CRITICAL REVIEW

Chemotherapy in Obstetrics and Gynaecology

BY

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TEN years ago, sterilization of the blood by chemical means had come to be looked upon more and more as an unattainable ideal. Famous and futile procedures had been undertaken with this object but it had not been proven that any germicide was capable of killing bacteria in blood in a concentration attainable clinically. Then, at one step the ideal of *therapia sterilisans magna* advanced from the domain of medical mythology and became a concrete fact of daily practice. In 1935 was introduced to the world the first of the chemotherapeutic agents which, the world agrees now, constitutes the greatest therapeutic discovery in modern medicine—Prontosil. The story of its development is interesting. In 1908, Gelmo[1] synthesized para-amino-benzene sulphonamide. In 1909, Hörlein, Dressel and Kothe[2] prepared azo dyes with sulphonamide which "were distinguished by greater fastness for washing than those of sulphonamide-free products," a quality they attributed to the intimate union of the protein cells of the wool and the dye. The precise date of the synthesis of the basic form of Prontosil (2:4 diamino-azobenzene-4′-sulphonamide) is not clearly known, but in 1932 Mietzch and Klarer[3] applied for a patent covering the original Prontosil (hydrochloride of 4′-sulphamido-2, 4 diamino-azobenzene) and several other sulphonamide-containing azo dyes.

Early in 1935, Domagk[4] announced that "haemolytic streptococci of human origin were injected into 26 mice . . . later, half of them received . . . a single dose of a dark red dye (Prontosil) which had been synthesized by Mietzch and Klarer (Hörlein[5]) and all survived . . . Of the remaining animals which served as untreated controls . . . the last was dead on the 4th day."[6]

In France, Levaditi and Vaisman[7] confirmed Domagk's experimental results with mice, using a similar compound synthesized by Girard, as they had been unable to obtain supplies of Prontosil from the Germans who had protected its manufacture by patent. Later that year, the Tréfouels, Nitti and Bovet[8, 8a] suggested that the effective azo-dyes were broken down at the azo linkage in the tissues of the treated host, and that the curative agent was para-amino-benzene sulphonamide, now known as sulphanilamide. In addition to the reports of animal experiments, there appeared about a dozen case reports in Germany[9, 10, 11, 12, 13] on the use of the drug in human infections—both streptococcal and staphylococcal—unanimously favourable, but of little value as evidence since in most cases the recovery of the patients was entirely ascribed to the treatment; too little allowance was made for the tendency to spontaneous cure of these infections. The cases were not assorted with sufficient care either clinically or bacteriologically, but the reports did serve to arouse the greatest interest in England, and laboratory experiments and clinical trials were carried out by Colebrook and Kenny on patients suffering from haemolytic

streptococcal puerperal sepsis at Queen Charlotte's Maternity Hospital. In June 1936, Colebrook and Kenny[6] described the results of these trials which "one can say without fear of contradiction or thought of disparagement of the observations made by the continental investigators" were to arouse the interest of the world upon the subject of bacterial chemotherapy[14]; 38 women with severe haemolytic streptococcal puerperal infections had been submitted to treatment and cautious conclusions, instructed by the fine judgment and long experience of the staff of the hospital, were drawn as to the curative effect of the new drug. "Subject to confirmation by further experience," they said, "the impression has been gained that in many of the more severe cases the drug has exerted a definitely beneficial effect . . . 3 patients in whom there was generalized peritonitis on admission (1 with a positive blood culture) have recovered." Confirmation was quick to come. In December 1936, the same workers[15] reported their results with 64 women treated thus. Three only had died, a mortality-rate of 4.7 per cent. The death-rate for similar cases in the previous 5 years was 22 per cent.

The death-rate for cases with positive blood cultures (haemolytic streptococci) dropped from over 60 per cent to 25 per cent. None of the treated patients developed pelvic or metastatic abscesses. The average stay in hospital for the 61 Prontosil-treated patients who recovered was 18 days, while that of the 61 consecutive non-fatal cases immediately before the introduction of Prontosil was 31 days. A year later Colebrook and Purdie[16] confirmed that one of the notable effects of sulphonamide therapy is the way in which it prevents a spread of the infective process from the placental site. In their series of 106 patients parametrial or extra-uterine spread occurred in only 5 per cent and in these the spread was only of small extent. These authors also showed that, nevertheless, sulphonamides do not lead to a rapid destruction of the haemolytic streptococci, for the organisms can be recovered from the birth canal of treated patients weeks after clinical recovery has taken place, and that, therefore, operative procedures must still be avoided as far as possible or postponed until an effective blood concentration of sulphonamide has been reached, when the chance of an extension of the infection resulting from operative trauma will be greatly reduced.

