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THE STORY OF PUERPERAL FEVER—1800 TO 1950*

BY

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Mr. Le Fanu's (1951) bio-bibliography of Jenner makes it clear that Jenner's active mind concerned itself with many things. Apart from his famous work on vaccinia and the prevention of smallpox, he wrote about the curious nesting habits of the cuckoo, the migration of other birds, the hibernation of hedgehogs, distemper in dogs, coronary occlusion in relation to angina pectoris, and the treatment of tetanus. But, so far as I can ascertain, he did not write anything about puerperal fever, although as a country practitioner it must have often come to his notice. Like smallpox it was one of the major hazards of adult life in those days, and there is little doubt that Jenner sometimes reflected upon its distressing and puzzling features.

It so happened, too, that the publication of Jenner's famous inquiry into the nature of vaccinia and the results of vaccination (Jenner, 1798) almost coincided with the first major advance in knowledge about the aetiology of puerperal fever. Both occurred in the last decade of the eighteenth century—those fertile years that produced the French Revolution and so many other notable events.

Of course, the history of puerperal fever goes back a long way beyond Jenner's time, but I propose to deal with its development only from that time till 1950. Those of us who are older know very well the tragedy that this fever used to be even in the early days of this century. We can recall the young mother who had gone through the hazards of her first pregnancy and the great adventure of her first confinement, and had brought forth a healthy child, only to be struck down a day or two later by the fatal fever. Or it may have been an older woman, who had already borne several children, and then, following a later confinement, developed fever and quickly died, leaving a father and his young family to fend for themselves. I imagine that all of us, if we were to trace back our family history for two or three generations, would come across one or, more likely, several instances in which this dreaded fever had carried off our female forebears. In my own family there have certainly been two or three such tragedies. Owing to these distressing circumstances there can hardly be any disease which has brought more poignant sorrow to the human race.

There are no reliable figures for the annual death rate from this cause before about 1880, because the certification of deaths was not satisfactory, but from that date until about 1930 the Registrar-General's returns show that there were about 2,000 deaths a year from sepsis connected with childbirth in England and Wales. In those 50 years we lost about 100,000 women of child-bearing age from this cause.

To the medical profession this was a serious challenge, and difficult to understand. In 1928 the Ministry of Health appointed a committee to inquire into the whole question of maternal mortality and morbidity. Four years later this committee reported (Ministry of Health, 1932) that there had been no appreciable diminution in the number of maternal deaths up to that time, and it called attention to the puzzling features of puerperal infection. It would appear "out of the blue" in the practice of one doctor or one hospital for no apparent reason, and would sometimes spread in epidemic form—at other times it did not. It occurred after normal as well as after difficult labours. Its clinical picture varied greatly.

First Light on the Disease

One of the first to throw real light on the aetiology of the disease was Alexander Gordon, who as a young man in Aberdeen was doing most of the obstetric work of that city in the latter years of the eighteenth century. He made two observations which were important—the first, that the disease was in some way related to erysipelas; the other, that it was being transmitted to women in labour by doctors and midwives. Gordon (1795), in his report on 28 cases, declared that he himself had been the unwitting agent in several instances, and he gave the names of several midwives, and the circumstances in which he believed they had transmitted the disease. This very forthright document did not make him popular in Aberdeen, and he found it expedient to leave that city and take service in the Navy, where there was no obstetric practice. He died of tuberculosis at the early age of 48. There is little evidence that Gordon's thesis became widely known or was accepted among obstetricians of his day, although his paper was reprinted as an appendix to a book on puerperal infection by William Campbell of Edinburgh in 1822.†

Twenty years later Gordon's ideas received strong support in America, by the advocacy of Oliver Wendell Holmes, of Boston, Massachusetts. Holmes was not

*Jenner Memorial Lecture delivered at St. George's Hospital, London, on October 25, 1955.

†Gordon's paper was reprinted a second time in 1849 in a book entitled *Essays on Puerperal Fever and other Diseases Peculiar to Women*, edited by Fleetwood Churchill for the Sydenham Society of London.

practising obstetrics—he was an anatomist, and later, of course, a notable writer—but at a medical meeting he heard a report on the death of a colleague after performing a necropsy on a woman who had died of puerperal fever. Before taking to his bed this doctor had continued his obstetric practice and several of the women he delivered in that period had also contracted puerperal fever. Holmes was so impressed by this story that he set about making inquiries among his medical confrères, and in 1843 he published his findings in his classical paper, "On the Contagiousness of Puerperal Fever." (In this paper he referred to Gordon's earlier observations.)

