The foregoing is likely to be oversimplified, for improved analysis may reveal new protein fractions and functions. Hypersensitivity and immune response to tuberculosis may then be found to be shared by leucocytes (and other body cells) and some serum protein fraction other than γ -globulin. In short, there may be some combined function of leucocytes and serum proteins.

The door is open to a more comprehensive conception of the immunology of tuberculosis.

Summary

A case of acquired hypogammaglobulinaemia, active pulmonary tuberculosis, and epilepsy is reported, and reference is made to the other recorded cases of hypogammaglobulinaemia associated with tuberculosis.

It is submitted that the association of hypogammaglobulinaemia and tuberculosis is coincidental, and that they bear no aetiological relationship one to the other.

The natural course of tuberculous disease appears to be unaffected by hypogammaglobulinaemia, and delayed hypersensitivity and immune response are normal in patients observed to date.

It is suggested that delayed hypersensitivity and serum antibody response to tuberculosis function independently of γ -globulin, and may rely on a cellular mechanism (leucocytes and other body cells), though the possibility of an unidentified serum protein fraction sharing such immunological powers is not excluded.

I thank Drs. K. R. Stokes and L. E. Houghton for permission to report the case; Dr. C. C. Evans for the electroencephalography; Mr. W. H. Hackett for the biochemistry; the Medical Research Council for the supply of γ -globulin; and Dr. H. Sherwood Lawrence (New York) for his advice and helpful criticism.

ADDENDUM.—Since this paper was completed I have encountered another patient, similar to mine, at Bellevue Hospital, New York City. A man of 28, with a history of recurrent pneumonia and other infections since the age of 6 months, had bronchiectasis and recently developing pulmonary tuberculosis. Sputum grew tubercle bacilli on four different occasions, and P.P.D. skin tests (second strength) were positive (with induration) on three occasions. No enlargement of lymph nodes, liver, or spleen was ever apparent. Chest x-ray films showed bilateral but not extensive upper-lobe disease. Hypogammaglobulinaemia was revealed by serum electrophoresis and fractional precipitation. Tuberculosis followed the expected satisfactory course on antituberculous drugs. He did not receive γ -globulin replacement therapy.

REFERENCES

- Arends, T., Coonrad, E. V., and Rundles, R. W. (1954). *Amer. J. Med.*, 16, 833.
 Baldwin, R. W., and Iland, C. N. (1953). *Amer. Rev. Tuberc.*, 68, 372.
 Bird, T., and Thomson, J. (1957). *Lancet*, 1, 59.
 Chase, M. W. (1945). *Proc. Soc. exp. Biol. (N.Y.)*, 59, 134.
 — (1946). *J. Bact.*, 51, 643.
 Citron, K. M. (1957). *Brit. med. J.*, 1, 1148.
 Cole, L. R., and Favours, C. B. (1955). *J. exp. Med.*, 101, 391.
 Cooke, W. T., Weiner, W., and Shinton, N. K. (1957). *Brit. med. J.*, 1, 1151.
 Coons, A. H., Leduc, E. H., and Connolly, J. M. (1955). *J. exp. Med.*, 102, 49.
 Craig, J. M., Gitlin, D., and Jewett, T. C. (1954). *Amer. J. Dis. Child.*, 88, 626.
 Elphinstone, R. H., Wickes, I. G., and Anderson, A. B. (1956). *Brit. med. J.*, 2, 336.
 Gitlin, D., Hitzig, W. H., and Janeway, C. A. (1956). *J. clin. Invest.*, 35, 1199.
 — and Janeway, C. A. (1956). In *Progress in Haematology*, vol. 1, edited by L. M. Tocantins, p. 318. Grune and Stratton, New York.
 Good, R. A. (1954). *Bull. Univ. Minn. Hosp.*, 26, 1.
 — and Mazzitello, W. F. (1956). *Dis. Chest*, 29, 9.
 — and Varco, R. L. (1955). *J. Lancet*, 75, 245.
 — Zak, S. J., Jensen, D. R., and Pappenheimer, A. M., jun. (1957). *J. clin. Invest.*, 36, 894.
 Gras, J., Latorre, J., and Gamissans, J. M. (1954). *Klin. Wschr.*, 32, 968.
 Hutchison, J. H. (1955). *Lancet*, 2, 1196.
 Jim, R. T. S., and Reinhard, E. H. (1956). *Ann. intern. Med.*, 44, 790.
 Kulneff, N., Pedersen, K. O., and Waldenström, J. (1955). *Schweiz. med. Wschr.*, 85, 363.
 Lang, N., Schettler, G., and Wildhack, R. (1954). *Klin. Wschr.*, 32, 856.

