Transmission experiments have also been performed with material from cases of dermatitis herpetiformis. Bullae do not occur in certain chronic phases of this condition, and out of ten cases examined fresh bullous fluid was obtained in only four. The undiluted fluid was inoculated intradermally in the shaven skin of the flanks and the plantar skin of the hind feet of guinea-pigs. Two of these specimens were bacteriologically sterile, and the animals inoculated with these developed no lesions. The other two fluids contained staphylococci and streptococci and, with these, herpetiform lesions were produced in the plantar skin of the inoculated animals; no lesions appeared in the hairy skin. Brief notes regarding the investigation of these two cases follow.

Case 8.—A girl aged 9 had a six-weeks history of bullous eruption, clinically dermatitis herpetiformis. Inoculation of a guinea-pig in the plantar skin with a vesicle fluid produced a pustulo-vesicular reaction in two days. The animal was killed, and the "pads" were removed and ground up with saline solution to give a 1 in 10 suspension, which contained staphylococci and streptococci. A "gradocol" (Elford, 1932) filtrate made from this suspension was sterile, and proved non-infective for the guinea-pig. The unfiltered suspension produced a similar reaction to that obtained with the primary material, and from this and from a sterile gradocol filtrate a further animal passage was obtained. A suspension made from the lesions in this last guinea-pig proved sterile bacteriologically and non-infective on inoculation. Control inoculations made with broth cultures and saline suspensions of agar cultures of the bacteria grown from this bullous material produced no lesions in the guinea-pig. Fresh bullous fluid collected from this case two weeks later was sterile culturally and non-infective in the guinea-pig. Intradermal inoculations of the patient with the streptococcal vaccine and a filtrate of it produced bullous reactions; a control test with a staphylococcal vaccine produced no reaction.

Case 10.—A man aged 64 had a three-months history of an eruption which was thought to be dermatitis herpetiformis. A guinea-pig was inoculated as in Case 8 with undiluted bullous fluid; a pustulo-vesicular reaction appeared in the skin of the hind feet after six days. A suspension made from these lesions was found to contain streptococci; further passage was unsuccessful.

Transmission experiments were conducted with different material from two other cases—namely, saliva from one case with many ulcerative lesions in the mouth; in the other case, showing many erythematous plaques, the fluid obtained by blistering with liquor epispasticus over the lesions was used. In both cases the material proved non-infective for the guinea-pig.

Bedson (1935) reported successful transmission to guinea-pigs with vesicle fluids from three out of six cases of dermatitis herpetiformis; passage to the third and eleventh generations was realized with two of these strains. Although this demonstration of an infective agent in the bullous fluid from some cases of dermatitis herpetiformis supports the observations of Urbach and Reiss (1931), Urbach and Wolfram (1933), and Taniguchi (1934), as Bedson points out, the presence of a streptococcus in the material used in our series of experiments may be of significance. In only one instance was a bacteriologically sterile filtrate found to be infective, although it should be added that attempts to produce lesions in the guinea-pig's skin with the streptococci obtained from the human lesions were unsuccessful. Using bullous fluid as antigen, I have attempted to demonstrate antigen-antibody reaction by complement-fixation and precipitin tests without any specific result, and it has to be admitted that our evidence to date of the virus aetiology of dermatitis herpetiformis is conflicting and far from complete.

Sterile bullous fluid from a case of pemphigus vegetans was inoculated into a guinea-pig, a rabbit, and mice without result. I have also to record the unsuccessful inocu-

lations of guinea-pigs with material from five other cases of bullous eruption, urticarial or erythema multiforme in type, kindly referred by Dr. W. J. O'Donovan. One of these bullous fluids contained staphylococci and streptococci; the other four were sterile. The sera from eight cases of psoriasis have been tested with various antigens prepared from psoriatic scales, but complement-fixation and precipitation reactions were entirely negative. It was thought that artefact bullae superimposed upon recent lesions of psoriasis or lichen planus might contain the hypothetical virus, but no specific antigenic reactions were obtained with such material.

