THE DIAGNOSIS AND TREATMENT OF MALIGNANT DIPHTHERIA

BY

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As the malignant type of diphtheria which is at present causing serious anxiety in many towns appeared in Bristol in 1920 and has been present here since, the writer has had unusual opportunities for studying this type of disease. It differs from the classical type of diphtheria by the extremely rapid intoxication of the patient and the slow appearance of membrane, which may be delayed for two to three days. It frequently attacks adults, and is easily mistaken for quinsy. The differential diagnosis between the two diseases can usually be made by observing the following points:

<i>Quinsy</i>	<i>Malignant Diphtheria</i>
Rare in children under puberty.	Common in children and not uncommon in adults.
Extremely painful.	Not very painful.
Mouth full of mucus and saliva.	Mouth comparatively dry.
Fauces deeply reddened and congested, mucous membrane of palate reddened.	Fauces swollen and oedematous, less inflammation, uvula often very swollen and translucent. Mucous membrane of palate pale.
Patient cannot open his mouth far.	Mouth can be opened without difficulty.
Difficulty in speaking.	Usually little difficulty.
Neck glands hard and painful.	Great painless oedema of neck, outline of glands lost in oedematous tissues.
Patient sleepless and restless.	Often very drowsy.
No fetor.	Fetor sometimes marked, but often absent during early stage.
No deposit on tonsils.	Gelatinous film, but true membrane not present for forty-eight hours or later.
Pulse full and bounding.	Pulse rapid and compressible.
Nasal discharge scanty and muco-purulent.	Nasal discharge profuse, often serous.

Of all these signs the most pathognomonic is the great painless neck oedema of diphtheria, but this may not be present until the second day. Early albuminuria is suggestive of diphtheria, but it is not always present until the third or fourth day. In malignant diphtheria the temperature is very variable and may be high, temperatures of 103° to 105° F. being not uncommon during the first two days. Another difficulty is that swabs taken in the early stages are often returned as negative, even when examined by a highly competent pathologist. Laryngeal involvement is comparatively rare.

Treatment

If a diagnosis of malignant diphtheria is made 30,000 to 100,000 units of serum must be given intravenously and 24,000 units intramuscularly. It is more easily administered by means of a 30 c.cm. syringe with an eccentric attachment for the needle, into the veins in the antecubital fossa. We find it is best not to attempt to dissect out a vein, as the vein clots so easily if touched or pulled on. A fine needle is necessary. When we have failed with an elbow vein we have frequently been successful in getting into the external jugular vein by an assistant pressing his finger on its lower portion to make it stand out.

For the last five years we have used the following accessories to treatment. The theoretical reasons for their adoption have been discussed at length elsewhere.¹ The most valuable one is the intravenous injection of 20 per cent. glucose combined with 1 in 500 colloidal iodine. This material is made up ready for use by British Colloids in 150 c.cm. containers. The amount given varies from 30 to 150 c.cm., according to the stage of the disease and the age of the patient: not more than 90 c.cm. to a child under 10; none should be given on the first day of disease. It should be administered with the antitoxin. To get any benefit in the later stages enough should be given to produce glycosuria for six hours. If the glycosuria persists for more than six hours 5 to 10 units of insulin should be prescribed, but not otherwise. A smaller repeat dose, followed by 10 units of insulin, should be given if the patient shows signs of heart failure. To restore the depleted alkali reserve² the following mixture should be given in half-ounce to one-ounce doses until the urine is alkaline to litmus.

R	Sod. bicarb.	...	...	...	...	gr. xxv
	Calc. carb.	...	...	...	...	gr. v
	Pot. bicarb.	...	...	...	...	gr. v
	Aq. menthe pip.	...	...	...	...	ad 3 j

This takes three to four days. In addition, tincture of iodine (*B.P.* 1914) should be given in milk, 1 minim for each year of age up to a maximum of 20 minims, four-hourly. If no more than 10 minims is added to each ounce of milk it is practically tasteless. The iodine must be given in four-hourly doses until all albuminuria has disappeared. This may take a month in the worst cases. We think that, as diphtheria toxin has a strong affinity for lipoids (heart muscle and nerve sheaths), and as iodine also has the same affinity, the iodine tends to turn out the toxin and prevent, to a considerable extent, the more serious paralysees. The presence of albuminuria indicates that all the toxin is not yet eliminated. In addition, we give 1/4 to 1 grain of thyroid. sicc. daily to stimulate the sluggish metabolism after diphtheria. If these drugs are given in these doses until, and only until, albuminuria has quite gone, no sign of renal irritation or hyperthyroidism is ever observed, even if given for as long as five or six weeks. If continued for some days after the albuminuria disappears haematuria may be produced. As intravenous injections of horse serum may produce rigors and hyperpyrexia, the rectal temperature should be taken every ten minutes for two hours after the injection, so that suitable measures to overcome this dangerous complication may be taken at once if it occurs.

We have been recently trying the relative values of the usual concentrated (globulin only) antitoxin and whole antitoxin (that is, the antitoxic serum as derived from the horse without concentration). These results are insufficient as yet for complete analysis, but it is worth while recording a very unexpected finding. On intravenous injection of concentrated serum (globulin only) rigors and hyperpyrexia are frequent, but in not one case has this occurred in 100 trials with whole-horse serum, although the material has been obtained from several horses from two different firms. Whole-horse serum, therefore, appears to be far less toxic, given intravenously, than the globulin-only serum, although the bulk of the former is generally double the latter. We have found that the injection of 2 to 4 c.cm. of haemoplastin (*P. D. and Co.*) is extremely valuable in preventing the haemorrhagic tendency which these severe cases so often show. It should be given before haemorrhage starts in all severe cases as soon as they come under treatment.