Holmes had no idea how the infection was being conveyed to the women in labour. Lacking knowledge of microbic agents, he postulated (as others had done) certain "miasms" in the air. At the end of his paper he made some practical suggestions which he hoped might help to avoid the transfer of the infection. Any doctor, he said, who had one case of puerperal fever should regard his next patient as in danger. If he had two cases the doctor should give up obstetric work for a month and "purify" himself (Holmes did not specify how this was to be done). If he had three cases the doctor should give up midwifery work altogether. And he added that no doctor doing midwifery should carry out post-mortem examinations on infected patients.

These heterodox views, like those of Gordon, were received with considerable scepticism, and some of the leaders in obstetrics in the United States did their utmost to refute them.

Semmelweis's Conclusions

A few years later the alarm was sounded yet again, and still more clamorously, by Ignaz Semmelweis in Vienna. Semmelweis had joined the staff of the largest maternity clinic in the world at that time. It was built in two separate divisions—one of them, Division A, run by male obstetricians who had the teaching of students, and the other, Division B, run by female midwives. Semmelweis soon noticed that there was far more puerperal infection in Division A than in Division B—roughly three times as much. (In some years no less than 10% of the women delivered in Division A were dying of sepsis.) Worrying over this discrepancy, Semmelweis came to the conclusion that it was almost certainly related to the fact that the male obstetricians (and the students) attended post-mortem examinations (and sometimes assisted in them) and then went direct to the lying-in wards. They did not always wash their hands, since that had not become a part of the regular ritual at that time.

Semmelweis, of course, did not know any more than Holmes how the puerperal infection was conveyed. He postulated the transmission of "cadaveric particles," or "decomposed animal organic matter," or sometimes simply "harmful things." His teaching was rejected by most of his fellow obstetricians and they made life difficult for him. In the end, however, he did persuade them to wash their hands in chlorinated lime before undertaking their obstetric work, and that apparently brought down the case mortality of Division A to the same level as that of Division B—namely 3%. After some years he found the atmosphere of Vienna so uncongenial that he retired to his native Budapest, but finally developed delusions (perhaps not so unreal?) of persecution, and died in a mental institution in 1865. His very wordy treatise on the aetiology, concept, and prophylaxis of childbed fever was published in 1861.

To these three men, then—and perhaps most of all to Semmelweis—we owe the knowledge that puerperal fever is a communicable disease and that it is frequently transmitted by those attending the woman in labour.

Investigation into the Infecting Agent

From then onwards the problem became largely one of detective bacteriology. The nature of the infecting agent was not known; nor where it came from; nor how it was transmitted. Many laboratory workers shared in that investigation during the next 70 years. First, two Alsatian doctors, Coze and Feltz, reported in 1869 that they had seen what they called *microbes en chaînettes*—our "chains" of streptococci—in the lochial exudate of women with puerperal fever. Pasteur (1879) confirmed this and added that he had seen similar *microbes en chaînettes* in the blood of women dying of the disease. He had no doubt that they were responsible for the fever. The story has often been told of the medical meeting in Paris at which a speaker was presenting the conventional vague views about puerperal infections when Pasteur arose in the audience and declared he was talking nonsense. "It is the doctor and his staff," he said, "who carry the microbe from a sick woman to a healthy woman." When the orator expressed doubt about whether anybody would ever see that microbe, Pasteur strode up to the blackboard and drew a picture of a streptococcal chain. "There," he said, "that is its picture."

At that time the cultivation of microbes in the laboratory was unknown, but in 1881 Koch introduced solid gelatin for the purpose, and that was soon followed by agar, which was more convenient. The streptococci Pasteur had seen were then grown, but much mixed with other species. Schottmüller (1903), of Hamburg, was one of the first to show that by adding fresh blood to the melted agar before it solidified the streptococci associated with human septic infections (including puerperal fever) could be differentiated from the many other bacterial types by the discoloration of the blood round their colonies. Howard Brown (1919), of Baltimore, carried the differentiation further when he showed that streptococci could be divided into three kinds by the blood plate—the haemolytic varieties which discoloured the blood; the viridans type which changed it green; and a third type, including the enterococci, which did not alter it at all.