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FURTHER INVESTIGATION OF A NEW ANTI-CHOLERA SERUM

BY

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Since our preliminary note on the "Treatment of Cholera with a New Anti-cholera Serum"¹ attempts have been made to increase further the potency of the serum. Several modifications of the original method of toxin production as discussed in our paper on the preparation of cholera toxin and its experimental pathogenic action² were made in order to enhance the titre of toxin. At the same time serum was also prepared by injecting agar culture to compare the therapeutic value of the serum prepared with our original toxin and that prepared by injecting agar culture. The therapeutic effect of serum obtained by immunizing horses with agar culture only was hardly noticeable, though tried both intraperitoneally and subcutaneously. We showed in our note that the agglutinating titre of the serum obtained by immunizing horses with the toxin was 1 in 8,000.

It may be possible that both exotoxin and endotoxin of cholera vibrio play important parts in the disease, and that by our method of toxin preparation both exotoxin and endotoxin are available in fair amount for the immunization of the horse. It is a common experience to those working in cholera hospitals to find that there are two distinct groups of cholera—namely, (1) with excessive purgation and a high specific gravity of the blood, and (2) with early onset of vasomotor paralysis, lower specific gravity of the blood, and absence of pro-

fuse diarrhoea. Whether the predominance of any one of these two groups in an epidemic is due to the preponderance of exotoxin or endotoxin in a particular strain of cholera may be an interesting subject for investigation.

The modification in the method of toxin production was made with the object of getting a maximum quantity of both exotoxin and endotoxin. The difference between our original toxin and that used this time for the production of serum was that a much larger quantity of seed culture was employed for inoculation of the special broth.

The conservation of the virulence of the strain of *Vibrio cholerae* used for the production of toxin for immunization was found to be extremely difficult. The strain No. 269 of our collection originally used for the production of toxin was found to have lost its virulence after four months. We had to examine about thirty new strains in order to obtain one suitable for the routine production of toxin. Work, however, has been in progress to ascertain the cause of the variability of the strains, and to find out a suitable method by which virulence can be fully conserved.

Intraperitoneal Serum

The serum prepared with our toxin was tried on forty-seven cases of cholera in the cholera ward of the Chittaranjan Hospital, Calcutta, during the first period of the recent epidemic, when most of the patients were admitted in a highly toxæmic condition. During the same period there were 170 control cases which had been treated without serum. The following table indicates the rate of mortality of cases treated with serum and of those treated without serum.

Effects of Serum Treatment

May 10th to June 5th	No. Treated	Deaths	Mortality
Cases treated with serum ...	47	5	10.63 per cent.
" " by other methods	170	35	20.5 "
<i>Cases with a Blood Specific Gravity of 1064 or more</i>			
Cases treated with serum ...	26	3	11.5 per cent.
" " by other methods	44	11	25.0 "

N.B.—Serum was administered only to those patients showing high toxæmia and a high specific gravity of the blood. The controls include all the patients admitted during that period but treated without serum.

During our last investigation concentrated serum was used, but this time only whole immune serum was administered, in quantities of 70 to 80 c.cm. Only one intraperitoneal injection of this dose of serum diluted with 200 c.cm. of sterile warm saline solution was given to each of the patients on admission, and serum was never repeated in any of the cases. The serum was given only to those patients showing high toxæmia and a high specific gravity of the blood. Except in four cases of this series the specific gravity in all the patients was between 1062 and 1066. In these four cases, though the specific gravity was lower, the patients were exhibiting a fairly high degree of toxæmia.

Most of these cases had only one preliminary intravenous saline transfusion on admission. In some cases where motions were very frequent and excessive in quantity from the time of admission, and the pulse did not show improvement after the preliminary saline transfusion, subcutaneous saline had to be given, on one occasion, within two or three hours of the first intravenous saline. It should be mentioned here that from observations made it seemed that the absorption of serum by the peritoneum was not so rapid as was originally supposed. This was experimentally confirmed in a case

of typhoid fever where an intraperitoneal injection of typhoid serum was followed after six hours by a sharp reaction, indicating that the maximum absorption of serum took about this length of time. We have also observed that cholera patients, whose pulse could be maintained for five or six hours after the administration of serum intraperitoneally almost invariably survived.