- Lawrence, H. S. (1949). *Proc. Soc. exp. Biol. (N.Y.)*, 71, 516.
 — (1952). *J. Immunol.*, 68, 159.
 — (1955). *J. clin. Invest.*, 34, 219.
 — (1956). *Amer. J. Med.*, 20, 428.
 — and Pappenheimer, A. M., jun. (1956). *J. exp. Med.*, 104, 321.
 — (1957). *J. clin. Invest.*, 36, 908.
 MacLean, L. D., Zak, S. J., Varco, R. L., and Good, R. A. (1956). *Surgery*, 40, 1010.
 Martin, C. M., Gordon, R. S., and McCullough, N. B. (1956). *New Engl. J. Med.*, 254, 449.
 — Waite, J. B., and McCullough, N. B. (1957). *J. clin. Invest.*, 36, 405.
 Mathias, J. Q., and Rees, E. G. (1956). *J. Path. Bact.*, 71, 512.
 Mayama, A. (1954). *Sci. rep. res. Inst. Tokoku, Ser. C*, 5, 273.
 Mazzitello, W. F., and Good, R. A. (1956). *Postgrad. Med.*, 20, 95.
 Pappenheimer, A. M., jun. (1955). *J. Immunol.*, 75, 259.
 Pescetti, G., and Orlandi, A. (1956). *Minerva med. (Torino)*, 47, 209.
 Pillemer, L., Blum, L., Lepow, I. H., Ross, O. A., Todd, E. W., and Wardlaw, A. C. (1954). *Science*, 120, 279.
 Porter, H. (1955). *Abstract of Combined Meeting of Paediatrics Societies, Quebec*, p. 135.
 Prasad, A. S., and Koza, D. W. (1954). *Ann. intern. Med.*, 41, 629.
 Raffel, S. (1955). In *Ciba Foundation Symposium on Experimental Tuberculosis*, pp. 261-282. Churchill, London.
 — (1956). *Ann. Rev. Med.*, 7, 385.
 Ramos, A. J. (1956). *J. Amer. med. Ass.*, 160, 1317.
 Rohn, R. J., Behnke, R. H., and Bond, W. H. (1955). *Amer. J. med. Sci.*, 229, 406.
 Rosecan, M., Trobaugh, F. E., and Danforth, W. H. (1955). *Amer. J. Med.*, 19, 303.
 Sanford, J. B., Favours, C. B., and Tribeman, M. S. (1954). *New Engl. J. Med.*, 250, 1027.
 Schlange, H. (1954). *Arch. Kinderheilk.*, 148, 12.
 Sundberg, R. D. (1955). *Ann. N.Y. Acad. Sci.*, 59, 671.
 Urbach, F., Sones, M., and Israel, H. L. (1952). *New Engl. J. Med.*, 247, 794.
 Veterans Administration (1955). *Quart. Progr. Rep.*, Army-Navy Study on the Chemotherapy of Tuberculosis, 10, 41.
 Young, I. I., Wolfson, W. Q., and Cohn, C. (1955). *Amer. J. Med.*, 19, 222.
 Zinneman, H. H., and Hall, W. H. (1956). *Amer. Rev. Tuberc.*, 74, 773.
 — and Heller, B. I. (1954). *J. Amer. med. Ass.*, 156, 1390.
 — (1957). Personal communication.

