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,

it has taken six and a half years to amass the data now analysed. Since the material was obtained from two sources over a long period the serum of several horses was used, thus eliminating a possible error, as the serum of different horses varies in its liability to produce reaction. The volume of the natural serum was two to three times that of the concentrated serum. The mortality rates and complications observed are given in Tables I and II.

hyperpyrexia and symptoms of collapse. Temperatures up to 107° F. have been recorded in this series. These reactions are dangerous unless the temperature per rectum is recorded every ten minutes and the usual measures are taken to deal with hyperpyrexia.

Misled by the advertisements of serum makers, we were very much surprised to find that these severe reactions occurred in 23 per cent. of those treated with concen-

TABLE I.

	Day of Disease on Admission							Total	Grand Total	Death Rate %	Difference %	S. E. of Difference		
	1st	2nd	3rd	4th	5th	6th	7th +							
Controls (concentrated serum) :														
Recovered	1	25	53	44	12	9	4	148	} 182	18.6	} 4.2	4.2		
Died	-	2	17	10	3	1	1	34						
Tests (natural serum) :														
Recovered	1	28	50	31	21	2	2	135	} 175	22.8				
Died	-	4	11	13	9	2	1	40						

TABLE II.—Complications of Cases Recovered.

	No. of Cases	Paralyses			Total	%	Difference	S.E. of Difference	Serum Rashes				Rigors, all Cases (Tests 182 Controls 175)			
		Palate	Palate, Pharynx	Pal., Phar., Dia-phragm					Total	%	Difference	S.E. of Difference	Total	%	Difference	S.E. of Difference
Controls (concentrated serum)	148	52	3	1	56	37.8	+11.9	5.5	78	52.7	+19.9	5.6	42	23.0	+21.9	3.47
Tests (natural serum)	135	30	3	2	35	25.9			47	34.8			2	1.1		

TABLE III.

	Day of Death from Onset of Disease														Total
	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	Over 14		
Controls (concentrated serum)	3	3	5	3	3	1	2	1	5	1	—	—	7	34	
Tests (natural serum)	1	3	4	2	2	3	4	5	2	3	2	2	7	40	

Mortality Rates

The percentage difference in the two series appears to favour the concentrated serum slightly (18.6 per cent., compared with 22.8 per cent.), but as the difference is only equal to the standard error it cannot be regarded as statistically significant. Therefore the two sera appear equal in life-saving properties.

Paralyses

In this series I have included only the more serious forms (palate, pharynx, and diaphragm), as ciliary paralysis is difficult to prove unless the patient is old enough to read. The difference here appears in favour of the natural serum, but as it is only twice the standard error it is not strictly admissible. This is also borne out by the fact that fatal paralysis occurred in four of the control series and five of the test series.

Late Serum Rashes

These occurred in 52.7 per cent. of the control cases and 34.8 per cent. of the test series. As the difference here is over three times the standard error it is probably significant.

Rigors and Hyperpyrexia

The great disadvantage of giving foreign serum intravenously is the occurrence of severe rigors associated with

trated serum and in only 1.1 per cent. of those given whole natural serum, although the latter cases received far more foreign protein than the former. It was observed that rigors occurred with equal frequency in the patients who recovered and in those who died. It was also found that in 50 per cent. of the fatal cases treated with concentrated serum death ensued within seven days of the onset of illness, but only 30 per cent. of those treated with natural serum died so early (Table III), suggesting some immediate toxic effect of the concentrated serum. However, whole horse serum is probably nearer human plasma in its buffering, electrolyte content, and the physico-chemical state of its protein than a single protein fraction that has been dehydrated and precipitated. The colloid chemist tells us that no lyophilic colloid reverts exactly to its former state after rough handling—the phenomenon they term “hysteresis.” These findings are not applicable to all therapeutic horse sera, as we found in attempting to carry out a similar series of observations with streptococcal antitoxin, natural and concentrated, administered intramuscularly to scarlet fever patients, using alternate cases as before, but without giving hypertonic glucose simultaneously, as we did with the diphtheria antitoxin. With both types of streptococcal antitoxin serious and alarming reactions occurred in so high a proportion of cases that we did not feel justified in continuing the trial in such a comparatively benign condition as scarlet fever.

Commentary

I do not think that the intravenous glucose is the factor concerned, as in several cases where the patient received only natural diphtheria antitoxin without glucose (not included in this series) no reaction occurred. It would therefore appear either that streptococcal antitoxin is more toxic than diphtheria antitoxin on intravenous injection or that the sensitivity of patients to foreign protein differs in the two diseases. The time taken for the membrane to separate and the duration of the albuminuria—which latter is an index of persisting toxæmia—were also tabulated, but they showed no significant difference with the two types of sera.

