REMARKS UPON THE PNEUMOTOXIN.

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THE pneumococcus is an important agent in the production of disease in the human subject. It is the most frequent cause of acute lobar pneumonia, having been found in about 80 to 90 per cent. of the cases examined. The organism likewise invades the pleura and the blood, and appears in the bile, urine, milk, etc., whilst pneumococcal infections outside the respiratory tract are constantly met with—for example, in meningitis, peritonitis, pericarditis, endocarditis, otitis, conjunctivitis, etc. The organism is also one of the exciting causes in the forms of acute catarrh clinically grouped as "influenza."

The pneumococci, in the variety of morbid conditions they are capable of producing, resemble a kindred group of micro-organisms—the streptococci.

The virulence of the pneumococcus is subject to wide variations. The most virulent forms are met with in acute inflammatory processes, and the virulence may be preserved and increased by passages through susceptible animals. The strains of pronounced virulence lead on injection to a fatal septicaemia in one to three days, those of feeble virulence simply to local lesions. In experimental work upon the pneumococcus it is essential to use cultures of undoubted and tested virulence.

Whilst acute pneumococcal infections are accompanied by symptoms of a severe toxæmia, little of a definite character is known with regard to the specific poison of the pneumococcus.

The attempts that have been made to obtain a soluble poison from cultures of the organism have not led to encouraging results. The toxic properties of filtered cultures are feeble, and large amounts are required to produce any morbid effect. The specific nature of the soluble poisons that have been described still remains a matter of doubt.

G. and F. Klemperer,¹ in the course of a careful experimental inquiry, employed a variety of methods and of material. The toxins obtained were not of a very potent nature, as doses up to 24 c.cm. were necessary to produce a lethal effect in rabbits. These observers regarded such poisons as specific, and used them for the preparation of an antitoxic serum. The toxic and antitoxic effects were of a feeble character, and large quantities of the filtered broth cultures were necessary to produce an active immunization of animals.

Foa and Scarbone² and Scabia³ conducted experiments on similar lines, but these did not yield any more striking results. Pane's⁴ investigations upon a soluble poison were practically negative, and led him to ascribe little importance to the action of a poison in pneumonia.

Mennes,⁵ working with highly virulent strains of the pneumococcus, found that the filtered cultures possessed little toxicity. It was only in large doses that filtered or heated cultures produced a lethal effect. Broth cultures, which had been heated to 62° C. for twenty minutes, caused on injection fever, loss in weight, and at times diarrhoea, but the results were inconstant. Rabbits treated with the toxins were in some instances resistant to a fatal dose of the pneumococcus. Mennes also immunized the goat and horse with heated, then unheated, broth cultures and the blood of infected rabbits.

In the case of the horse, its serum protected against the pneumococcus and the broth toxin, which produced fever and loss in weight. Mennes does not appear to have worked with an acutely lethal toxin, and this detracts from the value of his results.

Isaëff⁶ also found that sterilized cultures in general possessed feeble toxicity, and were not fatal in doses equivalent to 3½ per cent. of the animal's weight. On the other hand, the blood of infected rabbits yielded a filtrate toxic on intravenous injection, and sometimes lethal in doses equivalent to 1 per cent. of the body weight—that is, about 10 c.cm. per kilogram of rabbit. A dose of 10 c.cm. rendered rabbits immune to the pneumococcus but not to the toxin. Sterilized broth and serum cultures in amounts of 10 to 50 c.cm. produced a rise in temperature and loss in weight. Isaëff concludes that "one cannot admit the existence of an antitoxic property of the blood in animals vaccinated against the pneumococcus." The toxins obtained by

Isaëff were, however, not sufficiently powerful to justify the conclusion drawn from his experiments with them.

Carnot and Fournier⁷ describe toxic dialysates obtained from cultures of the pneumococcus after concentration by drying *in vacuo*, and by precipitation with phosphate of lime.

The antipneumococcal serums prepared by Pane, Washbourn,⁸ and Römer⁹ by the injection of various strains of pneumococci protected animals against multiple lethal doses of virulent pneumococci. No antitoxic action has been claimed for these serums.

The efforts to obtain potent soluble poisons from fluid cultures of the pneumococcus have not proved successful, nor have the soluble poisons described shown much value as immunizing agents. None of the experiments in this direction, it may be added, furnishes any conclusive proof of the existence of a genuine secreted toxin. There can be little doubt that the essential pneumotoxin is of the endocellular type, and that it is this toxin contained within the body of the organism which is to be regarded as the more important factor in the possible production of any antitoxic immunity.

As few direct experiments have been made in this important direction, it may be of interest to put on record the results I have so far obtained.