The use of the drug Prontosil and its modern successors is now widespread, but it is interesting to note that Colebrook and Kenny's first results have never been bettered, and appear to represent the maximum that can be reached until the ideals of quick clinical and bacteriological diagnosis and early and adequate treatment can be made universal. It is also of interest that the dosage devised by these first workers on mainly clinical experience has become the standard for nearly all the sulphonamide derivatives and has been shown to give the necessary bactericidal concentration of the curative agent in the blood in most cases. Hard experience has shown that the more massive doses of the newer sulphonamides sometimes advised are unnecessary, distressing, and occasionally dangerous in their toxic effects.[17] The intent is to reach a blood-concentration of the drug of 10 to 15 mg. per cent as quickly as possible[17] and to maintain these levels until the patient has been afebrile for a few days. The 4-hourly dosage scheme is important since only thus can even concentrations be maintained in the blood.[18] Occasionally, patients are encountered in whom the prescribed dose of sulphonamide does not give the desired concentration in the blood. In such individuals, clinically recognizable by their

unfavourable progress, the dose must be increased until the proper values are obtained. In the experience of many[17] in all branches of medicine, unfavourable results with the drug have been more often attributable to this failure to achieve correct concentrations of the drug than to the rare presence of insensitive or resistant strains of streptococci. In these latter cases penicillin should be the immediate resort. It is very often customary, in these days, to give a large initial dose of the chosen sulphonamide in order quickly to establish effective levels of drug in the blood of patients stricken with severe infections—this dose being usually of 4 g.[19] The reviewer hesitates to recommend this large dose in obstetric or gynaecological practice and prefers to build up the effective level over the first 24 hours, as was found possible by Colebrook and Kenny. In any method of administration adopted, an average of 1 g. of the drug per 10 kg. of body-weight per 24 hours is the standard dosage,[20] with, in women, a maximum daily dose of 6 g. during the febrile period and for 2 to 3 days after. Then the dose may be halved for 3 to 4 days and halved again for 3 to 4 days, making an average of 40 to 45 g. in all, in severe infections. Below is reproduced, for historical and topical interest, the original scheme of administration devised by Colebrook and Kenny.[15] Each 20 c.cm. of the Prontosil given intramuscularly represents 0.5 g. With the modern sulphonamides parenteral therapy is necessary only when oral therapy is impossible. The blood of the patient, whose clinical record is here shown from the books of Queen Charlotte's Maternity Hospital, gave a growth of more than 5,000 colonies of haemolytic streptococci per c.cm. on culture in the first 2 days, and of more than 3,000 colonies on the 3rd day. It may be seen, therefore, that the drug and the scheme of dosage were submitted to a very severe trial, and in view of the fact that such a large number of haemolytic streptococci are usually observed only in the terminal stages of a fatal infection, the patient's prompt recovery was astonishing but must have been imitated many thousands of times since 1936.[14] The picture will, however, explain the reviewer's personal predilection for the original Red Prontosil in cases of desperate illness.[20]

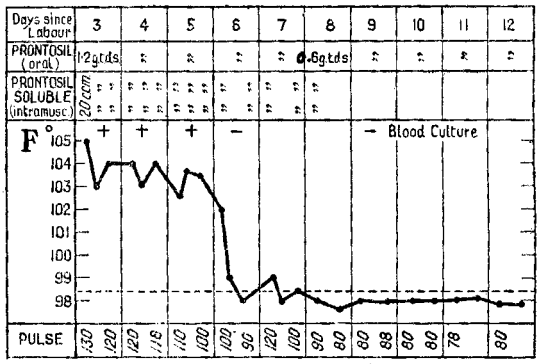

Chart showing a typical scheme of dosage in a case of puerperal septicæmia.

Despite the famous drop in the mortality from puerperal sepsis[21, 22] the picture does not call for complacency. Colebrook,[23] in 1935, in the course of a plea for the use of effective antisepsis in midwifery, calculated that 6,000 to 7,000 women became infected with haemolytic streptococci in childbed each year in England and Wales, and some 1,200 to 1,500 of these died. We know, from the falling death-rate, that the vast majority of these now recover under treatment with sulphonamides, but the incidence of this fearful disease shows no such happy decline but indeed a rise![21, 22] In 1934 there were 597,642 live births in England, with 8,431 cases of puerperal fever (14.1 per thousand) and 1,212 deaths (14.4 per cent). In 1939, 619,352 babies were born, 9,252 mothers were infected (14.9 per thousand), although only 476 died (5.2 per cent). These are the last figures we can analyse; they cover years of peace, before such considerations as increase in primi-

gravidity, scattering of population and deterioration of medical services could be advanced to mitigate the sad facts. The same has occurred between the years 1936 and 1940 in the United States of America. In some centres, notably, from the reviewer's personal knowledge, at Queen Charlotte's Maternity Hospital and the Obstetric Unit of the British Postgraduate Medical School,[24] years may pass without the occurrence of a single case of haemolytic streptococcal infection in the puerperium—the sincere application of preventive measures having brought about the virtual eradication of sepsis. But the increasing figures of incidence of the disease for the whole country forces the belief that the introduction of the sulphonamides may not have been an unmixed blessing for childing women—that against the improvement of obstetric technique in some centres may be set a new recklessness in others, engendered, paradoxically, by confidence in the power of the sulphonamides to cover errors of judgment. The boast of the obstetrician should not be that since 1935 he has not had a single maternal *death* from sepsis, but that, with a realization of the serious consequences of the disease, he has reduced or banished the *incidence* on his service.