The most interesting point in our observations was that uraemia, which is a common complication in cholera patients, particularly in those admitted with a high specific gravity of the blood, was absent in our series of cases treated with intraperitoneal serum. This was an indication of the neutralizing effect of the serum on the toxin, which could not, therefore, cause any further damage to the kidney. Another important effect of the serum was that tympanitis, which is a common complication in cholera, was rarely observed in cases treated with serum.

Out of the forty-seven cases of this series treated with serum two patients showed mild urticaria. In both of those cases, however, the urticaria disappeared after three or four doses of atropine or tinct. belladonnae and sponging of the body with a warm alkaline solution. Actual anaphylaxis was not observed in any of the cases.

Serum by other Routes

The effect of intravenous administration of 70 to 80 c.cm. of this serum was not favourable. We are now observing the effect of subcutaneous injection. During our last experience subcutaneous injection of serum did not produce the same effect as intraperitoneal administration, but last year only concentrated serum was used. It has been experimentally proved by Professor Madsen that the absorption of concentrated serum is much slower than that of whole immune serum. Consequently we may expect better results with subcutaneous injection of whole immune serum. The only objection to subcutaneous administration of large quantities of whole immune serum is that serum sickness with urticaria is very common, while with intraperitoneal administration it was found to be rare.

The intraperitoneal administration of serum may be thought difficult by those unaccustomed to this method, but our senior and junior house-physicians have been doing it without any difficulty or accident whatsoever. As a matter of fact, the house-physicians of our ward found the administration of 70 to 80 c.cm. of serum easier by this route.

TECHNIQUE

A trocar and cannula are always used for introducing the serum. The required quantity, 70 to 80 c.cm., is poured into a sterile cylinder, and 200 c.cm. of sterile normal saline are added to it. The lower extremity of the cylinder opens into a nozzle to which a rubber tube is attached. The other end of this rubber tubing is connected through a metal stop-cock with the cannula.

Commentary

From the data it seems clear that the intraperitoneal administration of this serum has a specific therapeutic effect. The uniformity of results obtained during the epidemic of last year and of this year leaves no doubt that the use of this serum can diminish the mortality of cholera to a great extent. In India the majority of the cases of cholera are not taken to hospital before collapse sets in. We believe that if serum can be given earlier the mortality from cholera will be appreciably lowered.

The intraperitoneal administration of serum seems to be the method of choice, though absorption is not so rapid by this route as was thought to be the case. The

absence of uraemia and tympanitis, and the rapid disappearance of existing tympanitis after administration of serum, are definite indications of its neutralizing action on the toxin.

We have not yet been able to find a suitable method for the titration of the serum. The method of titration on rabbits seems to be too expensive for adoption as a routine procedure.

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PENTOTHAL SODIUM IN MENTAL HOSPITAL PRACTICE

BY

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Pentothal sodium (sodium ethyl [1-methyl-butyl] thio-barbiturate) approximates in its action to evipan. It was introduced to this country by Jarman,¹ who has made a comprehensive investigation of its use as a general anaesthetic. An investigation has been undertaken with the object of determining the value of this drug in psychiatry. The cases were chosen arbitrarily, and included all the types commonly seen in a mental hospital. The indications for administration of pentothal sodium were considered to be: (1) to control manic excitement; (2) to induce sleep; (3) to facilitate hypnosis as in narco-analysis²; and (4) to perform various manipulations and minor operations.

Oral Administration

Pentothal is given by the mouth in capsules or in a 10 per cent. solution. Its flavour is sulphurous and rather unpleasant, but far less nauseating than that of paraldehyde. The minimum effective dose varies from 3 to 20 grains, and appears to be governed chiefly by the degree of excitement, and to a less extent by the general physical state of the patient. In all cases it must be given on an empty stomach. Sleep usually ensues within half an hour. The duration of sleep varies greatly, and, as is the case with nembutal,³ is strikingly dependent upon external stimuli. The average duration of sleep was four hours by day and five to seven hours by night. On waking there is quick recovery from the effects of the drug and a pleasing absence of the nausea and headache which follow the use of some hypnotics. Increased restlessness attributable to the drug only occurred in certain maniacal states. There were no other after-effects.