The object of the experiments was, in the first instance, to extract a toxin from the bodies of the pneumococci by means of the cold grinding method successfully employed in the case of typhoid, cholera, and other organisms.¹⁰ The pneumococci were isolated from the human subject, and their virulence raised by passages through the rabbit. The cultures were made directly from rabbits which had died of a pneumococcal septicaemia. The heart's blood of the animals was spread over the surface of nutrient agar in Roux bottles. This procedure favoured a rapid and good growth of the pneumococcus, the cultures after two to three days' incubation at blood heat furnishing ample material for each experiment. The resultant mass, after trituration of the cocci, was taken up in 1 in 1,000 caustic potash solution, then spun and filtered. If care is taken to use pneumococci of marked virulence for grinding, acutely toxic filtrates of their cell juices are readily obtained. The strains in which a loss of virulence had occurred did not yield cell juices of any marked toxicity; for example, 1 c.cm. on intravenous, and ½ c.cm. on intracerebral injection did not affect rabbits, nor did 1 c.cm., ½ c.cm., and ¼ c.cm. kill guinea-pigs or mice on intraperitoneal injection; on the other hand, the filtered cell juices from virulent strains killed acutely in the above doses. The parallelism between virulence and toxicity was unmistakable, and is further illustrated in the figures given below. It was found that by regarding this point one was in a position to obtain not only constantly toxic cell juices from the pneumococcus, but also to increase the toxicity by further exaltation of the virulence of the organism.

The toxicity of the filtered cell juices was tested on rabbits, guinea-pigs, and mice, the majority of the experiments being made on the guinea-pig. The following figures illustrate the results obtained after three to eight passages of the pneumococcus through the rabbit.

A.—Filtered Cell Juices of the *Pneumococcus* Directly Isolated from the Rabbit.

Rabbit.	—1.0 c.cm. intravenous.	Acute diarrhoea and death.
"	0.5 "	No effect.
"	0.2 "	Intracerebral. Dead.
Guinea-pig.	—2.0 c.cm. intraperitoneal.	Dead.
"	1.0 "	"
"	0.5 "	"
Mouse.	—0.1 c.cm. intraperitoneal.	Dead.
"	0.5 "	"
"	0.3 "	"

B.—Filtered Cell Juices of the *Pneumococcus* after Passages through the Rabbit.

Rabbit.	—1.0 c.cm. intravenous.	Dead.
"	0.5 "	Very ill.
Guinea-pig.	—1.0 c.cm. intraperitoneal.	Dead.
"	0.5 "	"
"	0.3 "	"
"	0.1 "	"

C.—Filtered Cell Juices of the *Pneumococcus* after Further Passages through the Rabbit.

Guinea-pig.	—1.0 c.cm. intraperitoneal.	Dead.
"	0.5 "	"
"	0.1 "	"
"	0.05 "	"

The toxic effects were of an acute character, the animals dying in twelve to eighteen hours. The main *post-mortem* appearance consisted in a more or less acute congestion of the lungs. The filtered cell juices contained about 5 mg. of solid matter in each cubic centimetre.

The above experiments will be sufficient to prove that it is possible to extract an acutely lethal toxin from the bodies of virulent pneumococci, and one of much greater potency than the soluble toxins described by previous observers, inasmuch as the ascertained minimum lethal dose was about $\frac{1}{4}$ mg.

The endotoxin of the pneumococcus is sensitive to the action of heat. A filtered cell juice heated to 55° C. for an hour failed to kill in doses of 0.5 and 1 c.cm., whilst 2 c.cm. only caused death at the end of five days. The unheated juice was acutely lethal in doses of $\frac{1}{2}$ c.cm.

The prolonged action of chloroform vapour is also injurious to the toxin. After an exposure of one hour to chloroform vapour, 0.5, 1, and 2 c.cm. did not kill the test animals, the lethal dose of the untreated toxic cell juice being $\frac{1}{2}$ c.cm.

The immunizing experiments with the above toxin of the pneumococcus are at present in progress, and will form the subject of another communication upon the feasibility of producing an antitoxic serum.

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RUPTURE OF INTERSTITIAL TUBAL PREGNANCY: HYSTERECTOMY.

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ALTHOUGH the formation of a gestation sac in the wall of the uterus is the rarest form of tubal pregnancy, the condition is one of general interest, as it is liable to unexpectedly present itself to any one who is called upon to open the abdomen for intra-peritoneal haemorrhage.

History.

A. H., a multipara, aged 30, was seized with sudden pain in the left side of the lower abdomen while getting up from bed at 8 a.m. The menstrual periods had been quite regular up to six weeks previous to seizure. Since the time of the omitted period there had been frequent but slight pain in the left pelvic region. The last pregnancy had been three years ago. From the onset of the acute pain the abdomen became more generally tender and the collapse increased. There was no haemorrhage from the vagina.