CLINICAL STUDIES ON THE ACTION OF BEMEGRIDE IN BARBITURATE OVERDOSAGE*

BY

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Since bemegride ($\beta\beta$ -methylethylglutarimide) was introduced by Shaw *et al.* in 1954, there has been much discussion on whether this drug is a specific antagonist to the barbiturates or a non-specific central analeptic. Many papers have described the stimulating effect of bemegride in barbiturate coma (Shulman *et al.*, 1955; Clemmesen, 1956), but more recent reports have suggested that it appears to have a restorative action in coma due to non-barbiturate sedatives, such as primidone (Dotevall and Herner, 1957) and glutethimide (Rowell, 1957). The factors which influence the outcome in patients suffering from sedative poisoning are so varied that it is impossible to assess the specificity of action of bemegride in such circumstances.

The use of thiopentone in general anaesthesia, however, might appear to provide a suitable background for the study of the action of bemegride in man. Harris (1955), Canbäck *et al.* (1955), and Bentel *et al.* (1956) have reported that 50-100 mg. of bemegride injected intravenously could rapidly terminate anaesthesia induced by 0.5 g. of thiopentone. In these studies the premedication drugs varied, as did the duration of administration of the anaesthetic; no control observations were made.

The pilot study reported here reveals some of the difficulties in demonstrating the antibarbiturate activity

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of bemegride in man. The technique is a modification of that described by Harris (1955).

Method of Pilot Study

Observations were made on 20 women undergoing minor gynaecological operations. Each received 1/100 gr. (0.6 mg.) of atropine sulphate 45–60 minutes before induction of anaesthesia with 0.5 g. of thiopentone, the anaesthesia being maintained with nitrous oxide and oxygen. At the end of the operation 10 ml. of unlabelled solution (either normal saline or 50 mg. of bemegride) was injected intravenously. The nature of the injection given to any one patient was not known to the observer. In an attempt to assess the level of consciousness, repeated examinations of the palpebral and tendon reflexes were made and the response to painful stimuli was noted. It was found that such methods of grading levels of consciousness were unreliable, as positive results were not obtained in a definite sequence and the responses were liable to observer error. The patient's ability to respond to questioning was therefore accepted as the criterion of being awake. The interval between the injection and awakening was recorded for each patient and named the "wakening time."

Results of Pilot Study

These results are summarized in the Table. Of the 20 patients, 11 received bemegride and 9 saline. Seven who received bemegride responded to questioning in 1.5 to 5

Wakening Times in 20 Patients After Injection of 50 mg. of Bemegride or Normal Saline

Case No.	Weight		Duration of Operation (Minutes)	Nature of Injection	Wakening Time (Minutes)
	lb.	kg.			
1	135	61.2	11	Bemegride	1.5
2	106	48.1	5	"	5
3	113	51.3	16	"	5
4	105	47.6	7	"	5
5	119	54.0	10	"	1.5
6	146	66.2	8	"	3
7	121	54.9	8	"	12+
8	135	61.2	9	"	8+
9	117	53.1	6	"	6+
10	119	54.0	4	"	8+
11	142	64.4	18	"	1.5
12	111	50.3	10	Saline	2.5
13	168	76.2	11	"	4
14	139	63.0	3	"	3
15	104	47.2	7	"	3
16	90	40.8	14	"	2
17	119	54.0	9	"	1.5
18	128	58.1	11	"	6+
19	117	53.1	8	"	6+
20	113	51.3	17	"	6+

minutes (mean, 3.6 minutes); of those who received saline, seven were awake in 1.5 to 4 minutes (mean, 2.5 minutes). There is no significant difference between the wakening times of the groups.

In this type of study the durations of administration of anaesthesia should be comparable in the two groups. In this instance they were similar, the mean durations in the bemegride and saline groups being 9.2 and 9.9 minutes respectively (see Table). There was no apparent relationship between the weight of the patient, the "wakening time," and the interval between the time of thiopentone administration and wakefulness (see Table).

This pilot study, employing the "double-blind" technique, does not substantiate the published claims based on similar trials (Harris, 1955; Canbäck *et al.*, 1955; Bentel *et al.*, 1956). It demonstrates that such an approach cannot provide objective evidence on whether or not bemegride is a specific barbiturate antagonist; the patient may already be in the phase of natural recovery before the drug under trial is given.