Rectal Injection

In the case of the resistive patient who "will not swallow" there is much to commend rectal narcosis. Pentothal fulfils the first requirement of a rectal narcotic—namely, it is non-irritant to the bowel wall. It appears to fulfil the second requirement of being effective in non-toxic doses. The solution is prepared by dissolving 1 gram of pentothal in 10 oz. of distilled water. It is introduced very slowly into the rectum, the injection taking some five minutes. By this time many patients are drowsy; some express a wish to be left alone; and many fall asleep almost immediately. The duration of sleep, again, shows individual variation, but is usually more prolonged than that induced by oral medication. In some excited patients there is no sleep, the patient becoming drowsy and more amenable. In one case of mania the only effect was to increase the patient's excitement. The

following case illustrates the effect and use of the rectal method.

Case Report.—A single woman aged 64, a paraphrenic, suffered from scandalizing hallucinations and delusions of sexual assault, which made her noisy, obscene, and hostile to all around her. For many years she had been asocial and violently resistive to all attention. She developed an acute infection of the middle finger with a spreading cellulitis of the right hand. Appropriate treatment was very difficult owing to her mental state. She was given a rectal injection of 1 gram of pentothal. Towards the end of the injection she said she felt tired; three minutes later she was asleep. She slept for thirteen hours. The following morning she quietly permitted her hand to be examined and dressed. As a result of this co-operation the spreading cellulitis was arrested.

Intravenous Injection

Pentothal sodium is supplied in ampoules containing 1 gram of the powder. The addition of 10 c.cm. of redistilled water makes a clear, straw-coloured solution. This 10 per cent. solution is suitable for all purposes except narco-analysis, in which a 2½ per cent. solution is more convenient. In all cases the drug is injected very slowly, at a rate which never exceeds 1 c.cm. per minute. The dose is estimated by the individual response, which is far safer than the schematic dosage (by body weight) originally recommended for avertin and evipan.

The effect is almost instantaneous. After 1 c.cm. there is a subjective sensation described by one patient as "floating on air"; others feel tired, and some fall asleep. After 2 c.cm. a few patients become garrulous, but the majority fall asleep. In a series of fifty consecutive cases every patient was in a deep sleep by the end of the third cubic centimetre. There is a further resemblance to evipan in that after the minimum dose the patient regains consciousness almost as quickly as he lost it. Such short anaesthesia is suitable for the performance of minor operations.

When pentothal is used to control mania a larger dose must be given. The injection is continued until deep surgical anaesthesia is produced, whereupon a further equal quantity is injected intramuscularly. This ensures a deep sleep for about an hour, with a further period of lighter sleep for several hours if the patient is undisturbed. This method is sometimes lastingly beneficial.

Case Report.—A married woman aged 41, with manic-depressive insanity, was in the manic phase characterized by persistently noisy, restless, and interfering behaviour. Her conversation was rambling and inconsequent, her language obscene, and her conduct offensive and violent. The usual sedatives had been given without effect. Pentothal was injected, 4 c.cm. intravenously and a further 4 c.cm. intramuscularly. The patient slept for three hours. On waking she was quiet, friendly, amenable, and very apologetic for having used such disgusting language. This changed attitude continued and has been maintained.

Summary

A new and powerful narcotic has been described, with special reference to its use in a mental hospital. It has been administered to patients whose ages varied from 20 to 75 years. It has been used for various purposes and by every known route. The intravenous route would appear to have the widest application, in that it meets all four of the indications mentioned. While there is a noteworthy absence of the difficulties and complications associated with most barbiturates, there is one effect which calls for very great care—namely, a very marked depression of respiration. The obvious safeguard is to maintain an adequate airway. The striking advantages of pentothal are: (1) its smooth induction of anaesthesia; (2) its certain action in facilitating narco-analysis; and (3) the rapid recovery rate, which allows of its use in psychiatric