On that foundation there has developed an investigation of the haemolytic group of streptococci which has gone on continuously from 1918 to the present time—and is not yet finished. It began with the work of Dochez, Avery, and Rebecca Lancefield (1919) at the Rockefeller Institute in New York, and has been continued by Mrs. Lancefield, by the late Fred. Griffith and V. D. Allison in this country, and by many others. It has been shown that the streptococci which haemolyse blood do not form a homogeneous microbic "community," but can be subdivided by serological methods into several "groups" and "types," and sometimes subtypes. Particular types were often found to be associated with outbreaks of streptococcal disease—for example, scarlet fever—and it was hoped that the riddle of puerperal infection would be solved by demonstrating the transfer of a few such types from one woman to another. But it was not so simple as that.

However, by gradually sorting out the evidence over a period of years, and by improving the techniques of differentiation and identification of streptococcal strains, it became possible in the early 'thirties to build up the aetiological pattern of the disease. It seemed clear that the infecting streptococci might be transferred from several sources: in some instances from a mother's own throat or nose or skin; in others from the nose or throat or hands of a doctor or nurse attending her confinement; in others, again, directly or indirectly, from a member of her family—for example, from a child's discharging ear or skin abrasion. The actual transmission, too, might occur in different ways—for example, by the obstetrician's hand, by unsterilized instruments or dressings or lotions, by dust, or even sometimes by flies.

A Policy of Prevention

For all the patient, very laborious work leading up to this conclusion credit is due to many people. After Rebecca Lancefield and Fred. Griffith, who did the pioneer work, I

think we should remember especially my sister, Dora Colebrook (1935)* and Ronald Hare, of Queen Charlotte's Hospital. John Smith (1931), of Aberdeen, and Dr. Paine (1931), of Sheffield. Their work, with that of others, made it possible to formulate a policy aimed at preventing the transfer of the dangerous streptococci to the mother in labour. The chances of transfer from the throat or nose could be at least much diminished by the conscientious wearing of masks, and by the detection of dangerous carriers of streptococci in the respiratory tract (especially those with a chronic nasal infection because of the risks associated

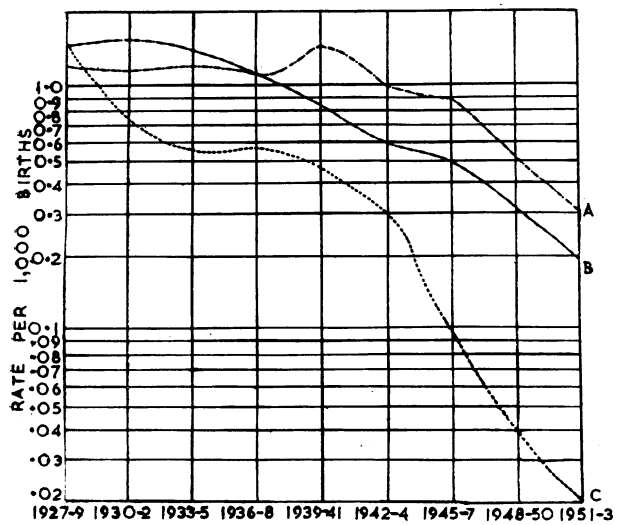


FIG. 1.—Maternal mortality in New Zealand; showing the number of deaths per 1,000 births, from all puerperal causes for triennial periods 1927-9 to 1951-3. A, Accidents, haemorrhage, and other mortality. B, Eclampsia and other toxaemia. C, Puerperal sepsis.

TABLE I.—*Maternal Mortality in New Zealand, Showing the Number of Deaths from All Puerperal Causes from* 1927-9 *to* 1951-3

	1927-9	1930-2	1933-5	1936-8	1939-41	1942-4	1945-7	1948-50	1951-3
Puerperal sepsis	128	58	39	44	46	30	12	5	3
Accidents, haemorrhage, and other mortality	124	124	104	91	135	94	110	79	47
Eclampsia and other toxaemia	101	97	93	94	80	58	62	44	30
Maternal mortality excluding septic abortion	353	279	236	229	261	182	184	128	80

with handkerchiefs). The chances of transfer by the obstetrician's hands could be minimized by the use of rubber gloves and by a wise use of suitable antiseptics. Transfer of infection within the mother's home could be avoided by arranging for delivery in a hospital whenever there was any reason to fear such a danger. Transfer from another infected woman could be guarded against by her immediate isolation. And the special dangers of difficult deliveries could be countered by the provision of more maternity beds, and by the better organization of the maternity services.

