are the infections in which we know that the organism is introduced from an extragenital source, and in which, therefore, the possibility of spread from attendants or from patient to patient has to be considered; and, thirdly, they are the infections for which we have now a specific method of treatment in sulphanilamide and its derivatives, so that early diagnosis is important for the patient herself as well as for others who may run the risk of infection transmitted from the same source.

From the bacteriological point of view, then, the issue is clear. We have first to investigate every case of puerperal pyrexia by taking a swab from the vagina (a cervical or intra-uterine swab is not necessary) and examining primarily for haemolytic streptococci. May I interpolate at this point my belief that there is no substitute for this examination, and that evidence gained from the clinical state of the patient can never give an accurate answer to the all-important question, "Is this a haemolytic streptococcus infection?" Having received a positive report on the swab, steps must be taken to find the source of infection, both in the patient herself and in attendants and other contacts. The finding of a source in the patient is of little use in preventing the spread to others, as she will in any case be isolated, but from a medico-legal point of view it may be of use as a line of defence. If the vaginal swab is negative for the haemolytic streptococcus no investigation of contacts is necessary, since other infections, with the possible exception of the very rare staphylococcal and pneumococcal ones, are not generally transmitted from an outside source.

This much is clear, but the problem still remains of how to get the necessary examinations carried out quickly and accurately. There can be few places in this country that are not within easy reach, by post at least, of a laboratory, but because of the necessity for speed it is essential that the laboratory should contain at least one full-time experienced bacteriologist. If haemolytic streptococci are to be "grouped"—and this is important, especially in examination of throat swabs, to avoid suspending nurses unnecessarily—the difficulty is greater still, as the number of laboratories in which this can be done is still small. At the Research Laboratories at Queen Charlotte's Hospital we attempted to fill this gap by instituting a service for the examination of any swabs from maternity cases or their contacts for haemolytic streptococci only, and for the grouping of any such organisms found. If a few more laboratories would undertake similar work in some of the large towns throughout the country so that practitioners resident anywhere in England could be sure of obtaining accurate, cheap, and, above all, quick reports, there would no longer be any excuse for attempting to solve the problems of a bacterial disease by clinical data alone.

Standard specifications for protective clothing, respirators, gloves, and other articles of personal safety equipment may result from a meeting called recently at the request of the National Safety First Association and the Associated Slate Quarries. The meeting was attended by both makers and users of safety equipment, as well as by representatives from employers' organizations, engineering institutions, trade unions, voluntary associations, and Government departments. A resolution was carried asking the General Council of the British Standards Institution to set up a representative industry committee to deal with all personal safety equipment. There are already B.S.I. committees dealing with individual articles of safety equipment, such as boots and goggles. The proposed industry committee would take over control of these committees, and would also deal with any future requests for the standardization of personal safety equipment.

TREATMENT OF UNDULANT FEVER WITH PRONTOSIL

BY

CHARLES ZAHRA NEUMANN, M.D.

The remedies which it has been proposed to use for the treatment of undulant fever are so numerous and varied that the natural conclusion is that few or none are really consistent in their action. Vaccines, so far, have proved of limited use, except in a few cases where they were injected intravenously and where the curative effect may be ascribed to shock therapy. In my experience the results of vaccines, with few exceptions, have been disappointing. The severe and uncontrollable reactions accompanying intravenous vaccine therapy militate against the general acceptance of this form of treatment.

When trypaflavine was introduced great hopes were entertained and good results were claimed. Certainly some patients recovered fairly rapidly after the dye, but in others no result was forthcoming. The same may be said of mercurochrome. Both these drugs are relatively toxic, and their direct introduction into the blood stream increases any potential danger. I have used foudadin, a trivalent antimony preparation, in a few cases, but the number is as yet too small to arrive at any conclusion. Good results have been reported by Manson-Bahr and by Young.

A great desideratum would be an effective remedy that could be administered orally and that did not exert any undue toxic action. If the claims put forward in the cases described below are confirmed, then prontosil and its congeners would be ideal remedies in undulant fever.

