showed an enlarged, tender, and boggy uterus with distinct tenderness in the right lateral fornix. A little glycerin was injected into the uterus, and four hours later the temperature and pulse rate fell and the patient was free from pain.

Another factor of importance is the abnormal prolongation or excessive degree of the red lochia, which is a significant sign, liable to menace health or even to cause death. If the uterine products are expelled after the third stage of labour, provided there is no sepsis, the red lochia should change from the fourth to the sixth day. Again, if the uterus is empty and is washed out with glycerin for the first few days, the lochia soon cease.

I was much impressed by a case of pneumonia complicating labour which was sent into hospital. The patient was delivered and died on the fifth day afterwards. As the lochia were excessive sections of the uterus were cut, and it was found to be full of small abscesses and most congested; in other words, the patient died not only of pneumonia, but also of secondary haemorrhage. It is evident, therefore, that if pneumonia and influenza complicate the puerperium there is usually a general infection. These events can explain at any rate one of the causes of the high mortality in epidemics such as influenza.

The importance of secondary haemorrhage is indicated by the following cases.

A patient had been ill for eight weeks after her confinement, the temperature ranging between 100° and 101° F. and the pulse between 110 and 120; she had a double femoral thrombosis. The doctor who had been called in said that the uterus was normal; but the second consultant informed me that the patient had had two haemorrhages since her confinement. The surgeon took this to be evidence of secondary haemorrhage, and the uterus was immediately treated with glycerin, with the result that the temperature quickly fell.

Another patient bled for six weeks after her confinement; this sign is evidence of sepsis. She was curetted, but the bleeding still persisted. A year afterwards she was curetted again, with the same result. She received x-ray treatment three times a week for three months, but the haemorrhage continued. She was then given a general anaesthetic and the uterus was washed out with sp. vini meth. and glycerin. She received half-hourly treatments morning and evening, and the haemorrhage stopped in five days. Daily treatments were continued for another ten days, and then she had her first normal period for two years. She has now quite recovered.

As the result of these investigations I am convinced that there is a dividing line where the red blood from a healthy wound ceases and the haemorrhage from an inflamed surface begins. It is difficult to be sure when secondary haemorrhage commences, but usually it is in the neighbourhood of the fifth to the seventh day. If women are not to be allowed to fall into a state of chronic invalidism the inflammatory surface must be treated with a drug like glycerin, which relieves the inflammation producing the haemorrhage.

Septic miscarriage is comparable with puerperal sepsis, differing only in that the former is more liable to be due to retained products of conception. No attempt is made to remove any retained products, except when pieces present at the os, or there is severe haemorrhage. By far the worst cases admitted to St. Mary Abbots Hospital have been those where attempts have been made to remove retained products either by the finger or the curette. The cause of the rise of temperature is retained septic secretions and not necessarily the products themselves. This fact has often been demonstrated by draining the uterus, when the temperature falls before the expulsion of the contents.

The following statistics illustrate the work carried out at St. Mary Abbots Hospital.

Total number of patients delivered since 1921 ...	1,657
Cases exhibiting temperature 99° F. and over ...	134
Cases of secondary haemorrhage (past two years 644 cases) ...	102
Number of deaths from puerperal sepsis ...	Nil
Number of anaesthetics administered after third stage of labour ...	2
(a) Dry labour—general peritonitis—laparotomy within 40 hours of delivery—recovery.	
(b) Secondary haemorrhage following manual removal of placenta—curetted for retained piece—nil found—report of curettings: acute endometritis.	
Number of abortions and miscarriages (2 years) ...	192
Cases with retained products (2 years) ...	104
Cases with curettings (2 years) ...	10
Number of explorations (2 years) ...	6

CONCLUSIONS.

We have arrived at the following conclusions as the result of the research work carried out at St. Mary Abbots Hospital during the past few years.

1. The definition of puerperal sepsis laid down by the Ministry of Health is inadequate and erroneous.

2. As regards the first part of the definition, puerperal sepsis is not by any means invariably accompanied by a rise of temperature. Pyrexia is merely a sign in the course of a septic process, and this is one of the main reasons why a large number of cases of puerperal sepsis are allowed to pass unrecognized through our best maternity hospitals.

