Another observation of some interest, and perhaps of value, is the following. Accurate records were not kept, their possible significance not being realized, but it was noticed that the second injection of A.P.T. at the same site as the first may not cause any increase in the amount of induration which, as is well known, forms at the site of the first injection. The first injection causes local hyperaemia, with congestion of the tissues and increased lymph flow—the normal response to the presence of a chemical irritant. When the second dose is given in the same place as the first, compensatory hyperaemia is already present, and so the A.P.T. is removed more quickly, the slow absorption and consequent prolonged antigenic action, which Glenny, Buttle, and Stevens (1931b) showed to be so important, being counteracted. To obviate this the second injection should be made in the opposite arm; in this way, by ensuring protracted absorption, the maximum effect is likely to be produced.

Conclusion

Allusion has been made elsewhere (Lewis, 1939a, 1939b) to the many methods by which anti-diphtheria schemes in this country are conducted. According to a survey of the schemes of some 150 of the larger urban authorities, made by means of a questionary issued by Dr. O. M. Holden, A.P.T. by two injections is used in about 40 per cent. of those studied, in many cases in a dosage of 0.1 c.cm. and 0.4–0.5 c.cm. at fortnightly or three-weekly intervals. A.P.T. by at least two injections, properly spaced and given in adequate dosage, possesses so many advantages over other antigens that it would be a misfortune of the greatest magnitude if it should fall into disrepute through wrong technique. It will be shown in a later paper that in two doses of adequate size, and properly spaced, it will give results that compare very favourably with those given by three doses of unmodified toxoid. Few would cavil at the desirability for some measure of uniform practice in diphtheria immunization, which undoubtedly is greatly hampered by the lack of such a standard. A.P.T. in two injections, with the modifications here advocated, supplies this need, and could with advantage be utilized by all authorities responsible for the control of diphtheria. It is of the utmost importance, however, that proper methods be used. Those advocated are: (1) the dosage to be 0.5 c.cm. and 0.5 c.cm. in children under 8 years; in children of 8 years or more the first dose to be 0.25 c.cm., to be followed by 0.5 c.cm. if there is no reaction; (2) the interval between the doses to be in no case less than four weeks; (3) the injections to be given in opposite arms.

Summary

The results are given of antitoxin titrations in forty-nine children who were bled sixteen months after 0.1 c.cm. of A.P.T. followed in two weeks by 0.5 c.cm.

It is shown that sixteen months after A.P.T. administered in this fashion at least 10 per cent. of children may be susceptible to a large dose of virulent organisms.

Certain modifications in dosage and technique are advocated as a means of increasing the antigenic effect without increasing the number of injections. It is suggested that this procedure may with advantage be adopted by all scheme-making authorities.

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BENZEDRINE SULPHATE

ITS USE TO INTERRUPT AVERTIN ANAESTHESIA

BY

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Avertin, used as a basal anaesthetic, has the great disadvantage that once it has been absorbed into the system it cannot be withdrawn. The counteraction of avertin, and especially of an overdose, has attracted the attention of many observers. Bolliger (1932) experimented with sodium thiosulphate, and he found that although this drug prevented the onset of narcosis it was of no avail in counteracting an overdose. Pribram (1929) experimented with thyroxine to expedite the detoxication, but considered that the drug acted too slowly to be of service in an emergency. Caffeine sodium benzoate has also been tried (Herzberg, 1928; Speidel, 1930). This was found to interrupt avertin anaesthesia in animals, but its action as a respiratory stimulant in man is doubtful, although Herzberg claims that it interrupts avertin narcosis, with slowing and deepening of respiration. Ephedrine has been used (Widenhorn, 1932) with a view to the restoration of the fall in blood pressure. The rise produced is not evident in all cases. Adrenaline frequently produces cardiac irregularity, and in heart–lung preparations ventricular fibrillation is sometimes seen. Kennedy (1932) observed that the first inhalation of ether often produced a marked improvement in the patient's condition. Those patients not benefited by ether were rapidly relieved by the administration of 5 per cent. carbon dioxide in oxygen. Killian (1931), Mörl (1931), and Kennedy (1932) tried coramine and found it an even better antidote. In man 2 to 3 c.cm. of coramine injected intramuscularly, and repeated if necessary, interrupted light avertin anaesthesia and counteracted the cardiac and respiratory depression. Mörl gave 3 c.cm. intravenously. If the anaesthesia is deep the injection of coramine, while helping the general condition, permits of the operation being carried on without further anaesthetic being given.

More recently benzedrine sulphate has been tried by Michelsen and Verlot (1939). They found that animals were protected from the deleterious effects of a lethal dose of avertin by the use of a preliminary intramuscular injection of benzedrine sulphate and that benzedrine given after avertin shortens the anaesthesia by about 50 per cent. They tried the drug in man in five cases, and report that, given 0.08 to 0.09 gramme of avertin per kg. of body weight and subsequently 20 mg. of benzedrine sulphate, the patients "opened their eyes, reacted readily to pain stimuli, gave clear answers, followed commands,

calculated, and so forth. The blood pressure rapidly rose and stayed elevated for two to five hours."