That, briefly, was the programme which gradually evolved between 1928 and 1935. It seemed to offer the best hope of reducing the annual heavy toll of maternal deaths. In one small country—namely, New Zealand—where it was vigorously pursued from 1927 onwards, the records suggest that it did have an appreciable effect. Fig. 1 and Table I show that the death rate per 1,000 births from puerperal sepsis fell rather sharply during the years 1927 to 1932, when the policy outlined above was put into action.† In England and Wales evidence for a decided effect was less convincing (Fig. 2 and Table II).

The outlook for curing, as opposed to preventing, the disease was not encouraging at that time. Although Dochez, Avery, and Lancefield (1919) had demonstrated the possibility of protecting animals by the serum of animals immunized against some of the streptococcal types, the use of antistreptococcal sera of various kinds in infected human beings was generally unsuccessful, and there was even some evidence (Colebrook, 1935) that they sometimes were harmful. Blood transfusions and various drugs, including some of the organic arsenicals (Colebrook, 1928; Colebrook and Hare, 1934) were also tried without success. Almroth Wright (1915) and Wright, Fleming, and Colebrook (1918)

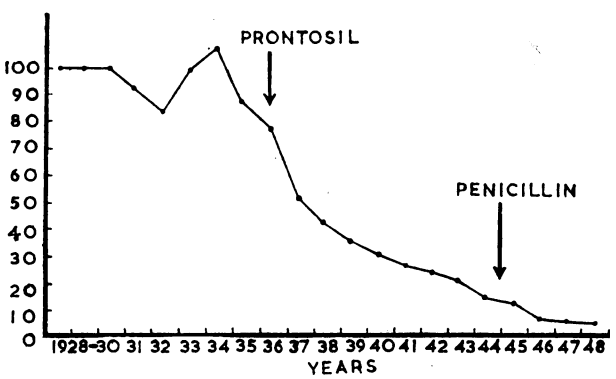


FIG. 2.—Deaths from puerperal sepsis in England and Wales from 1930 to 1948 in terms of the average for the years 1928 to 1930.

TABLE II.—*Deaths from Puerperal Sepsis and Other Diseases in England and Wales from* 1928 *to* 1948. (*By courtesy of Dr. Percy Stocks*, 1950)

Year	Puerperal Sepsis	Erysipelas, Scarlet Fever, Septicaemia, Pyaemia, Cellulitis, and Acute Abscess	Ear and Mastoid Disease
1928–30	100*	100*	100*
1930	100	104	100
1931	92	97	95
1932	84	93	98
1933	100	109	108
1934	109	128	118
1935	88	94	98
1936†	79	88	98
1937	51	60	91
1938	43	57	81
1939	38	44	78
1940	31	44	61
1941	28	39	57
1942	26	31	57
1943	22	34	64
1944	16	34	64
1945	14	28	57
1946	9	19	51
1947	8	16	47
1948	6	—	—

* The average figure for the three years is expressed as 100 and the totals for subsequent years are in terms of that figure.

† Prontosil began to be widely used in the second half of 1936. Penicillin was not widely used for the civilian population until the end of 1944.

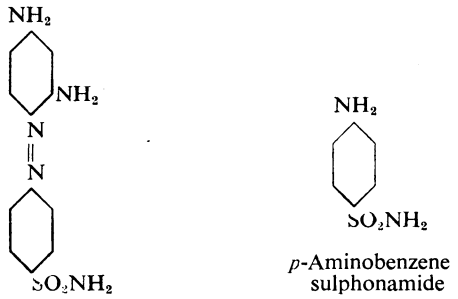
had shown, during the first world war, that the streptococci associated with septic infections of man were particularly well adapted to growth in human blood and tissues, and it was difficult, in 1935, to envisage any form of therapy that would overcome that advantage.