The whole method of treatment herein recorded has been applied to all our malignant cases for the last five

years (22 per cent. of the total admissions), with a death rate for the whole admissions of 3.1 per cent. on 3,824, compared with a mortality of 5.7 on 3,131 cases in the previous five years. If the malignant cases only are considered in each group, the death rates in these groups are 14 and 27 respectively. The proportions of malignant cases have been almost identical in the two last five-year periods, although fluctuations occur from year to year. Below is a table of the number of cases treated in this hospital during the past thirty years. Hospital figures are more reliable than notifications, as we find anything up to 20 per cent. of our total notifications are not cases of diphtheria, and, of course, cannot be included in these figures. The percentage of notification errors tends to increase during epidemic times, causing a reduction of the mortality rate based on notification figures, and thus masking the severity of an outbreak.

Years	Total Hospital Discharges	Died	Death Rate per cent.
1905-09	1,956	109	5.5
1910-14	1,852	82	4.4
1915-19	1,684	90	5.4
1920-24	3,439	260	7.6
1925-29	3,131	179	5.7
1930-34	3,824	118	3.1

It may be suggested that these figures show only a natural decline in the virulence of an epidemic which reached its most virulent peak in 1921 (mortality 8.7 per cent.). The writer, after a fever hospital experience of twenty-five years, can only say that in his opinion half of the types of case we previously lost now recover, with the disappearance almost entirely of the distressing persistent cardiac vomiting syndrome from our wards, from the first day we put this method of treatment into operation.

REFERENCES

- ¹ Peters, B. A.: *Medical Officer*, January 24th, 1931; *Lancet*, September, 1930, p. 579.
² Idem: *British Medical Journal*, January, 1918.

Clinical Memoranda

Retroperitoneal Sarcoma with Pain Referred to the Thigh

The clinical interest in this case lies in the demonstration of the ease with which one may, in the beginning, overlook the serious significance of pain felt in the leg when the real cause is infiltration of the nerves in the abdomen by growth. The microscopical examination, carried out by Dr. Grace, pathologist to the Chester Royal Infirmary, showed the growth to be a round-celled sarcoma.

A man, aged 25, reported on April 12th, 1934, complaining of pain in the anterior and lateral parts of the right thigh. Examination of the leg proved negative, and the condition was considered to be one of muscular rheumatism. The complaint dated back to about the beginning of March.

The patient reappeared on May 24th, complaining once more of pain in the right thigh and right loin. The pain in the leg was experienced chiefly on the lateral aspect, and pressure over this area caused much distress. Examination of the thigh showed nothing abnormal, but it became fairly clear that the original diagnosis was a mistaken one and that the pain was caused by involvement of the nerves at a higher level. By May 28th the pain had become so severe that the patient had to remain in bed. Sleep was almost impossible. He was admitted to hospital on June 6th. The urine contained a definite amount of albumin, with some pus cells. The blood urea was found to be high—240 mg. per 100 c.cm. There was marked rigidity in the right loin, but no definite mass could be felt. The temperature ranged from normal to subnormal. There was a moderate leucocytosis. The general condition gradually deteriorated, and death occurred on June 12th, the patient having more or less been unconscious for two days before.

The only other symptom of note was the presence of a considerable quantity of frothy sputum, which, however, was not blood-stained.

Post-mortem Findings.—The kidneys, macroscopically, appeared normal, but just below the lower pole of the right kidney infiltrating the right ilio-psoas muscle was a large fixed sarcomatous mass, with many outlying nodules. Its size was about that of a child's fist, and it involved the nerves running down towards Poupart's ligament. The liver showed no secondaries, but both lung bases presented numerous small growths, the largest being about marble size.

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Muscarin Poisoning and Melancholia

The predominant part played by the toxic factor in certain mental disorders is now generally recognized. In general, the small amount of toxin, and its complex constitution, render its identification impossible.

In the course of an investigation of the toxæmias associated with mental disorder, a definite group has come to light in which the toxin is allied to muscarin. Four independent considerations led us to expect that such a group existed.

1. The injection of a foreign protein gives rise to an antibody, and, according to Friedberger, the combination of these two when acted on by complement is toxic.
2. Le Marquand, in 1923, working at Bethlem Royal Hospital, found that in a series of toxic-looking melancholics, in whom wasting and a poor physical condition were outstanding features, there was an excessive complementary power of their sera.
3. Clinically, bromides, which are anti-complementary, often prove of benefit in these cases.
4. Also, it has been known for a long time that certain cases of melancholia recover under treatment with atropine.

The patient's serum, controlled for pH, osmotic pressure, and temperature, was perfused through the heart of a killed frog. The tracing shows the effect on the frog's heart of the serum of such a case, and the recovery under atropine.

This patient (F.) was a man aged 50. He had a bad quinsy, and lost 1 st. in weight. A month later he was admitted to Bethlem Royal Hospital; melancholic, thin, and toxic in aspect. He was given full doses of atropine, and became very restless. The atropine was stopped for three days, and then recommenced in small doses. Steady improvement followed. A month later his condition became stationary and he was transferred.

The number of these cases is small—some eighty patients were examined before this case was discovered. Since then similar cases have appeared from time to time: in general, the result of treatment is better than in the case described. Clinically, these cases have a toxic aspect; moist skin; they swallow frequently, from excessive salivation; they have small pupils and no fever. In our cases the heart rate has been normal.

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