3. The second part of the definition requires amending also. Inflammation can be caused by agents other than bacteria. Retained blood-clot and fragments of membrane or placenta will act as foreign bodies and will lead to inflammatory changes in the uterus.

4. Pain and tenderness must be recognized as the commencement of uterine colic and obstruction. Pain and tenderness are never physiological, but are invariably pathological after the third stage. Moreover, so long as the symptoms and signs of acute uterine colic and obstruction are not added to the list of abdominal inflammations, and are not treated as soon as these signs appear, so long will patients be subjected to abdominal explorations, whereas they might have been saved.

5. It will soon be no longer the fashion for women to bleed for weeks, months, or even years after their confinements, because students will be taught that glycerin will relieve the inflammation which produces the haemorrhage.

6. The uterus never was, and never will be, cleaned in one attempt.

7. After curetting and swabbing with strong styptics the uterus must be drained for the succeeding few days.

8. The best time for treatment is in the early days of the puerperium.

9. Every septic case following labour or miscarriage should be investigated by the health visitor and reported to the medical officer of health.

10. A special ward should be attached to every maternity hospital so that every septic case could be transferred and treated, and, if necessary, treated after leaving the hospital, since many women take their discharge on the fourteenth day and before they are cured.

11. A doctor who is skilled in the detection of the early symptoms and signs of puerperal sepsis and the modern treatment thereof must in future be attached to every large maternity hospital.

REFERENCE.

¹ *British Medical Journal*, December 31st, 1927, p. 1223.

PUERPERAL SEPSIS AND SENSITIVENESS TO STREPTOCOCCAL TOXINS.

BY

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THE anomalous distribution of puerperal sepsis has long puzzled epidemiologists. It is stated that women in good surroundings have suffered more frequently from this disease than the poor, and that rural districts show a higher incidence than towns. The number of cases in hospitals and nursing homes is likewise in excess of those occurring among women delivered in their own homes. True a greater number of abnormal cases, requiring manipulation, are to be found in institutions, and similarly the incidence of septic cases among primiparae has been considered due to the difficulties which necessarily attend a first labour.

It is especially significant that great advances in obstetric technique have done little to lessen the incidence of puerperal sepsis. That puerperal sepsis is caused by the *Streptococcus pyogenes* is now generally accepted, but a source of virulent *S. pyogenes* must be present before the disease may develop. Where is it to be sought?

As already shown in a recent paper by R. R. Armstrong and myself,¹ streptococci are not by any means invariable

inhabitants of the cervical canal during pregnancy. The true virulent disease-producing *S. pyogenes* occurs very rarely in the female passages, in all probability only when a woman has been recently associated with a source of infection. It seems that infection is not necessarily by actual contact, although the exact means of transference is at present obscure. Proof of this is furnished by the clinical histories of local and institutional epidemics of puerperal sepsis. Again, our experiments prove that a woman does not necessarily succumb to puerperal sepsis, even though she be actually harbouring the infection.

Neither first pregnancy, difficult labour, nor aggregation of cases in institutions in which the relative density of *S. pyogenes* infection is inevitably high will account fully for the capricious incidence of puerperal sepsis. Our general knowledge of infection and response suggests that in this, as in other diseases, individual reaction and personal immunity against the infecting micro-organism are important safeguards. This view receives support from the work of Okell and Parish, who believe that all the disease-producing strains of *S. pyogenes* are identical, in the sense that their main aggressive weapon is a toxin, which is the same for all strains.² Hence an attack, during her girlhood, of streptococcal sore throat, of cellulitis, erysipelas, or even scarlet fever, may be expected to have conferred on a woman a greater or less degree of protection against the most virulent and fatal form of streptococcal infection, puerperal septicaemia. It is a recognized fact also that a woman who has once suffered from puerperal sepsis is seldom or never attacked in subsequent pregnancies.

Attempts in the laboratory, with experimental animals, to demonstrate and measure antistreptococcal immunity have proved quite unexpectedly unsuccessful. Yet the value of some foreknowledge of the reaction of a primipara to *S. pyogenes*, with the implied possibilities of prophylactic immunization before delivery, is beyond dispute.