In 1937, Kenny[25] drew attention to one of the most evil of the remote effects of puerperal sepsis. In a group of 100 young women who had recovered spontaneously from the disease, during 4 to 5 years of the subsequent active childbearing period of life, there had been achieved only 5 pregnancies and only 4 live births. The average age of the patients at the time of this follow-up was 27 years—thus, it appeared that the ravages of the disease had definitely diminished the fertility of 95 young women aged 22 to 23. These distressful figures were confirmed almost exactly by Barr in 1939.[26]

Cure, therefore, however certain and dramatic with the new chemotherapeutic agents, is not enough. Colebrook and Kenny[6] were the first to advance the possibility that the prophylactic use of sulphonamides might control the development of puerperal infection in women who, either from the nature of the delivery or its environment, had undergone the risk of streptococcal contamination. Kenny[27] warned that small doses were ineffective for prophylaxis, and the earliest large-scale clinical experiment carried out by Johnstone[28] giving only 2 to 3 g. daily for the first week of the puerperium to all women delivered on his service in 1938, showed that these doses had no power to diminish the incidence of streptococcal infections, the results being in no way better than those of the control period, the previous year. It seems, therefore, in the present state of our knowledge, that prophylaxis can be achieved only by the attaining of "curative" levels of the drug in the blood by "curative" dosage. Recently, that this may be so has been demonstrated by Geisendorf and others[29] who gave full curative doses (large initial dose and maintenance doses for 1 week—31 g. in all) to all women delivered on a large service in Switzerland, for they found that postpartum urinary infections were reduced to one third of the incidence found in untreated controls, and that pelvic sepsis as manifested by thrombophlebitis also occurred one-third as frequently. Le Lorier,[30] quoted by Geisendorf and by Domagk,[31] gave sulphanilamide prophylactically to 3,390 parturient women in 1 year, and not only achieved a decrease in the incidence of uterine sepsis, but also observed only 18 cases of urinary infection as compared with 76 such among the same number of untreated controls. The reviewer shares Colebrook's[23a] opinion that the drug should be administered prophylactically in certain

cases in which delivery has been difficult, or when exposure to streptococcal infection at or near the time of delivery has been known or suspected to have occurred. Also, that bacteriological investigation of the birth canal must be carried out as soon as possible thereafter, especially in cases in which gross traumatism has been incurred, as the infecting organisms are then frequently the anaerobic streptococci against which the sulphonamides have not as yet been shown to prevail, and where the toxicity of the drugs may weight the balance against an already poor chance of recovery. The administration of the drugs to all women in labour is open to strong objection. "The flair of the accoucheur is reduced to the *rôle* of a distributor of pills."[30] The proportion of intolerants to the sulphonamides is not large, but if the number of cases treated increases, the problem of intolerance will become important; the price of the medicament is not negligible if employed in full doses in thousands of cases a year; the number of cases of sulphonamide-resistance would also increase.

Local Implantation of Sulphonamides.

Colebrook and Kenny in 1936[6] showed that in mice a large subcutaneous implant of Prontosil in suspension formed a depot from which absorption of the drug and protection from experimental infection might continue for some weeks. Purdie and Fry[32] in 1937 reported a case of chronic infection of the skin and subcutaneous tissues which had refused to heal for 3 years following puerperal sepsis, but healed completely within 6 weeks under local treatment with sulphanilamide powder. They pointed the way to the now widely used measure of using intraperitoneal deposits of the drug for both local and systemic antiseptic effect in the presence of known or suspected infection. Enormous concentration of the drug (200 to 1,000 mg. per 100 c.cm.) can be obtained at the site of implantation and maintained for many critical hours before gradually subsiding.[17] The most valuable application of this manoeuvre in the obstetric field has been the habit of scattering 10 to 15 g. of the more soluble sulphonamides (sulphathiazole or sulphadiazine) over the uterine incision in Caesarean section in infected cases. In the reviewer's opinion, supported by those of many others[17] this may enable the obstetrician not only to perform abdominal delivery with confidence in doubtful cases, but also to avoid the mutilation of the Porro operation, and to conserve the uterus even in infected cases. A seemly method is to place the drug in a finely powdered and *sterilized*[33] condition under the peritoneal flap of the bladder, which is then drawn up over the wound in the lower uterine segment and sutured at a higher level to complete the operation. Systemic therapy should not be begun for 2 days after implantation, and thus a possibly nauseated patient may be spared the oral intake of the drug. The intraperitoneal deposition of the drugs is also valuable in gynaecological operations in the presence of peritonitis[17] or in cases in which soiling of the peritoneum cannot be avoided, and is useful also when the abdomen has been inadvertently opened in acute salpingitis.

Intrauterine deposition of sulphonamides has not been used to any known extent in this country although such tamponage has been suggested in both Latin and North America.[34, 35] It is probable that absorption of the drug through the large uterine sinuses would be abrupt, and, in the case of the less soluble sulphonamides, possibly dangerous.

Urinary Tract Infections.

The last 10 years have seen as great a change in the diagnosis, management and treatment of infections of the urinary tract