Cases Treated by Injection

In Cases 17 to 20, prontosil was administered intramuscularly, the dosage being one injection of 5 c.cm. on alternate days. The urine was stained red within a few minutes, which showed that the excretion was very rapid. With the dosage adopted, concentration of the drug in the blood, was not likely to be high enough to influence the disease, and in three cases the results were disappointing. The first of these (Case 17) was that of a youth aged 18; as soon as his Widal reaction proved positive in a titre of 1 in 150 he was given a *melitensis* vaccine every third day in gradually increasing amounts. After three weeks he still ran a high fever and I decided to inject prontosil. He was given 5 c.cm. every other day for another three weeks. At the end of one and a half months of persistent treatment the patient was still feverish and suffering from rheumatic pains. The other two (Cases 18 and 19), young children 3 and 4 years old, failed to respond after more than three weeks' treatment by prontosil injections. The fourth case (No. 20) was that of a boy of 6. During the first week of his illness his temperature was as high as 104° F., the blood-serum reaction was strongly positive to *Br. melitensis*, and he was then treated with intramuscular prontosil injections on alternate days; at the third injection the temperature was 100° F. in the evening, and he was completely afebrile on the tenth day of treatment. No second wave of pyrexia occurred, although the patient was kept under observation for six months.

It will be realized that in three of these cases the results were meagre, while in the fourth the normal

duration of the disease seemed to have been materially curtailed. In the light of further experience with prontosil by mouth it is probable that the dosage administered intramuscularly was too small.

Oral Treatment

In all, sixteen patients were treated with prontosil red orally; they were mostly children, and the results in the majority were gratifying. It must be premised that none of the patients was severely intoxicated and that the average duration of symptoms at the beginning of treatment was a week to ten days. In all a strongly positive Widal reaction to *Br. melitensis* was obtained. The initial dosage for children was four tablets of prontosil daily. Youths and adults received six tablets. After three or four days, according to the gravity of the case and its response to treatment, the number of tablets was reduced to three in the case of children and to four or five tablets in adults. Usually at the end of a week children were given two tablets and adults three tablets daily, and this was continued for a few days. It is advisable to give the drug for several days after the patient has become afebrile.

Children sometimes dislike the red colour of the tablets, and it is a good plan to powder these and to mix them with some jam or marmalade, which is then spread on a cream cracker. Alternatively, one can use prontosil album. The effect of the drug on the temperature is usually prompt, and a daily fall of 1° F. may be expected. In some cases prontosil acts in an almost specific manner, while in others, a minority, the effect is disappointing. If no result is evident within a week the drug will be ineffective even after prolonged administration. Why there should be this variation in individual cases cannot be explained.

If given early in the course of the disease a great deal of the debility caused by the long duration of the fever is avoided and the patient can often return to school or to work within two or three weeks after treatment has been started. It must be remembered that the "disability period" of undulant fever averages two to six months.

No severe toxic effects were observed after the administration of prontosil. In a few cases a curious lassitude, perhaps more correctly an abnormally quiet attitude, was noticed. This began about two days after the first dose and lasted for two or three days. Anorexia is usually asserted to be one of the toxic sequelae of the drug, but as this symptom is very common in undulant fever and does not become worse after taking prontosil little importance need be attached to it. In three cases slight vomiting occurred during the treatment, and in one case strangury; both these symptoms disappeared in a day or two when the dose was diminished. In two cases a slight degree of cyanosis of the cheeks was seen. In no case was there any ground for alarm, and although the dose was with advantage reduced the drug was never entirely suspended.

It is important to continue the treatment for a few days after the fever has disappeared. In two cases where this was neglected the pyrexia reappeared, but it as promptly vanished when prontosil was again given.

Analysis of Cases

Most of the patients were treated in the acute stage of the disease, and more experience in the chronic cases of undulant fever would be desirable.

Case 1.—A child aged 4 had been feverish for over a month when first seen. His evening temperature oscillated between 101° and 102° F. His general condition was good, and he was usually active enough to play with his brothers. He was given four prontosil tablets daily for four days, the number being then reduced to two in the twenty-four hours. On the third day after the onset of treatment the evening temperature was 99° F.; on the fifth day it was normal, and has remained so ever since. There were no rheumatic pains, so common a complication of undulant fever.