Results of Present Test

This report deals with the use of benzedrine sulphate solution in ampoules—kindly supplied by Messrs. Menley and James—in the cases of twelve children given a relatively larger dose of avertin than that employed by Michelsen and Verlot. Each child had received a dose of avertin equivalent to 0.16 gramme per kg. of body weight. Supplementary anaesthesia was necessary in six cases. All the patients except one (who received 5 mg.) were given 10 mg. of benzedrine sulphate dissolved in 1 c.cm. of distilled water. This was administered intravenously immediately after the operation. The immediate reactions and the length of time before the child had recovered sufficiently to answer questions were noted, and the following observations were made:

Immediate Response.—The patients usually roused a little after the injection of the benzedrine sulphate. Within a few minutes the corneal reflex was present and the patients tended to resist painful stimuli and moved about restlessly. Only one spoke just after the injection. She uttered a few unintelligible words and went off to sleep again. In the others there was no response even to shouting.

Post-operative Sleep.—In those patients who were sufficiently anaesthetized with avertin not to require additional inhalation anaesthetic the average duration of post-operative sleep was four hours. In those needing supplementary anaesthesia the average duration was two and a half hours. This represents a considerable reduction in post-operative unconsciousness as compared with cases not receiving benzedrine, the average time in these patients being six and three-quarter hours (Boyd, 1935).

Condition of Patients.—Instead of the usual circulatory and respiratory depression after operation, characterized by pallor and shallow respiration, the patients were flushed, had a good respiratory excursion, and showed improved pulse volume and rise in blood pressure.

Post-operative Vomiting.—This was present in all cases but one, and was severe in 75 per cent., the patients retching all the evening and in some instances right into the next day. Of those given avertin alone five (82 per cent.) vomited. Vomiting occurred in all the cases in which avertin anaesthesia had to be supplemented. This is in marked contrast to control cases not given benzedrine sulphate: in these the figures for the unsupplemented and the supplemented anaesthesia were 9 per cent. and 17 per cent. respectively (Boyd, 1935).

Two cases call for special mention. One, a girl aged 7 in preparation for appendicectomy, returned some of the avertin solution and was conscious while coming to the theatre. She was given open ether. Two minutes after the administration of the benzedrine sulphate, and before leaving the table, she vomited, and continued to vomit all the evening. She had recovered consciousness sufficiently to answer questions twenty minutes after the benzedrine was given. The other case was interesting in view of the fact that the previous week the patient had been given a similar anaesthetic but without the benzedrine. After the first operation he slept six hours, had no post-operative vomiting, and had a normal peaceful awakening. On the second occasion, after the benzedrine, he slept three hours only, was a little strange in manner on wakening, and vomited a lot all the evening.

Summary

Benzedrine sulphate, 10 mg., was given to children after avertin anaesthesia.

The only immediate effect was the return of the superficial reflexes.

There was a definite reduction in the duration of the post-operative sleep as compared with control cases.

Most of the patients vomited profusely after the benzedrine sulphate.

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Clinical Memoranda

Acute Appendicitis in a Baby

The following somewhat unusual case of acute appendicitis in a baby aged 8 months is, I think, worth recording.

CASE REPORT

A breast-fed baby boy aged 8 months was admitted to hospital on February 14 with a history of having vomited repeatedly (but not all feeds) for three days. He had been fretful and whimpering, occasionally drawing up his legs when crying. The stools were said to have been quite normal.

On admission the baby was very well nourished, and weighed 19½ lb. The temperature was 98°, pulse 120 (volume good), and respirations 48. He was very apathetic, slightly cyanosed, and showed marked dyspnoea. From time to time he started to whimper and draw up his legs. The chest, heart, and lungs were normal. The left side of the abdomen was soft, and the child ceased to cry and appeared more comfortable when slight pressure was applied to this side. The right side seemed slightly more resistant, and I thought I could feel a small sausage-shaped lump lying transversely just above the umbilicus. Per rectum nothing abnormal was felt.

In the evening the eyes were sunken and the breath smelt of acetone. Since admission the baby had been fed on small amounts of glucose water and had vomited only once, the vomit looking somewhat dark. The abdomen, however, was then quite soft and no resistance was felt anywhere. In the absence of any definite signs in the chest or abdomen or abnormal stools, and in view of the baby's facies and marked apathy, a tentative diagnosis of a cerebral or meningeal condition was made. At midnight the child was drowsy. Lumbar puncture produced clear fluid, not under pressure. This fluid was reported on by Dr. J. Kilian Clarke, Ransom Memorial Laboratory, Nottingham, as follows: "Faintly blood-stained fluid with no coagulum. Chlorides, 0.73 per cent.; sugar increased; albumin, 0.06 per cent. Films show no apparent increase in white cells; no micro-organisms seen." The condition remained practically unchanged during the next day. He vomited twice. The stools were normal. On the third day in hospital (sixth day of illness) the temperature was 102° at 10 a.m., and the pulse was very rapid and feeble. Fine crepitations were heard at both bases. The baby collapsed early in the afternoon and died.

Post-mortem Findings.—The brain and meninges macroscopically were normal. The chest and heart were normal. Both lower lobes of the lungs were congested, and there was a small amount of pus in the bronchioles (a condition which I presumed to be terminal, not causative). The stomach and transverse colon were much dilated. The whole of the caecum and lower part of ascending colon were firmly adherent to the parietal peritoneum and were much discoloured. An appendix almost three inches in length with a kinked tip was found adherent to the caecum. The tip was gangrenous and on the point of perforation. Other organs were normal.

I am indebted to Dr. Warnecke for permission to report this case.

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