as of puerperal sepsis. Fuller's[36] discovery in 1933 that beta-oxybutyric acid produced by the ketogenic diet was a urinary antiseptic gave excellent results in ideal conditions, but the diet is so difficult to adhere to in the acidosed, nauseated, pregnant woman as to be impracticable. In 1935, Rosenheim[37] introduced mandelic acid which, while simple to administer and very effective, is open to the same objection as it has a definite therapeutic effect only when the *p*H of the urine is 5.0 or lower, a figure usually impossible to attain in pregnancy or early puerperium. In 1937, Kenny, Johnston, von Haebler and Miles[27] showed that sulphanilamide in small doses produces a rapid decline in clinical symptoms and bacterial infestation of the urinary tract in pyelitis of pregnancy and infections of the urinary tract encountered in obstetrics and gynaecology generally. Cuthbert,[38] in 1938, reported good results with sulphonamides in urinary tract infections in the puerperium, whether or not these were complicated by genital sepsis. All these and other workers[19, 39] had the best results when the infection was due to Bact. coli, in mixed infections the results were not so good. Penicillin combined with sulphonamide may well provide the remedy in these cases.[91] It is important to judge each case considered suitable for chemotherapy not only by purely clinical evidence, but on microscopic examination of the urine and the bacteriology of the urinary tract. Jäämeri[40] found that the urine of 600 pregnant or parturient women contained organisms of the colon-aerogenes group in 16.3 per cent of cases, and four-fifths of them had no clinical signs of the disease. Dodds[41] showed that the Bact. coli can be demonstrated in the urine of 7.5 per cent of pregnant women, but that less than 1 per cent develop pyelitis. Douglas[19] found a significant infestation of the urinary tract with Bact. coli in 15 per cent of cases of puerperal fever. The predisposing hormonal factors associated with pregnancy, labour and the puerperium are obviously directly responsible for the development of conditions of the urinary tract of increased vascularity, dilatation, atony, hyperplasia and oedema, all combining to produce urinary stasis,[42] apparently the primary inducing factor in the introduction of sepsis but possibly the reason, too, for the therapeutic concentration of the drug obtainable with small doses. Trauma during labour is an important factor in puerperal urinary infections as injury to the bladder, a very susceptible organ, is usually followed by infection. Also, neglect to observe atony of the bladder during the early puerperium which necessitates repeated or continuous catherization constitutes another predisposing factor in the production of puerperal urinary tract infections and the sulphonamides should be administered prophylactically in such cases. In gynaecological practice, with rare exceptions, we do not have to deal with these hormonal influences, but the proximity of the genital and urinary systems frequently leads to complications spreading from the one to the other. Relaxations of the anterior vaginal wall often cause residual urine in the bladder which is followed by infection, and in gynaecological surgery trauma to the urinary tract is very often inflicted.

For all these infections specific treatment is now limited to the various sulphonamide drugs. Sulphanilamide is most widely used in this country because of its cheapness, availability and infrequent production of renal complications. Sulphapyridine should never be used in pregnancy because of its high toxicity. Sulphathiazole is effective against staphylococci as well as Bact. coli, but has the highest capacity for the production of crystalluria.[19] We therefore do not recommend its use when renal com-

petence is in question. Douglas[19] writes highly of sulphadiazine, but his recommended dosage of all the sulpha drugs is unnecessarily high as are those advised by Browne[43] quoting the Medical Research Council War Memorandum.[43a] Kenny and Johnston[27] and Cuthbert[38] showed that a satisfactory concentration of the drugs could be achieved in the urine of pregnant or puerperal women by the administration of 1.5 to 3 g. per day, and over and over again experienced observers[44, 45, 46, 47] have shown that 2 to 2.5 g. per 24 hours in adult patients is all that is needed. This dosage rarely needs to be exceeded except in fulminating pyaemia or pyonephrosis, the now very unusually seen developments of pyelitis. Usually, with these small doses, the causative organisms are eliminated within 4 days.[27] If a satisfactory therapeutic response is not obtained in a few days, further investigation of the urinary tract becomes necessary and pathological obstruction or anatomical abnormality will usually be found. One should never persist with therapy in the hope that prolongation of the period of treatment will accomplish cure. Failures or recurrences should be subjected to complete urological investigation.[19]

There is not usually the necessity to add alkalis to the sulphonamide course although Helmholtz[39] and others[43] consider this important. This is particularly true of sulphanilamide, which drug Kenny and Johnston[27] showed to have a tendency to alkalinize the urine. But Gilligan[49] says that sulphadiazine and sulphathiazole are respectively 20 and 13 times more soluble in a urinary *p*H of 7 to 7.5 than of 5.0, also that the latter drug has a tendency to acidify urine. Therefore, if either of these drugs is used, sodium bicarbonate in adequate doses should be exhibited as well. Fluid intake (3,000 c.cm.) and urinary output (1,500 c.cm.) should be carefully maintained and oliguria treated as a warning sign of crystalluria. It occurs usually with unnecessarily large or prolonged dosage.[50]

The prophylactic administration of the drugs for 3 to 4 days before and after gynaecological operations is recommended for the prevention and control of urinary tract infections. Good convalescence is promoted especially if retention of urine occurs and necessitates catheterization. Waugh, McCall and Herrell[48] have shown that sulphonamides deposited intraperitoneally at operation are excreted in effective amounts from the urinary tract for many days and thus reduce materially postoperative morbidity due to urinary infection.

Venereal Disease.

The treatment of gonorrhoea by the sulphonamides has marked a milestone in the history of venereal disease. The reported results of the treatment in women are even more brilliant than those reported of males.[51, 52, 53, 54, 55] There has been much discussion and dissension of opinion on when the treatment should be begun for optimal results, and whether the patients should be hospitalized during treatment. The original rate of cure, 93.4 per cent, obtained in 1938 by Mahoney,[54] in a group of 61 women ill with chronic infections and hospitalized, has not been surpassed. Therefore, it has seemed good to many workers to delay treatment in the female patient as in the male, until a partial degree of immunity to the gonococcus has been developed. But the remote effects of the untreated spread of the disease in females can be so serious, or even dangerous (if subsequent pelvic surgery becomes necessary), that informed opinion now urges the treatment of the infection as soon as it is recognized in the early stages. This opinion has been fortified by the observations of