But, contrary to our expectation, success was just round the corner. It came from Germany, and from experiments on mice. Early in 1935 Professor Domagk reported that he had infected 26 mice intraperitoneally with streptococci derived from a human infection. Fourteen of them were left alone and they all died within four days. The remaining 12 received a single dose, one and a half hours later

*I have placed my sister's name first in this list, although her work was reported last, because, in an investigation bristling with difficulties and possibilities of error, I think her conclusions were more completely checked, and counterchecked, than those of any other worker in this field—and are therefore, perhaps, of the greatest value.

†I am indebted to Dr. L. Averill, of Christchurch, New Zealand, for calling my attention to these figures and for Fig. 1.

by stomach tube, of a red dye which Domagk subsequently named "prontosil." It had the structural formula shown below.



Prontosil

p-Aminobenzene sulphonamide

All these 12 mice survived, at any rate for the seven days of observation. That was an astonishing result. There were also a few reports from Germany of the clinical trial of the drug in human infections, but they were not very convincing. Levaditi and Vaisman (1935), in France, repeated Domagk's experiment with mice and got considerable success, although not the 100% which Domagk had reported.

At Queen Charlotte's we had at first less success, using streptococci freshly isolated from our puerperal infections, but these were somewhat less virulent for mice than the strain Domagk had employed. When we repeated the test with a strain which we had originally supplied to Dr. Buttle at the Wellcome Laboratory and which he had subsequently passed through a number of mice, we got good protection of our mice by prontosil, but ultimate survival only if we gave them several doses.

In view of this success it seemed clearly worth while to try the drug on some of our puerperal fever cases which we knew to be infected with haemolytic streptococci. At first we treated only the more severe cases, for which we had no promising therapy. The grave prognosis in such cases had become all too familiar to us. The death rate had ranged consistently between 20 and 30%.

Almost at once, with the new drug, there was a surprising and most gratifying change. Signs of incipient peritonitis did not develop as we expected; positive blood cultures changed quickly to negative—I recall one woman in particular whose blood for the first three days of treatment grew over 3,000 colonies of streptococci per c.cm., on the fourth day it grew none, and at the same time her temperature fell from 104° F. (40° C.) to normal, and never rose again above 99° F. (37.2° C.). This was something that we had never seen before in ten years' experience of the disease.

The Sulphonamides

The case mortality in the first series of 64 patients (all infected by haemolytic streptococci) was 4.7%. In the previous five years before prontosil it had ranged from 16.6 to 31.6%, averaging about 25%. It seemed clear to most of us that in red prontosil we had at last got a drug which could change the course of a haemolytic streptococcal infection in human beings as well as in mice.

Nevertheless, the triumph of red prontosil as such was short-lived, for Tréfouël and his colleagues (1935) at the Pasteur Institute soon surprised us all by the suggestion that the red dye was probably broken down in the body to a much simpler compound, *p*-aminobenzene sulphonamide, which had been known for many years, and that this was in fact the active agent in curing streptococcal infections. They supported that view by demonstrating curative effects in mice similar to those obtained with the red dye. And very soon my colleague, A. T. Fuller (1937), at Queen Charlotte's, was able to obtain evidence of the breakdown of the dye in our patients.

These findings naturally led to a change-over in human therapy from red prontosil to the simpler and cheaper compound which we soon came to know by the name sulphanilamide, the first of the "sulpha drugs." In 1937 we were able to report from Queen Charlotte's (Colebrook and Purdie, 1937) that in the first 106 patients treated by sulphanilamide we had obtained results which were just about as good as those with red prontosil. We were also able to show that the improvement in the patients coincided with an increased killing power of their blood for haemolytic streptococci. Apparently (to quote Florey's (1945) words later with regard to penicillin), "the drug was being kept in the blood stream and was absolutely restraining the growth of the streptococci and killing them without interfering with the normal defence mechanism of the body."

That, I think, was a great advance. Few of us realized at the time where it was going to lead. We had no idea that within a couple of years the grim shadow cast by lobar pneumonia over the human race would be practically lifted, and that cerebrospinal meningitis, gonorrhoea, many urinary infections, middle-ear and mastoid disease, and a host of other infections would lend themselves to successful treatment by the new drugs. However, that is not my story.