The investigation to be described was initiated to test the reaction of pregnant women to the scarlatinal toxin, without any preconception as to results. An experiment at St. Bartholomew's Hospital by Sir Frederick Andrewes³ on a number of hospital students showed that a proportion were sensitive to scarlatinal and other streptococcal toxins. This experiment did not altogether make clear the correlation of toxin-sensitiveness with a past history of scarlet fever or streptococcal infections. With the accumulation of data the test on women has come to assume positive significance, as each has been followed through her pregnancy, labour, and puerperium.

A supply of standardized scarlatinal toxin, prepared at the Wellcome Research Institute, was kindly furnished by Dr. C. C. Okell, whose pioneer work on the toxins of the *Streptococcus pyogenes* group is generally recognized and acclaimed. The preparation has been used in all tests. Four intradermal injections, respectively one-fifth of a cubic centimetre of a dilution of 1 in 1,000, 1 in 3,000, and 1 in 6,000 of toxin with control, were made into the skin of the palmar surface of the forearms. A positive reaction consists in the appearance within twenty-four hours of an erythematous patch, varying somewhat in size with the intensity of the reaction and the dilution employed, from one-quarter of an inch in diameter to an area one inch or more in length. In about half the cases gradation in response is apparent, corresponding with the strength of toxin employed. But in many cases there is little to choose between the high and low dilutions. In general practice it will probably be found sufficient to employ only a dilution of 1 in 1,000 to discriminate between reactors and non-reactors.

The tests were made on women at St. Bartholomew's Hospital and the City of London Maternity Hospital. One hundred cases have been tested, and their labours and puerperia observed. Of these 100 women, 27 were toxin-sensitive, while 73 did not react to any dilution. The cases may be grouped as follows.

(a) Women Giving Positive Reactions.

Of 27 women, 8 experienced morbid puerperia, according to the British Medical Association standard. In only 2 cases were the cervixes swabbed, but each yielded a pure

growth of *S. pyogenes*. The high percentage (30 per cent.) of morbidity is remarkable when it is considered that 6 of the 8 women passed through normal labours without any interference, while the other two sustained only slight post-partum haemorrhages. The details of each case may be summarized.

1. Normal labour; morbid puerperium.
2. Normal labour; post-partum haemorrhage; temperature 100° F.; second to eighth days, maximum temperature 102° F.
3. Normal labour; morbid puerperium; temperature 100.2° F., fourth and fifth days.
4. Normal labour; morbid puerperium; *S. pyogenes* isolated from cervix.
5. Normal labour; morbid puerperium; post-partum haemorrhage; *S. pyogenes* isolated from cervix.
6. Normal labour; morbid puerperium.
7. Normal labour; morbid puerperium.
8. Normal labour; morbid puerperium.

The remaining 19 women passed through normal puerperia; 18 of these experienced normal labours, one was delivered by forceps.

(b) Women who did not React.

In this group there were 73 women. Two of these experienced morbid puerperia, but in each case the constitutional disturbance was very slight, and in neither could *S. pyogenes* be found in the cervix or blood. The series was of special interest in that it contained many abnormal cases in which sepsis was to be expected, yet, as will be seen from the summary below, no such event occurred.

1. Severe post-partum haemorrhage; admitted pulseless. Manual removal of placenta performed after blood transfusion. Normal puerperium.
2. Patient delivered on district; severe post-partum haemorrhage, associated with a morbidly adherent placenta which required manual removal. Patient collapsed for some hours. Slight rise of temperature on third, fourth, and fifth days; lochia offensive. Cervical culture gave growth of *S. salivarius* and staphylococci.
3. Caesarean section; normal puerperium.
4. Caesarean section; normal puerperium.
5. Severe tear of perineum; normal puerperium.
6. Severe tear of perineum; normal puerperium.
7. Normal labour; temperature slightly raised in puerperium; haemolytic streptococci not found in cervix.
8. Severe pyelitis of pregnancy; secondary anaemia, red blood corpuscles 2,400,000 per c.mm. Placenta praevia. Transverse lie; artificial rupture of membranes; later, internal version. Temperature slightly raised in puerperium, maximum 100° F. on fifth and seventh days. No streptococci found in cervix.
9. Concealed and external ante-partum haemorrhage; artificial rupture of membranes, vagina plugged; puerperium normal.
10. A multipara with contracted pelvis. Interspinous diameter 9 in., intercrural 10 in., external conjugate 6½ in. Transverse lie; external version; difficult delivery with forceps after long second stage lasting six hours. Normal puerperium.
11. A case of severe post-partum haemorrhage; manual removal of morbidly adherent placenta. Normal puerperium. Cervical culture showed *Staph. albus*, *B. coli communis*, and *S. salivarius*.
12. Case of ante-partum eclampsia; persistent right occipito-posterior, delivered as such with forceps. Puerperium normal till twelfth day, when rigor occurred; patient developed pyelitis and *B. coli communis* septicaemia. No streptococci in cervix or blood on repeated examination.
13. A case of severe post-partum haemorrhage. Manual removal of placenta performed. Normal puerperium; cervical swab sterile.