McElligott[53] and others[54, 55, 56] that the treatment with sulphonamides of gonorrhoea in women almost entirely abolishes the spread of the disease, especially when combined with hospitalization so that conditions of treatment and rest can be controlled;[17] and if extension to the adnexa does occur, rapid resolution can be expected with this therapy. Grodberg and Carey[57] show that even when acute masses significant of salpingitis develop, these resolve with treatment in 10 to 14 days. This has been confirmed by others.[56] As to dosage, the reviewer considers that the moderate amount of the drugs advised by Long,[14] i.e. 4 to 5 g. daily for 3 days, followed by 2 to 3 g. daily for a week, is enough. Even smaller doses[57] have given as good results and larger doses no better.[58] A convenient and memorable scheme is that devised by Durel[59] with sulphapyridine in the treatment of male gonorrhoea, 3 g. daily for 3 days, 2 g. daily for 3 days, and 1 g. daily for 3 days. The single massive dose of sulphonamides suggested by Pappas[60] in the treatment of the disease in males has also been tried in females by Strauss[61] who finds that a single day's therapy with 8 g. of sulphathiazole or sulphadiazine cured 90 per cent of his chronically infected cases. Cohn and Grunstein[58] compared 2 schedules of chemotherapy in women with gonorrhoea, some 80 per cent of whom had adnexal involvement. In one group, 12 g. of sulphathiazole was given over 3 days and in the other, 21 g. over 7 days, with almost identical therapeutic effect. A blood level of 5 to 7 mg. per cent during the period of treatment seems to be sufficient.[14, 19] We are not dealing with a deadly but with a mutilating infective process in gonococcal disease. Our aim is to limit its local virulence and prevent its spread. The relatively heroic doses required in septicaemia and other generalized infections are directed to life-saving. Local treatment is not usually necessary in females when sulphonamides are used, and this makes the treatment most valuable in pregnancy. However, heat therapy by Elliott's apparatus or diathermy is useful in chronic disease.[56] It is a wise practice to give a course of a sulphonamide shortly before and after an infected pregnant woman is delivered, even if there has been apparent cure previously, both to protect the mother from the now rarely seen puerperal spread of the disease and to lower the virulence of possibly still-existent organisms in the birth canal in the interests of the baby. There is yet much information that must be gathered on the incidence of permanently damaged Fallopian tubes in treated cases of salpingitis. A recent paper by Barrows,[56] confirmed by Hunt and others,[17] claims that in treated cases of gonococcal salpingitis the pelvic masses disappear in 80 per cent as compared with a resolution-rate of 20 per cent in untreated controls. Even severe cases have a 60 per cent chance of success, but late cases have poor results. There is however no note on the patency of the tubes thereafter. All[17, 56] advise that even old-standing cases should have treatment with sulphonamides as some tubal salvage may result, the period of illness is shortened and eventual surgical treatment made safer and easier.

Pronouncement of cure in the infected female has not been made easier by the new chemotherapy, for so greatly has the sulphonamide group of drugs changed the state of affairs that it has become very important to classify separately tests for cure in those who have and those who have not had sulphonamides. Jones[62] maintains that the sulphonamides "change the characteristics of the gonococcal slide," the changes consisting in marked alterations in the morphology and staining reactions of the gonococcus. Great care must be exercised therefore to prevent the asymp-

tomatic carrier being loosed upon the public. Pelouze[63] insists that re-examination should be made on several occasions after apparent cure, preferably after or during a menstrual period and after resumption of sexual life (in which the partner should be protected by a condom) for some months. He also claims that it is possible for a treated patient to transmit asymptomatic disease, the victims being unaware that they are infected until they transmit the disease to another. The incidence of sulphonamide-resistant cases is probably low in properly treated cases and it is likely that some of them are due to reinfection. Penicillin, when available, seems to be of use here.[71]

Vulvovaginitis in Infants and Children.

After several early favourable reports upon the use of sulphonamides in this condition (Brown,[64] Hoffmann,[65] Gaté and coworkers[66]), there have recently been publications showing that their scope is limited and the results disappointing. Brown emphatically declared her results to be brilliant, yet Hoffmann claimed but 16 cures among 25 young girls and found that only 2 of the remaining 9 were cured by further courses of the drug. Gaté and Cuilleret claimed 100 per cent cure in 8 affected infants. Alyea[67] reported only a 20 per cent permanent cure-rate and Grodberg,[57] Compton[14] and Long[14] were also discouraging. Sandes[68] has found that little girls between the ages of 2 and 10 years develop toxic symptoms readily and do not tolerate the drug well. Her paper and those of the others all deal with the use of the earlier sulphonamides and it may be that the later preparations will be at least better tolerated by small children. The results in general remain far inferior to those obtained by the administration of the oestrogens.[69] In a small number of cases of vulvovaginitis in young children in whom the infecting organism is the *streptococcus haemolyticus* and *staphylococcus aureus* the reviewer has obtained rapid and permanent cure with a combination of oestrogen and sulphanilamide.

A recent paper by Cohn, Steer and Adler[70] has claimed a very high rate of cure with sulphapyridine in anorectal gonococcal infection in young children.

With the increasing availability of penicillin for civilian use and its already known value in the treatment of sulphonamide-resistant cases of adult gonorrhoea,[71] it may be hoped that a treatment will be evolved for these sad infants wherein local therapy and examinations may be kept to the minimum consistent with the required knowledge of the progress of a case.

Ophthalmia Neonatorum.