Dr. Murray, who was called to the patient, made a diagnosis of ruptured tubal gestation and ordered immediate removal to the Scarborough Hospital.

Condition on Admission.

On admission the collapse was very marked, pulse 120 to 130 running; face and extremities cold, clammy and blanched. The abdomen was fixed, distended and tender. Palpation revealed a sort of boggy resistance. Strychnine was given hypodermically and an infusion of a pint of saline with 5 minims of adrenalin made under the breasts.

Operation.

Owing to the prompt action of Dr. Murray the patient was submitted to operation within four hours of the onset of the attack.

The peritoneal cavity when opened was found to contain a large quantity of blood clot. On bringing first one tube and then the other into the wound without finding any sac or abnormality, I thought that the diagnosis was erroneous and that the bleeding had some other source. The uterus, however, was felt to be distinctly enlarged, and on bringing it up a small ruptured sac full of clot was seen projecting from its wall just above the point of emergence of the left tube. Being unexpectedly confronted with a condition which I had previously merely heard of as a pathological curiosity, I saw no way of effectively stopping the bleeding but by removing the uterus. The patient was accordingly placed in the Trendelenburg position, and with Dr. Salter's assistance the uterus, with the left tube and ovary, was amputated from the cervix, the right ovary being preserved.

Result.

The after-history was entirely uneventful, the patient making a good recovery.

Description of Specimen.

On dividing the removed uterus an oval sac about 1 in. in its longest diameter was seen lying in the wall of the womb and slightly projecting from its surface, in connexion with and immediately above the uterine portion of the left tube. The sac, which had a rent about $\frac{1}{4}$ in. long on its peritoneal surface, was full of soft, friable tissue infiltrated with blood. No trace of the embryo was found. The cavity of the uterus was enlarged and empty, and the uterine mucosa thickened. The left ovary contained a large corpus luteum.

Cases of interstitial gestation are rare (1 to 77 of all cases of ectopic gestation, Martin), and when ruptured lead to exceptionally profuse bleeding owing to the wall being formed by vascular uterine tissue. The condition is also of interest practically, as the operation required when rupture occurs is necessarily different from that performed in ordinary cases of tubal gestation.

Although my patient made a good recovery after removal of the uterus, even more rapid than a simple case of ruptured tubal gestation I treated by removal of the tube and ovary a short time ago, yet one cannot help feeling that hysterectomy may be rather a severe operation to perform on a gravely collapsed patient, and possibly entails more mutilation than absolutely necessary. This feeling was rather strengthened by reading a case reported by Battle,¹ in which, finding a condition of ruptured interstitial pregnancy very similar to the present, he scraped out the sac and brought the uterine peritoneum together over it with Lembert sutures, the patient making a good recovery. Other cases in which the treatment consisted in removal of a wedge-shaped piece of uterus, including the sac, bringing the raw surfaces together by suture, are quoted from Franqué² and Hofmeier.³ However, one is relieved to find that hysterectomy, which was the treatment adopted on the spur of the moment, is recommended by some.⁴

The surer prevention of any further haemorrhage after removal of the uterus seems to me to render it advisable if the patient is operated on early enough to stand it; and when one considers how often tubal gestation appears to repeat itself, the natural reluctance to inflict the increased mutilation, especially in a woman who already has children, will be much lessened.

REFERENCES.

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MEMORANDA: MEDICAL, SURGICAL, OBSTETRICAL.

NERVOUS SHOCK.

ON March 12th last the patient, a stolid unemotional Scotchman, was travelling on the London and North-Western Railway to Preston, when the carriage in which he was seated ran off the line. It "telescoped" into a van in front, which had also become derailed without turning over, and the front of the carriage was slowly but steadily forced into within a foot of the patient's chest. He received no physical injuries, and for some hours felt perfectly well. He then became "nervous," and the night subsequent to the accident appears to have been one of undiluted horror. He returned to London on the 14th, and I saw him for the first time on the 16th.

The nervous symptoms were then particularly well marked and typical of the condition. He had a startled appearance, was perspiring freely, respiration much increased, pulse 120, general tremor, and there was some slight headache. He was unable to sleep, the remembrance of the gradual telescoping of his carriage being so vivid as to become a complete mental obsession. He complained of some dimness of vision and the pupil reaction was rather sluggish. There was no digestive disturbance except for some loss of appetite. He was, of course, unable to concentrate his attention on any mental work, but there was no impairment of memory.

He was given nerve sedatives, and veronal as a hypnotic. He thus got some sleep, but otherwise the condition remained practically unchanged for three days. The excessive perspiration and the rate of respiration then began to diminish, and the pulse fell to 100. The tremor still persisted, and he was very nervous at crossing a street, though curiously enough he did not object to train journeys. His weight did not decrease, and gradually he