A Changed Outlook

To come back to puerperal fever. The years following 1936 confirmed our early impressions and brought about a completely changed outlook in treatment, which was quickly, and unmistakably, reflected in the national death rate. Dr. Percy Stocks (1950), of the Registrar-General's Office, has given us a valuable résumé of the deaths in England and Wales for the nine years before sulphanilamide (or prontosil) came into general use, and for several years after. His figures are set out in Table II, and in Fig. 2 I have presented those for puerperal infection in the form of a graph. As a baseline for the pre-prontosil years he took the average of the total deaths during 1928, 1929, and 1930 and called it 100. The deaths for all the subsequent 18 years are calculated in terms of that baseline figure. It will be seen that in 1932 there was a drop to 84, but in 1934 the figure rose again above the baseline, to 109. From the year 1937, when the new drugs were widely used for the first time (they had become known in England during June of 1936 by the first of the two articles by Colebrook and Kenny (1936) from Queen Charlotte's), there was a very decided drop, to 51, and progressively each year until by the beginning of 1945, the year in which penicillin became generally available to the British civilian public, it had already fallen to 16.

However, our early experience with prontosil and sulphanilamide was not accepted by everybody as proving that these drugs had really done what was claimed for them. Some critics thought that the arrival of the drugs had coincided with a rather sudden change in the virulence of the haemolytic streptococcus. At Queen Charlotte's we had seen no such change (the case mortality in the six months prior to the first use of red prontosil was 26.3%). But at the other side of London, at Hampstead, the puerperal fever cases in the L.C.C. unit did appear to have been somewhat less severe in 1935 and the early part of 1936 than they had been before that time. A similar change was observed at Sheffield by Dr. Paine. There was therefore some conflict of evidence on this point.

Dr. Stocks's recent résumé, covering all the diseases in which fatal infection by haemolytic streptococci predominates (see Table II), is particularly valuable in this respect. It shows that in his second and third groups, as in the puerperal sepsis group, there was no unmistakable decline before 1936—but a very definite fall after that year. His own comment was in these words: "I do not think there is good evidence for a downward trend in streptococcal virulence before 1937—and after that date proof of it would be difficult."

I think few people to-day would deny that 1936 was the turning-point in the history of puerperal infection, and that the arrival of prontosil brought about that change. When penicillin became available in 1945 the situation became

better still, because that antibiotic is an even more potent antistreptococcal agent than the sulphonamides. But it is evident that, even if penicillin had not arrived when it did, the story of streptococcal puerperal fever would not have been very different.

Two Pertinent Questions

Before I leave the subject of prontosil and sulphanilamide there are two questions which I would like to discuss briefly. The first is this: How did Professor Domagk hit upon red prontosil? We have only recently learned the answer to that question. Domagk has told us that it happened in this way. He was demonstrating phagocytosis by the Kupffer cells of the liver to students, using mice. When he injected his animals with living streptococci they all died. But if he had previously injured the streptococci, either by heat or by chemicals, some of the animals did not die and he was able to show phagocytosis. That set him wondering whether it might be possible to arrest an existing streptococcal infection in the mice by any of these chemical agents. He found that red prontosil (which had been included among the chemicals for trial almost at random) was the only one which did so. Professor Domagk's comment on this was that the use of prontosil had resulted from the careful pursuit of an interesting observation rather than as a direct attempt to find a therapeutic agent. It was, in fact, rather like Fleming's earlier discovery of penicillin.

The second question is this: Were we right to conclude that red prontosil had cured our patients by virtue of the sulphanilamide set free from it in the patient's body? So far as I know, that conclusion has never been questioned. The reason I venture to do so now is this: The dosage of red prontosil which gave such striking results in 1936 was considerably smaller than that which was subsequently found necessary with sulphanilamide, and, since prontosil has a larger molecule, one would have expected just the opposite. Eighteen grammes of red prontosil was the average quantity for the whole course in our puerperal fever cases, usually spread out over five to seven days. That represents only about 10 g. of sulphanilamide, which would be regarded as a very small dose to-day. For that reason I have always had some doubt whether the breakdown of prontosil was really the whole story. Was it possible that the liberation of sulphanilamide in a nascent form in the body was much more effective than that produced by the chemists? I do not know. Possibly the pharmacologists may think the matter is worthy of re-examination some day.