The annual returns from the Ministry of Health[72] show that for the 7 years, 1934 to 1940, 44 children in England and Wales were blinded from ophthalmia neonatorum; during 1941 and 1942, only 1 case was reported. The incidence of impaired vision from this disease likewise has declined, the figures for the two periods being 190 and 14 respectively. In 1931, blindness from ophthalmia constituted 21 per cent of all cases of blindness in children admitted to schools for the blind managed by the London County Council, in 1943, the proportion was 9.8 per cent.[72] In the United States of America, in 1941, the proportion was 5.6 per cent compared with 28 per cent earlier.[73] Authors in both countries[72, 73] stress that while silver nitrate is still the best preventive measure, it has very definite limitations, and the improvement in the figures they quote is largely due to the sulphonamides "in which we have a therapeutic agent that makes blindness or impaired vision from this affection no longer tolerable."[72] Treatment should be both prenatal—diagnosis and treatment

of infections in the prospective mother, and postnatal use of a prophylactic agent in the eyes of the newborn infant and vigorous use of the sulphonamides in declared disease. The drug of choice is now sulphathiazole in doses of 1 gr. per pound of body-weight, given orally.[73] Cases resistant to sulphonamides should receive penicillin therapy[72a, 74, 75] and there still seems to be a place for artificial fever therapy should chemotherapy fail.

Choice of Drug, Toxicity, etc.

At the present time we have available for general use in this country, adequate supplies of sulphanilamide, sulphapyridine, sulphadiazine, sulphamezathine and sulphathiazole, and limited amounts of others such as sulphamerazine and sulphacetamide.

The drug of choice is that with the greatest specific bactericidal effect and least toxicity. All the sulphonamides are toxic, the poisonous effects are commonly believed to be due to sensitivity or idiosyncrasy—neither the quantity of the sulphonamide used nor its level in the blood seems to be definitive in producing fatal lesions although in general large and especially prolonged doses are dangerous.[76, 77] The dangerous complications of sulphonamide therapy are those affecting the haemopoietic system and causing agranulocytosis and haemolytic anaemia; and the urinary tract by mechanical damage leading to anuria and uraemia. This last is effected by the deposition of calculi composed of crystals of the drugs in the renal tubules or pelvis.[78] Fatal doses have ranged from 96 g. to 0.6 g. in the production of agranulocytosis and renal injury respectively.[76] Agranulocytosis usually appears after 2 weeks of treatment. The minor complications such as met- and sulph-haemoglobinaemia producing the now well-known lividity of the skin described by the early workers[6] are never serious; development of drug fever or rashes is usually an indication of a degree of intolerance, but there is no definite evidence to suggest that these reactions are precursors of the more serious ones.[79] Drug fever and drug rash usually appear after 9 to 12 days of treatment, and are considered to be a sensitivity reaction and may be related to previous administration of the drug.[80] Drug fever may be high with rigors and should be suspected when improvement produced by sulphonamide is followed by recurrence of temperature while sulphonamide is still being given.[77]

Recent reviews of deaths from the sulphonamides[79] show that all the popular preparations are incriminated, sulphanilamide being still apparently the least dangerous next to sulphadiazine, but comparing poorly with the latter drug in its range of bactericidal action. Sulphathiazole, while effective in a wide field of diseases and well tolerated by pregnant women, has the highest incidence of renal complications and can cause agranulocytosis. It is also prone to produce drug-sensitivity and should not be used again if subsequent therapy is needed. Sulphapyridine is widely effective but most toxic for all systems, and should not be used in pregnancy or the puerperium. Sulphadiazine is both effective and of low toxicity; it has not as yet appeared in the literature of agranulocytosis but has caused fatal uraemia. It appears to be effective in quite low concentrations in the blood (3.5 to 5 mg. per 100 c.cm.[19]) so that a dosage of 4 to 5 g. per 24 hours may be used with success. Sulphamerazine is as bactericidal as sulphadiazine, more soluble and more rapidly absorbed, so that even smaller doses give a constant therapeutic level in the blood. Its toxicity is about the same.

Sulphamezathine, a recent British production, is less toxic than sulphapyridine,[79a]

is rapidly absorbed and being freely soluble the risks of urinary complications are minimal.[79b] Agranulocytosis or the disturbance of erythropoiesis has not been observed even in cases where the blood-concentration of sulphamezathine has reached 30 mg. per cent.[79a] Its use is therefore recommended in pregnancy or in cases where renal efficiency is doubtful. It appears, however, from the latest available evidence that sulphamezathine gives only variable clinical results in gonorrhoea.[79c]

The toxic effects of all these drugs on the haemopoietic system may be controlled by a watch on the blood picture if there is a necessity for a long course of treatment, appropriate measures of stimulation and replacement being taken if signs of damage appear, and the drug discontinued. It is important to remember that the clinical manifestations of blood dyscrasias from these drugs are faint in the early tractable stages; when they are marked, it is usually too late for effective remedy, and that, therefore, repeated blood-counts must be carried out after the first week or 10 days of treatment and before a second course of the drugs. Mechanical damage to the renal tract by crystalluria can be prevented by avoiding initial massive doses of the drugs, especially of sulphapyridine and sulphathiazole, encouraging a daily fluid intake of at least 3 pints during therapy and watching for signs of oliguria. Personal opinion reinforced by that of others[50, 80] suggests that if there is a necessity to continue the administration of a sulphonamide despite the appearance of toxic complications or if a second or subsequent course becomes necessary in the treatment of a patient who has shown signs of intolerance in the initial course, another sulphonamide should be chosen; for example, if sulphapyridine be poorly tolerated, treatment may be continued or resumed with sulphamezathine or sulphadiazine or sulphacetamide, this last drug especially in recurrent pyelitis of pregnancy.[50] In any review of the respective toxicity of the sulphonamides, it must be recalled that the smaller incidence of toxic effects claimed for any of the newer drugs may be due not only to lower toxicity, but in part to the fact that these have not yet been as widely used as the older preparations, and full reports of their application are not yet to hand.