Clinical pharmacological studies of hypnotics and anaesthetics often lack precision because of the difficulty in knowing the exact moment when the subject becomes awake. There is a transitional phase between sleep and wakefulness. An objective method of recording this phase would be valu-

able. It was decided therefore to see if the electroencephalogram would provide more precise information on the "wakening time."

E.E.G. Experiment on Wakening Time

Continuous E.E.G. recordings were made on subjects asleep after sodium amylobarbitone, and the arousing effect of bemegride was observed. Eight men aged 22–55 years volunteered for the experiment. In the fasting state, each swallowed 9–15 gr. (0.6–1 g.) of sodium amylobarbitone over a period of one and a half hours. While drowsy, an intravenous drip infusion of physiological saline was started, and this was continued throughout the period of observation. Scalp electrodes from an eight-channel Ediswan electroencephalograph were placed in position and E.E.G. (bipolar) recordings taken at intervals during the experiment. The patient lay undisturbed on a couch until he was clinically "asleep" and the E.E.G. tracing showed a consistent deep sleep pattern. Then 50 mg. of bemegride in saline solution was injected rapidly into the rubber tubing of the infusion apparatus close to the needle. Both the patient and the continuous E.E.G. records were observed carefully. If there was no change in either within two minutes, a further 50 mg. of bemegride was injected.

A note was made on the E.E.G. tracing at the time of the first sign of arousal. Each patient was then examined with special reference to his mental alertness, memory for recent events, gait, and muscular co-ordination. The E.E.G. records were studied for evidence of deep sleep pattern and barbiturate activity; the first change in the pattern after the injection of bemegride was noted and its time relationship to the first clinical sign of arousal recorded.

Results of E.E.G. Experiment

Each subject wakened after the administration of bemegride. A brief description of one patient will illustrate the clinical state, which was similar in all. After opening his eyes and grimacing, he gazed drowsily at his surroundings and within a few seconds began to speak. Speech was slurred, and this dysarthria persisted sometimes for 10 hours. There was diplopia on viewing near objects for 10 minutes after wakening. His memory for events preceding the experiment was normal. His gait was ataxic. Objectively the clinical state closely resembled that of moderate alcoholic intoxication. If placed in favourable surroundings the patients relapsed into sleep within 30 minutes and did not waken spontaneously until up to 16 hours later.

The E.E.G. pattern in each subject was that of deep sleep; in addition, three showed barbiturate activity. When bemegride was given, the deep sleep rhythm on the E.E.G. continued unchanged until the moment when the patient moved and wakened. The rhythm immediately reverted to normal (see Fig. 1). The E.E.G. records gave no indication that wakening was about to occur. In the four patients who required a total of 100 mg. of bemegride to cause arousal there was no premonitory change in the E.E.G. tracings in spite of increasing body levels of bemegride. In none of those showing barbiturate activity was this dispelled by bemegride.

Fig. 2 shows the persistence of fast barbiturate waves after the patient (Case 7) awoke. The normal resting record for this patient is shown in Fig. 3.

Discussion

This technique clearly demonstrates that bemegride will waken subjects asleep after sodium amylobarbitone. On arousal, however, such patients do not have normal muscular co-ordination and their emotional state is labile. For his personal safety each patient in this study required close supervision for at least six hours after wakening or until he had relapsed into sleep. It is probable that the state of intoxication was due to sodium amylobarbitone; three further volunteers who did not sleep after ingesting 15 gr. (1 g.) of this drug and who were not given bemegride presented a very similar picture.

It had been hoped that the E.E.G. record would give objective evidence of the onset of the transitional phase between sleep and wakefulness; that the rhythm would revert to normal before the patient awoke. This did not occur. Clinical observation gave as early information as did the E.E.G.

Two patients admitted to hospital in barbiturate coma were given bemegride, and their course was followed by intermittent E.E.G. recordings. Each patient returned to consciousness while on treatment with bemegride, but the E.E.G. records gave no indication of the depth of coma, and indeed evidence of barbiturate activity on the E.E.G. persisted for many hours after the patient awakened. This confirms the findings of Peacock (1956).