Improvements in Midwifery

To come back now to the story of puerperal fever. So far I have spoken as if the haemolytic streptococcus was the only villain in the piece. That, of course, was an oversimplification. I stated at the beginning of this lecture that one of the puzzling features of puerperal infection was the varied clinical picture it presented. We sometimes saw cases which did not develop in the alarming manner of the typical haemolytic streptococcal infection, with high fever and severe illness. In these cases the temperature rose much more slowly, was irregular, and was often associated with frequent rigors. No haemolytic streptococci were found in the lochia or the blood, but often one or several species of unfamiliar anaerobic cocci and cocco-bacilli (Colebrook and Hare, 1933). If death occurred it was usually after several weeks, and necropsy revealed extensive thrombophlebitis of the larger pelvic veins. Other cases, again, were infected with staphylococci or *Bacterium coli* and ran an atypical course. None of these infections spread in an epidemic manner.

A large proportion of these puerperal fevers associated with organisms other than the haemolytic streptococcus had followed a difficult labour involving severe trauma to the mother. They were, in fact, analogous to the wound infections associated with a very mixed bacterial flora which we had seen in the first world war. Apparently the injury to the maternal tissues had paved the way for invasion by many organisms which had little pathogenicity apart from such favouring circumstances. It was evident, then, that injury in labour was a very important predisposing factor in puerperal fever. And, broadly speaking, that injury was the result of unskilful or mismanaged delivery. Happily, the last half-century has seen great changes in obstetrics in this country. Thanks to the activities of the Royal College of Obstetricians and Gynaecologists; perhaps in some part to the report of the Ministry of Health Committee of 1928–32; but most of all, perhaps, to the conscientious effort of a host of people doing maternity work all over the world, the teaching and practice of midwifery have been greatly improved. There is now better supervision of the antenatal period; better provision for the conduct of difficult deliveries; better hospital accommodation for the cases requiring it; and more frequent resort to caesarean section when that alone can avert severe trauma. I am informed that the "failed forceps" case and the mutilating operations of my own student days are now rarities.

All this means that severe injury to the mother in labour is very much less common than it used to be, and the resulting infection much less often seen. Happily, too, it has been found that most of the anaerobic organisms which were concerned in many puerperal infections are sensitive to penicillin or one of the newer antibiotics (Hare *et al.*, 1952) so that the death rate from these has also fallen to a much lower level.

The final picture, then, which emerges to-day—at least in the more fortunate countries—is that childbirth has been largely robbed of the terror of infection.

That, surely, is one of the happiest triumphs of medicine in this century. I said at the beginning of this lecture that from 1880 to 1930 there were roughly 2,000 maternal deaths from infection in England and Wales every year. In 1950 that figure had dropped to 85 deaths, of which 64 had followed abortions. Summarizing, I think we may say that two factors have been chiefly responsible for this great change: We have gained much greater control over our microbic enemies; and there has been great progress in all that makes for safe midwifery.

Points to Remember

To this happy ending I ought to add a postscript. The puerperal fever hazard is *not* a thing of the past. It is still with us. There is still, indeed, more infection than there should be, although it is not reflected in the national death rate. Quite recently, at Queen Charlotte's, where the avoidance of infection has been kept very much in mind, there was a troublesome little epidemic of streptococcal infection involving 25 mothers—happily none of them seriously. Gibson and Calman (1953), who reported it, were unable to trace its origin. It started "out of the blue" after a year in which there had not been a single instance of infection by the haemolytic streptococcus. And there have been other outbreaks of a similar kind in recent years.

We must always remember, and teach our students, that the normal result of labour is to leave the mother with a large wound of her uterine tissues, and sometimes those of the pelvic floor, and that that wound is particularly liable to infection because of the anatomy of the parts concerned.

The second point we should remember, and teach our students, is that the microbes that have caused us so much trouble in the past are still with us, and one of them, the staphylococcus, seems to be becoming more formidable. I shall not be surprised if we hear a great deal more in the next few years about staphylococcal infection of both mothers and babies.

Finally, we must be on our guard in our practice and teaching against the dangerous doctrine that because puerperal fever is now largely curable its development does not matter. There is evidence (Kenny, 1937) that a mother who has recovered from a streptococcal infection is very often sterile; and such sterility may be a cause of lifelong unhappiness. We have not done our job as obstetricians if

we allow mothers to be infected. For all these reasons we cannot afford to let up in our aseptic and antiseptic precautions.

And we should perhaps remember that large parts of the world have not yet achieved the high standard of obstetric practice that now obtains in the most progressive countries. In those less fortunate countries unskilled midwifery will still take its heavy toll.