Penicillin.

The chemotherapy of bacterial infections passed, as we have noted, from an ideal to reality with the advent in 1935 of Prontosil. During the rapid development of sulphonamide treatment which followed, other organisms than haemolytic streptococci were found to be vulnerable and it seemed likely that with the discovery of new drugs of this type all bacterial infections could be vanquished. But it was soon found that the sulphonamides had their limitations; even among the susceptible bacteria some strains are exceptionally resistant to the sulphonamide drugs and many species are wholly resistant. The time was ripe for a great new chemotherapeutic discovery which would provide a remedy where sulphonamides fail, and this was made by Fleming, the discoverer of Penicillin. Penicillin was discovered in 1929[81, 82, 83] and used by its discoverer for differential culture, but, like Prontosil, its use for practical therapeutics was completed neglected until the Oxford workers started their investigation in 1938. It is now known to combine enormous antiseptic power with such a degree of freedom from toxicity in the human body that much more than a therapeutic concentration can be achieved in the blood without ill effect. Penicillin has fulfilled the hopes entertained with the sulphonamide drugs—deadliness to bacteria and harmlessness to the body to an

extent undreamed of by the most sanguine chemotherapist. All of our present knowledge of its clinical possibilities is based on the studies of Florey, his wife, and his colleagues.[84] Penicillin salts are used therapeutically, the sodium salt for systemic treatment and the more stable calcium salt for local application. Potency is expressed in Oxford units, an arbitrary amount devised by Florey by comparison with a standard preparation. The only penicillin-resistant organisms that interest the obstetrician and gynaecologist are the tubercle bacilli, and almost all the gram-negative bacilli including the typhoid-dysentery group, the *genus Brucella* and the frequent wound and urinary tract invaders, *Proteus* and *Ps. pyocyanea*.[85]

Penicillin can be used by local application in suitable cases or by parenteral injection. It cannot be given by the alimentary tract as too much of it is destroyed by acid in the stomach or by bacteria in rectal infusion. Unfortunately, in view of its cost and scarcity, it is very rapidly excreted in the urine, so that to keep up a therapeutic level it is necessary to use continuous intravenous or 3-hourly intramuscular injection day and night, the daily dose for an adult being 120,000 Oxford units, in serious disease continued for 7 days or longer. The sudden and dramatic improvement often noted with the sulphonamide drugs is rarely seen; sustained and arduous treatment is the price of success.[85]

In the present circumstances penicillin should be used systemically only in conditions intractable by the sulphonamides or when sulphonamide sensitivity, resistance or intolerance has been demonstrated clinically. Until recently, supplies of penicillin were not available in this country for general civilian use since the armed forces were justly receiving the bulk of the supply. Its use here is still restricted to cases of grave illness so that the few papers on its use in obstetrical or gynaecological disorders and venereal disease have appeared mainly in the North American Press.

Puerperal Sepsis.

Keefer[86] reported 8 cases of postabortal and puerperal sepsis treated with penicillin. Five of these were postabortal anaerobic streptococcal infections, 3 got better and 2 died. The 2 deaths occurred in women with septicaemia; the 3 recovered patients had negative blood cultures. The puerperal cases had localized uterine infections with haemolytic streptococci or staphylococci, and recovered. The effect of penicillin, therefore was not apparent in this series of cases. However, Mitchell and Kaumeister[87] gave 40,000 Oxford units of penicillin daily to a moribund patient with puerperal sepsis due to haemolytic streptococci, sulphonamide-resistant, blood culture positive, pelvic thrombophlebitis present. The woman recovered. The hopes of obstetricians have been raised by reports of the sensitivity of anaerobic streptococci to penicillin *in vitro*. I am indebted to Dr. Robert Cruickshank[88] of the L.C.C. Group Laboratory at Hampstead for the following account of his experience of penicillin and the sulphonamides in anaerobic streptococcal puerperal infections, and Mr. James Wyatt, Consultant to the puerperal fever unit at the North-western Fever Hospital, who confirms the clinical impressions in the letter: "We have tested half-a-dozen or more of the 'septicaemic' variety of anaerobic streptococci against penicillin and all have been highly sensitive *in vitro*. Unfortunately we had no luck with penicillin therapy—4 cases treated and 4 deaths —although in 1 at least the primary septic thrombophlebitis seemed to have cleared up at autopsy, in my experience a most unusual finding. We have treated 20 more

of the typical anaerobic streptococcal septicaemic cases with sulphonamides without any response, the fatality-rate was around 80 per cent. Of course, a number of these infections were 'mixed' with *B. necrophorus* or were pure necrophorus infections, and the 3 strains of this organism I have tested for penicillin have all been resistant. . . ." It is known[23a] that bruised, lacerated, ischaemic tissues favour the growth of anaerobes. So that, thus far in chemotherapy, we have found no escape from the knowledge that good midwifery, the avoidance of undue traumatism of the birth canal, is our only present means of preventing the dangerous development of this disease.

Venereal Disease.

