fast bacilli, and examined over a period of three months, bacilli were found on microscopical examination in the thoracic glands alone 17 times, and in the mesenteric glands alone 5 times. In 7 of the animals bacilli were present in both sets of glands, while in 26 cases they were entirely absent. *Johne's* bacillus was also found in the cervical and axillary glands of rabbits and mice. All varieties of acid-fast bacilli do not seem to react exactly the same as regards their distribution in these glands—for example, tubercle bacilli seem to have a greater tendency than *Johne's* bacillus to remain in the mesenteric glands, and the species of animal used in the experiment also appears to influence the result to a certain extent. For a prolonged experiment it is better to use a living emulsion than a heated emulsion, as with the latter there is a greater tendency to accumulate at definite sites and to produce a more rapid cessation of the tissues. It is also possible to perform culture experiments parallel with the microscopical examinations, cultures often being obtained when no bacilli could be demonstrated in the smears from the glands. This is especially the case with *Johne's* bacillus, which survives for a great length of time in most of the small animals,

cultures from both the mesenteric and thoracic glands being positive in every animal. With the tubercle bacilli growths were more difficult to obtain, and it is obvious that rats and mice destroy these bacilli much more quickly than they do John's bacillus. If one is dealing with a bacillus that develops preferably in a special part of the anatomy of the animal used, then it will be found in this situation as is the case with John's bacillus. An emulsion of John's bacillus inoculated into the peritoneal cavity of a rabbit or mouse will, in some of the animals, eventually produce disease of the intestines and mesenteric glands, where a large number of bacilli may be found, while in the thoracic glands they may or may not be rare. One has here, however, an entirely different factor coming into play—that is to say, the question of the site of the animal body most suitable for the growth and multiplication of the particular bacillus. The place of predilection for the development of a bacillus has often little or no relation to the site of the primary distribution immediately after inoculation.

The inoculation of a certain quantity of oil into the peritoneal cavity to prevent any absorption of septic material has been recommended and has been practised fairly extensively, especially by continental surgeons. A few experiments bearing on this question were also performed, oil being inoculated from 15 minutes to 24 hours before the injection of the bacilli. Although the number of experiments in this direction have not been numerous, they demonstrate clearly that the oil does not prevent the escape of bacteria from the peritoneal cavity and their absorption by the thoracic glands, and it is doubtful if it in any way hinders the dissemination of the bacilli.

Incidentally, the above experiments point to a method by which acid-fast bacilli may be isolated from contaminating micro-organisms and recovered in pure culture in a relatively short space of time, and this means was utilised to isolate John's bacillus from the putrid gut of a sheep infected with John's disease. Tubercle bacilli were also isolated in the same way from emulsions of cultures purposely contaminated.

The time necessary for the escape of infectious material from the peritoneal cavity is thus often only a question of minutes, and it is obvious that even during an operation if the general peritoneal cavity is accidentally contaminated from the rupture of a localised abscess, &c., ample time is given before the end of the operation for the thoracic glands to become infected, and if these glands are penetrated there is a danger of the infection becoming generalised. These facts may explain the beneficial effect of Fowler's position after abdominal operations.

The expenses of these researches were partly paid for by a grant from the London University (Henry Dixon Fund), and I have also to thank the Royal Society for the grant which has enabled me to purchase the animals used in these experiments.

THE USE OF ARSENICAL COMPOUNDS FOR SYPHILITIC DISEASE OF THE NOSE AND THROAT:

A NOTE ON 16 CASES. BY HAROLD L. WHALE, M.D. CANTAB., F.R.C.S. ENG., ASSISTANT SURGEON, THE METROPOLITAN EAR, NOSE, AND THROAT HOSPITAL.

I HAVE treated and followed the history of these 16 patients as follows: 12 in Mr. W. D. Harmer's and Mr. F. A. Rose's clinics at St. Bartholomew's Hospital, 1 in my clinic at the Metropolitan Ear, Nose, and Throat Hospital, and 3 in private patients.

The number of doses given.—These 16 patients have had 43 injections, varying from 1 per patient to 9 (two cases).