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IMMEDIATE AND REMOTE RESULTS OF CHLOROETHYLAMINE TREATMENT OF HODGKIN'S DISEASE

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The use of chloroethylamines in the treatment of Hodgkin's disease was proposed by a group of American workers in 1946 (Gilman and Philips : Goodman *et al.*). It was pointed out that chloroethylamines were chiefly used for the palliative treatment of generalized advanced cases of Hodgkin's disease and for cases resistant to *x*-ray therapy. It was emphasized that localized earlier stages of the disease should continue to be treated with *x* rays. This opinion was essentially supported by other authors, although some investigators, particularly British (Wilkinson *et al.*, 1953), gave a higher evaluation of the treatment with chloroethylamines, especially tri-(2-chloroethyl)amine.

The therapeutic activity and clinical use of chloroethylamines have been studied by us since 1947. As regards the method of application of these compounds, the indications for their use, and their value in treatment we disagree to some extent with the American authors. While we started treatment with di-(2-chloroethyl)-methylamine hydrochloride ("embichin"), we began using another chemical compound from 1950 onwards. It is the object of this paper to present our findings, paying special attention to the remote results of treatment of Hodgkin's disease with chloroethylamines, no account of which has apparently been published.

General Dosage Scheme

The intravenous injection of chloroethylamines in a daily dose of 0.1 mg. per kg. body weight for four days (maximum six days) is the most widely used method of therapy. Some authors recommend two injections of a double dose (Ap Thomas and Cullumbine). Even after such a short course of treatment the maximum therapeutic effect as well as depressive side-effect upon haemopoiesis becomes evident, therefore treatment cannot be properly individualized.

Experimental studies on rabbits carried out by my assistant G. L. Zhdanov showed that the depressive effect of embichin upon haemopoiesis depended to a high degree upon the intervals between injections. Prolongation of the intervals up to 48 hours, and particularly up to 78 hours, when haemopoiesis in the bone marrow has had time to recover to some extent, considerably reduces the action of embichin upon the blood-forming organs. For this reason, and on the basis of the statement above concerning individualization of treatment, we injected the drug three times a week—that is, with 48- and 72-hour intervals. With such intervals it became possible, and even necessary, to make not four to six but eight to twenty injections. The therapeutic effect can be noted during treatment, and this makes it possible to control the latter. In addition full advantage is taken of variations in sensitivity of granuloma to chloroethylamine drugs on the one hand, and in the bone marrow on the other, especially their ability to regenerate, which is greater in the bone marrow than in granulomatous tissue.

Experience has shown that the desired therapeutic effect —that is, complete regression of all involved nodes—can be obtained only by simultaneous and marked depression of haemopoiesis, the leucocyte count being reduced to 2,000–3,000 per c.mm. It is our experience, however, that this level of depression of the bone marrow is not dangerous and haemopoiesis is recovered within three to four weeks. Accordingly we continue injections until the leucocyte count falls to 2,500–3,000 per c.mm. Sometimes a few days after the last injection the leucocyte count falls to 1,500–2,000 per c.mm. The number of injections needed to cause this leucopenia in different patients varies according to the condition and reaction of the blood system, on the stage and type of the disease, and whether *x*-ray therapy, which increases the sensitivity of the haemopoietic system to chloroethylamines, has been given previously. We usually succeed in making from eight to sixteen injections. If one course of injections is insufficient to cause complete regression of the nodules, a further course is given six to eight weeks after the first one. In this way we are able to obtain the maximum therapeutic effect.

No other special measures to stimulate haemopoiesis other than transfusion of 100 ml. of blood once or twice a week are adopted. According to our findings such drugs as nucleic acid salt of sodium or pentoxyl will stimulate the essential pathological process to a greater degree than normal haemopoiesis.

Search for a New Drug

Di-(2-chloroethyl)methylamines are known to cause vomiting and nausea in a large proportion of cases. A special study of this phenomenon by our co-worker E. I. Khomchenovsky showed that vomiting was caused by a reflex from the small intestine which was transmitted to the vomiting centre through the vagus nerve. The failure of our efforts to overcome this side-reaction of embichin led us to seek another compound having a less marked effect. We also wished to find drugs with a more pronounced effect upon the lymphatic system and a weaker action on the bone marrow.