The E.E.G. evidence might suggest that bemegride is not a specific barbiturate antagonist, but the site of action of sodium amylobarbitone may be principally in the hypo-

thalamus, as may also be that of bemegride. The E.E.G. records only electrical potential changes in the cerebral cortex.

Summary

The effects of bemegride and saline in terminating thiopentone anaesthesia in 20 women were compared, using the "double-blind" technique. There was no significant difference in the "wakening times" after either substance. The fallacies of using such a method to evaluate the action of bemegride are stressed.

Continuous E.E.G. records were taken in eight volunteers who were roused with bemegride from sleep induced by sodium amylobarbitone. The E.E.G. pattern of deep sleep did not alter until the subjects awakened. In three patients who showed barbiturate activity on the E.E.G. this was not dispelled by bemegride.

The significance of these findings is briefly discussed.

I thank Dr. D. McKay Hart for permission to study the gynaecological patients; Dr. O. Watt, who administered the anaesthetics; and Dr. S. Renfrew, Mrs. I. S. Haggart, and Miss M. Watson, of the E.E.G. department of the Glasgow Royal Infirmary, for their co-operation and guidance. My thanks are also due to the volunteers.

REFERENCES

- Bentel, H., Barlow, M. B., and Ginsberg, H. (1956). *Med. Proc.*, 2, 198.
 Canbäck, T., Diding, N., Ohlsson, W. T. L., and Werkö, L. (1955). *Svenska Läk.-Tidn.*, 52, 2356.
 Clemmesen, C. (1956). *Lancet*, 2, 966.
 Dotevall, G., and Herner, B. (1957). *Brit. med. J.*, 2, 451.
 Harris, T. A. B. (1955). *Lancet*, 1, 181.
 Peacock, J. M. (1956). *Electroenceph. clin. Neurophysiol.*, 8, 289.
 Rowell, N. R. (1957). *Lancet*, 1, 407.
 Shaw, F. H., Simon, S. E., Cass, N. M., Shulman, A., Anstee, J. R., and Nelson, E. R. (1954). *Nature (Lond.)*, 174, 402.
 Shulman, A., Shaw, F. H., Cass, N. M., and Whyte, H. M. (1955). *Brit. med. J.*, 1, 1238.

FIG. 1.—E.E.G. record showing change in pattern coinciding with clinical arousal.

FIG. 2.—Persistence of barbiturate activity in Case 7 after waking.

FIG. 3.—Normal resting E.E.G. record for Case 7.

A COMPARISON OF MATERNAL AND FOETAL FOLIC ACID AND VITAMIN B₁₂ AT PARTURITION

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In a previous study comparing folic acid (P.G.A.) and vitamin B₁₂ during normal pregnancy (Baker *et al.*, 1957) it was reported that maternal vitamin B₁₂ blood levels were low and P.G.A. levels high. Recent studies on the vitamin B₁₂ serum levels in mothers and infants at delivery show that maternal levels decline through pregnancy and infant levels are approximately twice that of the mother (Okuda *et al.*, 1956; Boger *et al.*, 1957; Dumont, 1957). Since both P.G.A. and vitamin B₁₂ play significant parts in pregnancy and foetal development (O'Dell *et al.*, 1951; Nelson *et al.*, 1956; Nelson and Evans, 1956), a comparison of vitamin B₁₂ and P.G.A. serum levels in mothers and infants at parturition was carried out.

Methods.—Vitamin B₁₂ assays on maternal and infant serum were carried out in parallel with *Euglena gracilis* and *Ochromonas malhamensis* by methods previously described (Hutner *et al.*, 1956; Baker *et al.*, 1956). The P.G.A. levels were assayed with a thermophilic bacillus (Baker *et al.*, 1955, 1957). Maternal blood was collected from an antecubital vein at the time of delivery. Infant blood was obtained from the cord. Samples were collected from 113 patients admitted to the obstetrical service of the Mount Sinai Hospital.