The relative advantage of different preparations.—12 injections were intravenous, "606"; 1 intramuscular, "606"; 26 intravenous, neo-salvarsan, "914"; and 4 intramuscular emulsion of "Allenburys" hyposol. All the cases were adults, and the dose was always the equivalent of 0.6 gm. of "606." When more than one injection has been given to any patient, sometimes the second injection was of a different drug from the first. As regards the clinical results and Wassermann tests obtained, in this small series no one preparation appears to be better than another. The advantage

of hyposol emulsion is the extreme simplicity of giving it. For "914" may be claimed a very low toxicity. Not a single injection of the 26 given caused a sufficient general reaction to incapacitate the patient for a day, and the drug is given with justifiable confidence in the out-patients' clinic. Against "914" it may be said that many more injections are required to produce a clinical cure or a negative Wassermann reaction; this is illustrated in the tables given below. Some patients weary of the repeated injections, and defeat their cure by refusing to reattend hospital. After an intravenous injection the vein presumably becomes thrombosed and obliterated, either completely, or partially by a concentric phlebitis obliterans; and it is often found that on the next occasion another vein must be used. In 2 cases out of this series I was obliged, after several injections, to do an open dissection. The advantages and disadvantages of "606" are the converse of those of "914."

The interval between injections was one week, unless there were some local or general reaction, when it was two weeks.

The frequency of Wassermann tests.—As a rule the blood was tested after every second injection, except when a sudden change in the clinical picture indicated this test at other times. The blood was tested 48 hours after the injection.

Adjuvant treatment.—Between injections some of the patients had mercurial inunctions, others potassium iodide; the former yielded the better results.

The relation of Wassermann's tests to the clinical findings.—This is not exact. It is true that in none of these cases has a positive Wassermann reaction changed to negative without the patient being cured; moreover, if several doses are required the clinical cure will be complete sooner than the blood test becomes negative. But the converse does not hold good; and when after several injections the patient becomes cured of symptoms and progressive signs, but the Wassermann reaction remains positive, the injections have been stopped pending further recurrences of disease, which in this small series have not supervened during three months. The improvement of the general condition is sometimes most marked, more particularly when there has been some general reaction. In one case the red cell count rose, with two injections of hyposol, from 3,500,000 to 5,200,000 per c.mm.

The diseases treated may be classified as follows:—

Inflammation or Necrosis of Bone or Cartilage.			
No.	Bone or cartilage affected, and lesion.	Drug and number of injections.	Result.
1 ...	Ethmoid necrosis.	... 8, of "914."	{ Separation of sequestrum; disease arrested.
2 ...	Perforated hard palate (old-standing).	... 1, of "606."	Unaffected.
3 ...	Perforated hard palate, 3 years' duration, ulceration now active.	... 3, of "606."	{ Improved, partly healed.
12 ...	Perforated hard palate, one week's history.	... 1, of "914."	{ Cured, healed over.
4 ...	Gummata of septum nasi and frontal bone.	... 2, of "606."	Cured.
5 ...	Gumma of septum.	... 7, of "914."	"
6 ...	Gummata of skull and of epiglottis.	... 1, of "606."	"
10 ...	Periostitis of nasal bone.	... 2, of "606."	Improved.

Laryngitis with no Gross Lesion.			
No.	Injections.		Result.
1	9, of "914."		Cured.
5	9, of "914."		"
9	1, of hyposol.		Uncertain.
11	2, of "606."		Improved.

Gummatous Laryngitis, Nodular or Pachydermatous.*			
12	1, of "914."		Improved.
13	2, of "606," then 1, of "914."		"
14	2, of "914."		Unaffected.

* As a result of the absorption of excrescences in the anterior commissure or on one cord Nos. 12 and 13 were subsequently able to phonate "a," which they had been previously unable to do.

Inflammation of Pharynx without Ulceration.			
2	1, of "606."		Cured.
5	7, of "914."		"
7	2, of "914."		"
9	1, of "914."		Improved.
15	1, of "914."		Uncertain.
16	1, of "606," then 1, of hyposol.		Cured.