A small number of reports on the treatment with penicillin of venereal disease in women have appeared in the American press and are uniformly encouraging Herrell and fellows[89] state that the drug is most useful in the treatment of sulphonamide-resistant cases of gonorrhoea; Cook[90] claims results far surpassing those obtained with the sulphonamides in the initial treatment of gonorrhoea in women. Greenblatt[71] suggests that the problems of the asymptomatic carrier and the possible development of penicillin-resistant strains of gonococci may be answered by using larger than apparently necessary doses of penicillin in treatment. He and his co-workers consider that, although cure may be obtained with as little as 60,000 Oxford units, doses such as 150,000 units should be used. Thompson[91] finds that, with this larger dosage, 98 per cent of cases are cured and that it is quite free from toxic effect. The possibility that a coexistent early syphiletic lesion may be masked by treatment aimed at gonorrhoea has been raised.[91a] It seems advisable to test the Wassermann reaction of all penicillin-treated cases some 3 months later.

Penicillin has also been used by Lentz and his fellows[92] in the treatment of 14 pregnant women with early syphilis and 9 infants with congenital syphilis. They used total doses of 1,200,000 to 2,400,000 Oxford units, given by intramuscular drip in 8 days, and found that this was well tolerated by pregnant women. They think that the higher dosage is desirable. Although the period of observation has not been long enough to be certain that either mothers or babies have been cured, they state that miscarriage, stillbirth, and neonatal death are averted, the infants are born apparently healthy, and the course of the disease profoundly and favourably affected. The infected infants responded well to doses of 18,000 units per pound of body-weight, but grossly affected babies must be treated with smaller doses under careful paediatric supervision. A more recent paper by Lentz's colleagues, Platen and others[93] concerning 69 infants with manifest early congenital syphilis treated with 16,000 to 32,000 units per pound of weight shows somewhat unsatisfactory results, and the authors suggest that larger doses still, such as 40,000 units per pound, may give the optimal effect. In general, however, the immediate response of early congenital syphilis to penicillin, and its lack of toxic effect, has been gratifying; cutaneous and mucous lesions heal very rapidly and dark-field positive lesions become negative in 24 hours after the start of the treatment. Rhinitis is more lingering, but X-ray evidence of osteitis disappears in about the same time as with the metal salts. I feel that when treatment is being instituted primarily in the interests of the unborn child—the maternal syphilitic state being secondary, as in early infection in late pregnancy—penicillin should be chosen for its rapid beneficial effect, however imper-

manent, and its freedom from ill-effect. In a single case in my care, treated with large doses of penicillin, a woman in late pregnancy with a syphilitic rash and severe vulval sepsis, after a week's treatment both the rash and the vulval lesions disappeared entirely. The Wassermann reaction remains positive but this is to be expected during some weeks to come. She is as yet undelivered.

Ophthalmia Neonatorum.

Penicillin is now also being used in the treatment of ophthalmia neonatorum. Sievers[74] reports that 8 patients were treated with intramuscular injections in total dosage varying from 60,000 to 330,000 units. Six of the 8 responded promptly with pronounced clinical improvement within 24 hours and complete recovery in 3 to 6 days. The specific organisms disappeared in smears and cultures in 9 to 24 hours after beginning the treatment. These results are equal to those obtained with sulphonamides and it may be that penicillin should be chosen for use in very ill or premature babies afflicted thus, because of its slight toxicity.

Sorsby,[72a] too, claims that the dramatic results obtained by the use of the sulphonamides are paralleled by those given by penicillin. He has published results in a total of 47 cases of ophthalmia neonatorum treated by the local application of penicillin in the form of drops. He obtained optimum results with a concentration of 2,500 Oxford units per c.cm. in cases where the disease was caused by a whole range of organisms, gonococci, staphylococci and even the virus of inclusion blenorrhoea. The drug is well tolerated by the infant's eye, irrigation is generally not necessary after 6 hours, clinical recovery sometimes takes place in a few hours.

In the Obstetric Unit of the British Postgraduate Medical School penicillin eye-drops in 1,000 Oxford units per cent concentration are now being used routinely as a prophylactic measure in the newborn in place of silver nitrate. One drop is instilled immediately after cleansing the eyes and 1 drop an hour later after the bath.

Breast Abscess.

Since this complication of the period of lactation is usually due to infection with staphylococci, penicillin should be used as soon as possible to avert the need for surgery, and in combination with surgery when it is unavoidable. Private communications from London hospitals report its present use with oestrogens in mastitis, with favourable results in preventing the development of breast abscess. Fraser[94] reports on the use of penicillin locally, combined with simple aspiration of breast abscesses or with surgical drainage. He thinks that healing is much more rapid than usual in the treated cases and the organisms quickly disappear. Suppression of lactation by stilboestrol was necessary in his cases to achieve the best results.

In the reviewer's small experience with staphylococcal infections affecting mother or child in the early days of the puerperium, there has occurred very rapid healing of localized lesions of the infants' scalps after injection under the surrounding skin of small doses of penicillin; and in a single case of staphylococcal osteomyelitis of the humerus in a 3-days-old baby, there was immediate favourable response with penicillin after extensive spread intractable to surgery and sulphadiazine.

Thus far, then, the wide bactericidal range and freedom from toxicity of penicillin make it the drug of choice in nearly all of the infections encountered in the field of obstetrics and gynaecology; and our

hope remains that newer chemotherapeutic discoveries will set still wider bounds to the victory over disease, or, better, that a general improvement in obstetric practice may soon reduce the number of cases requiring the use of penicillin, or the sulphonamides, or other curious measures.

" 'Tis not enough that through the cloud thou break,
To dry the rain on my storm-beaten face,
For no man well of such a salve can speak,
That heals the wound, and cures not the disgrace . . ."[95]

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