As a result of this investigation we have decided in future to use natural diphtheria antitoxin for intravenous injection. The smaller bulk of the concentrated serum is still to be preferred for intramuscular injection in the milder cases.

Conclusions

When given intravenously with 20 per cent. glucose, (1) the therapeutic effects of natural and concentrated diphtheria antitoxin on the death rate and paralytic complications are equal; (2) concentrated antitoxin is twenty times as likely to give severe immediate reactions and one and a half times as likely to give late serum rashes as whole natural antitoxin. (3) On this account natural diphtheria antitoxin is to be preferred for intravenous injection. (4) These findings are not applicable to streptococcal antitoxin.

TREATMENT OF PELLAGRA WITH NICOTINIC ACID

BY

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The work of Elvehjem and his associates (1937) on the treatment of canine black-tongue with nicotinic acid, and the resultant cures, have stimulated clinicians to use this substance in the treatment of human pellagra. Fouts and his co-workers (1937) reported four cases treated with nicotinic acid. These patients, after having been placed on a control diet poor in the pellagra-preventing factor, were observed for three days. During this time their condition remained stationary or became worse. Treatment was then begun with nicotinic acid in doses varying from 0.5 gramme to 1 gramme daily. Within forty-eight hours after the initiation of the treatment all the patients showed distinct improvement in their general condition and the stomatitis was completely healed. In two patients suffering from diarrhoea normal stools were obtained on the third and the fifth day respectively. The dermatitis disappeared within six to twenty-five days. All the patients noticed warmth and tingling of the skin ten minutes after ingestion of the nicotinic acid.

Almost simultaneously, Spies, Cooper, and Blankenhorn (1938) reported eleven cases of pellagra placed on basic

control diets poor in the pellagra-preventive factor. The most striking effects were observed on the glossitis and stomatitis, which usually disappeared forty-eight hours after the beginning of treatment. The pellagrous glossitis, stomatitis, ptialism, urethritis, and proctitis did not reappear while the patients received nicotinic acid. In one case the glossitis and stomatitis, which had disappeared with the use of nicotinic acid, recurred when it was discontinued. Mild cases of dermatitis in which the epithelium remained intact blanched within twenty-four to forty-eight hours after the administration of the drug. However, severe cases of dermatitis in which the lesions were moist, ulcerated, and thickened did not seem to benefit by nicotinic acid. In several cases there was flushing of the dermal lesions with tingling of the skin shortly after the administration of the drug. These authors conclude that 0.5 gramme daily, in five doses of 100 mg. each, is a safe and effective amount in the usual case of pellagra.

In a further report Spies (1938) describes fifteen cases similarly studied and treated. In these the urine was tested for porphyrin. In one case the porphyrin disappeared from the urine forty-eight hours after the beginning of treatment, only to reappear when the nicotinic acid was discontinued. In a later communication Grant, Zschiesche, and Spies (1938) again confirmed these observations, and pointed out that the healing of the dermatitis was completed by the end of the second week.

Smith, Ruffin, and Smith (1937) report a chronic case of pellagra with typical dermatitis, hyperkeratosis of the face, diarrhoea, and mild dementia which responded to nicotinic acid. Yudkin, Hawksley, and Drummond (1938) report a case which was successfully treated with a "liver filtrate" factor. In a later communication Hawksley (1938) records a case ending in recovery after treatment with nicotinic acid. He concludes that the liver filtrate factor used in the previously treated case must contain nicotinic acid.

We shall briefly describe two cases of pellagra which were successfully treated with nicotinic acid.

Case I

A woman aged 62 was admitted to hospital on April 12, 1938, having previously been observed for eight days in the out-patient department. Four months before admission she began to complain of severe diarrhoea consisting of four to six foul liquid stools daily. The diarrhoea persisted in spite of medication. The patient then put herself on a diet of white bread, crackers, zwieback, rice, milled cereal, white cheese, and black coffee. Sugar, meat, vegetables, fish, butter, eggs, and milk were rigidly excluded from the diet. The patient felt weak and listless, and lost considerable weight. The diarrhoea persisted. One month before admission she noticed that the skin on the dorsum of the hands was rough and scaly. The lesion progressed rapidly until the dorsum of the hands became fiery red and scaly. At the same time she noticed red circles under the eyes, somewhat similar to the skin of the hands. One week before admission she began to complain of burning of the tip of the tongue.

Physical Examination.—The patient was well orientated and co-operative. She appeared chronically ill and undernourished. The skin of the face was dry, atrophied, and wrinkled. Under the eyes it was reddened, rough, and scaly. Around the neck there was a wide band of brown pigmentation. The dorsum of the hands was wrinkled, fiery red, and covered with a scaly dermatitis extending from the nailbeds to the wrist. There were areas of deep brown pigmen-