Case 2.—A young man aged 28 was seen after four or five days of high fever. His blood-serum reaction was strongly positive to *Br. melitensis*. His general condition was fair, but occasionally at night he was restless and his mind wandered. He was given six tablets of prontosil daily. On the second day the temperature had dropped from 104° to 102.5° F. By the fourth day the patient said that he felt much better, and the temperature was barely 100° F. On the sixth day the patient was normal, and the prontosil was stopped. Two days later the temperature suddenly rose to 102° F., whereupon the drug was again administered, with the result that within two days the fever disappeared completely and the patient has been free from it since. No rheumatic pains or other complications marred an otherwise uneventful convalescence.

Cases 3, 4, 6, 7, and 8.—These patients varied in age between 3 and 6 years. In all the blood-serum reaction was positive to *Br. melitensis* and the spleen palpable. Four tablets were given daily in jam; this was reduced to three and subsequently two tablets as the condition of the patients improved. None of the cases was seriously intoxicated, and recovery was prompt. In Case 4 slight cyanosis of the cheeks was observed on the third day; this disappeared on reducing the number of tablets to one daily.

Case 5.—A young man aged 25 had been ill for three months, and the fever had lately been oscillating between 100° and 102° F., with apyrexial periods lasting for a week or ten days. He complained of rheumatic pains about the ankles and the knees, and had lost weight considerably, for which his severe anorexia was mainly responsible. The spleen was palpable and the blood reacted strongly to *Br. melitensis*. The usual dosage of prontosil red was prescribed—that is, six tablets daily. After five days the patient was free from fever. His rheumatic pains persisted for a week and no further, then gradually disappeared. Although he was kept under constant observation for three months no further waves of pyrexia were recorded.

Cases 9, 10, 11, 12, and 13.—These consisted of children, the youngest of which was barely 3 years old and the eldest 10. The latter, as well as Case 10—a girl of 7 years old—was given six tablets for three days and four tablets subsequently. The average evening temperature among this group varied between 102° and 104° F. In a few days the fever chart showed a definite response to the drug, and in ten days all the cases were apyrexial. In all, the first was also the last wave of fever. No relapses were observed during the three months of observation.

Case 14.—A child aged 5 years was afebrile after a week of treatment, and to prevent possible toxic effects prontosil was suspended. When three days had elapsed the patient developed a slight evening temperature, which rose to 102° F. the next day. Four tablets of the drug were given for a further five days, although the temperature had dropped to normal after the second day of treatment.

Case 15.—A woman of 70 had been suffering from malaise and generally increasing pyrexia for over a week when a Widal reaction confirmed the suspicion that she had undulant fever. When prontosil was prescribed she was in poor condition: her temperature was 104° F., there was a certain amount of bronchial catarrh, and traces of albumin were found in her urine, with a few hyaline casts. In five days the evening temperature fell to 100° F., and on the seventh day she was free from fever for the first time. Her general condition improved considerably in the next few days, until a severe sciatica developed which lasted for two weeks.

during which period there was no fever. She was comparatively well for a month, when pyelitis set in, with eventual heart failure and uraemia.

Case 16.—A boy aged 12 was diagnosed as suffering from undulant fever, and this was confirmed by the positive blood-serum reaction. His temperature at the beginning of treatment was 104° F., and he had a considerable amount of bronchial catarrh; this improved with an expectorant and with poultices, but the fever remained high and was still 103° F. on the evening of the tenth day, although he had been given six tablets of prontosil red daily. This was now suspended, as albuminuria and casts appeared in the urine, and it was feared that prontosil, if not the actual cause, might still further accentuate the renal condition. After a month the boy gradually improved and his appetite returned. Albumin disappeared, but tachycardia set in during convalescence. This condition is fairly common during convalescence; it rarely leads to any serious results, but usually persists for two or three weeks. Occasionally there would be a rise to 100° or 101° F. for three or four days and then an apyrexial period of a week or ten days. The total duration of the fever in this case was a little over two months.