No case has yet occurred, so far as is known, of a woman, sensitive to toxin, who has harboured the *S. pyogenes* in her genital tract without developing puerperal fever. Since the observations recorded above a morbid puerperium has occurred in a woman, who failed to react to toxin, from whose cervix the *S. pyogenes* was isolated. This woman, when tested three weeks before delivery and again at the time of delivery, was suffering from suppurating scabietic sores of the hands and feet. These sores may well have been infected with pyogenic streptococci. Unfortunately cultures were not taken.

The conclusion that toxin-sensitiveness indicates susceptibility to puerperal sepsis is not disturbed by this observation, however. There seems no reason to doubt the existence of a degree of resistance to *S. pyogenes* infection sufficient to neutralize the dose of toxin employed for

intradermal inoculation and to prevent a severe septicæmia, but insufficient to prevent a local infection of the uterus; just as every grade of susceptibility to scarlet fever or tonsillitis is well recognized.

No skin tests on women actually suffering from puerperal fever have been made, but it is hoped to undertake these as opportunities arise. A fatal case of *S. pyogenes* septicæmia in a man, recently tested, proved vigorously toxin-sensitive. In a few instances toxins prepared from strains of *S. pyogenes* from puerperal sources have been tested simultaneously with the standard scarlatinal toxin, and so far with the same results, thus supporting Okell's findings.

It is realized that one hundred cases are insufficient to afford conclusive proof of the significance of the toxin test. The investigation is being pursued, therefore, and it is hoped soon to have further evidence. Finally, it may be stated that the possibilities of the toxin-sensitive test as a guide to preventive treatment against *S. pyogenes* infections have not been overlooked. If the conclusions reached receive support, the time may come when prophylactic immunization of toxin-sensitive women will be practised as a routine. But the indications for such immunization, the optimum time in relation to labour, the means employed—by active dosage with toxin or by passive immunization with antitoxic serum—have yet to be studied.

Summary.

1. Of 100 pregnant women, 27 were sensitive to a dose of 1/5 c.cm. of a dilution of 1 in 1,000 scarlatinal toxin injected intradermally.

2. Eight, or 30 per cent., of the "toxin-sensitive" women experienced morbid puerperia. From the cervixes of those examined a pure growth of *S. pyogenes* was obtained. Labour was altogether normal in 6 of these cases and normal in the remaining 2, except for slight post-partum hæmorrhage.

3. Of 100 pregnant women, 73 gave no reaction to scarlatinal toxin; two of these exhibited morbid puerperia (British Medical Association standard), but in neither case could streptococci be found in the cervix or blood.

4. Thirteen of the non-reacting women, or 19 per cent., sustained difficult labours but healthy puerperia; 6 of these were examined bacteriologically, but in no case was *S. pyogenes* found.

Conclusions.

1. The optimum dose of scarlatinal toxin for intradermal test is 1/5 c.cm. of a dilution of 1 in 1,000 strength.

2. Women who react positively to intradermal inoculation of scarlatinal toxin are more liable to develop puerperal sepsis than non-reactors.

3. Difficult labour, with or without laceration, predisposes to puerperal infection only in so far as the risk of introduction of *S. pyogenes* is thereby increased, provided an external source of infection be present.

The work was carried out during the second year of my tenure of the Lawrence Scholarship at St. Bartholomew's Hospital. My thanks are due to Dr. R. R. Armstrong for active collaboration and advice throughout the inquiry.

REFERENCES.

¹ *Proc. Roy. Soc. Med.*, 1928, vol. xxi, p. 28. ² *Lancet*, April 14th, 1928, p. 748. ³ *St. Bartholomew's Hospital Journal*, September, 1926, p. 181.

A YELLOW FEVER VACCINE.

BY

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(From the Wellcome Bureau of Scientific Research.)

THE urgent necessity of some method of protective vaccination against yellow fever has been strikingly demonstrated by the occurrence of epidemics of increasing severity in West Africa, and also by the recent tragic deaths of three distinguished investigators from this disease. Consequently it seemed of interest to see whether a protective vaccine could be prepared by using any of the methods employed in the case of other diseases caused by filterable viruses, and in particular those recommended by Todd (1928) for fowl plague, Laidlaw and Dunkin (1928) for dog distemper, and Bedson, Maitland, and Burbury (1927) for foot-and-mouth disease.

The strain of yellow fever employed was isolated from a case at Dakar, and has been maintained by passage in rhesus monkeys and mosquitos until the present time (see Sellards and Hindle, 1928). Although the minimal dose of virus has not been estimated the subcutaneous inoculation of 0.0001 gram of the liver of an infected monkey produces death in four to five days, and sixteen monkeys have been inoculated with the virus, with fatal results in every case. The results of Stokes, Bauer, and Hudson (1928) in West Africa have also shown that the infection is almost invariably fatal in rhesus monkeys, and therefore in the following experiments the possibility of natural recovery from the disease need hardly be considered.

Formalinized Vaccine.

Part of the liver and spleen of monkey H 10, which had died from the disease, was ground up in a mortar with broken glass, and the resulting paste mixed with five parts its weight of normal saline, to which was added sufficient formalin to make a strength of 1 in 1,000 formaldehyde. The emulsion was filtered through muslin and kept in the ice chest at 0° to -3° C. until used. This vaccine has been tried on only one monkey, with the following results.

Rhesus H 13 was inoculated subcutaneously with 1 c.cm. of formalinized vaccine on April 19th, 1928. It showed a rise of temperature of two to three degrees on the fourth and fifth days, but no other obvious reaction. On April 27th it was inoculated subcutaneously with 0.2 gram of infected liver from monkey H 11, which had died from the

disease, and after an incubation period of three days had a mild attack of yellow fever, with four days of fever followed by a subnormal temperature and then a return to the normal. Two untreated control monkeys, inoculated subcutaneously at the same time, one with 0.001 gram and the other with 0.0001 gram of the liver of monkey H 11, died of yellow fever after five and five and a half days respectively.

This vaccinated monkey was again inoculated on May 24th with approximately 1 gram of liver material from an infected monkey, and again showed nothing more than a slight febrile reaction, which was probably the result of the large dose administered. Further experiments with this vaccine are in progress.

Phenol Glycerin Vaccine.

Part of the liver and spleen of the same monkey (H 10) used in the preparation of the above-described vaccine was treated in a different manner. The organs were cut up into small pieces and washed well with normal saline in order to remove all traces of blood. The tissue was then ground up in a mortar with broken glass, and the resulting paste mixed with four times its weight of the following mixture:

Glycerin	...	...	...	...	...	600 c.cm.
5 per cent. phenol	...	...	...	...	...	100 c.cm.
Distilled water	...	...	...	...	...	300 c.cm.

The emulsion was then filtered through muslin and kept at room temperature for seven days, after which it was placed in the ice chest. This vaccine has been tested on seven monkeys, with the following results.

Rhesus H 12. This monkey was inoculated subcutaneously on April 19th, 1928, with 1 c.cm. of phenol glycerin vaccine which had been kept in the ice chest for twenty-four hours, and, except for one day, when it had a poor appetite, the animal showed no reaction as a result of the inoculation. Eight days later it received a subcutaneous injection of 0.2 gram of infected liver material from monkey H 11, but showed no reaction. Six days later it was again inoculated with 1 gram of infected liver, and on May 24th, five weeks after vaccination, received yet another inoculation of 1 to 2 grams of liver material from two monkeys which had died from the disease.

This monkey, therefore, has been inoculated on three separate occasions with enormous doses of the virus, but in no case was any rise in temperature observed, and the animal has remained in perfect health.

These results were so favourable that it was decided to