Table giving Results of Treatment

Case No.	Age (years)	Sex	Dosage	Duration of Fever	No. of Waves	Remarks
<i>Intramuscular Injections of Prontosil</i>						
17	18	M.	14 inj. of 5 c.cm. each	2 months	5	Had previous vaccine treatment (intramuscularly)
18	3	M.	6 inj.	1 month	2	Had previous vaccine treatment (intramuscularly)
19	4	M.	8 inj.	3 weeks	2	
20	6	M.	5 inj.	10 days	1	
<i>Prontosil Red given Orally</i>						
1	4	M.	4 tablets daily	6 days	1	
2	28	M.	6 tablets daily	10 "	2	Prontosil suspended at end of fifth day. Had a second wave lasting two days
3	6	M.	4 tablets daily	8 "	1	Vomiting from second to fourth day
4	5	F.	"	12 "	1	Cyanosis of cheeks on third day
5	25	M.	6 tablets daily	5 "		A chronic case—no other waves after the first week
6	5½	F.	4 tablets daily	5 "	1	
7	3	F.	"	2 "	1	Vomiting from second to fifth day
8	6	M.	"	6 "	1	
9	4	M.	"	8 "	1	
10	7	F.	6 tablets at first; 4 tablets afterwards	10 "	1	Vomiting from third to fifth day
11	10	M.	"	7 "	1	
12	3	M.	4 tablets daily	10 "	1	Strangury on fourth day
13	10	F.	6 tablets at first; then 4 tablets daily	10 "	1	
14	5	F.	4 tablets daily	12 "	2	
15	70	F.	6 tablets daily	7 "	1	Died 1½ months from end of treatment
16	12	M.	"	2 months	5	Prontosil suspended after ten days

Summary and Conclusion

1. Twenty cases of undulant fever treated with prontosil are reviewed.
2. In four the drug was administered by intramuscular injections on alternate days. In only one of these cases was the period of the disease perceptibly shortened.
3. In the remaining sixteen cases oral administration was carried out. In fifteen of them the average duration

of the fever was seven days, ranging from two to twelve days. In one case the drug was apparently ineffective. As a rule cases which are untreated become fever-free in two to six months, though considerable variations are met with.

4. None of the cases was seriously intoxicated, though some had high temperatures.

5. Because of the limited number of cases, definite conclusions cannot as yet be drawn, but these results make further research desirable.

6. Prontosil red and other oral sulphanilamide preparations so far represent the most convenient treatment for undulant fever, and if the results described here be confirmed these drugs may eventually find a valuable place in the fight against this crippling and long-drawn-out disease.

Malta, May 5, 1938.

A COMPARATIVE TEST OF NATURAL AND CONCENTRATED ANTITOXIN IN TREATMENT OF MALIGNANT DIPHThERIA

BY

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Owing to the convenience of its administration the use of concentrated diphtheria antitoxin, containing only the globulin fraction of the serum of the immunized horse, is probably universal. The serum manufacturers claim that by depriving it of all its inert protein and other useless constituents it is less toxic to human beings, and they continue to offer more and more concentrated antitoxins at higher prices. Since the appearance of malignant diphtheria in Bristol in 1921 there have been a few cases in which the administration of antitoxin in large doses intravenously failed to save life, even when the patient was treated within forty-eight to fifty-six hours of onset of the disease. It therefore occurred to me to investigate the relative values of natural (whole serum) antitoxin and concentrated (globulin only) serum to see if in the process of concentration the antitoxin had lost any of its therapeutic efficiency. Concentrated serum might still neutralize the same quantity of toxin *in vitro*, but it might not have the same avidity for combining with toxin *in vivo*, especially as the peptization of the globulin is not so perfect when redissolved after precipitation as it is in the unaltered natural serum. This can be demonstrated by examining each microscopically with a dark-ground condenser.

The cases chosen for this trial are those which on admission were considered by the admitting medical officer to be so gravely ill as to need a large intravenous injection of antitoxin (usually 30,000 units) and 60 to 100 c.cm. of 20 per cent. glucose, together with 16,000 units intramuscularly. I have included only those cases in which it has been possible to give the full dose of antitoxin and glucose considered necessary: sometimes, with a restless patient, the needle has slipped out of the vein before the completion of the injection. The cases received natural or concentrated antitoxin alternately.

As the number of cases suitable for the test has varied between only 11 and 23 per cent. of our total admissions,