THE Special Libraries Association published in August "A List of Subject Headings for Chemistry Libraries." It was compiled by a committee of the Section of Chemistry of the Science-Technology Group of the Special Libraries Association, under the chairmanship of Mrs. Grace R. Cameron, of the Louisiana State University Library. This list was compiled for use in assigning subject headings to the entries in a catalogue of books, pamphlets and other literature in a chemical library. General or main headings are used which can be expanded as needed. Subdivisions which may be used under general headings are also given. Examples of expansions for specialized fields such as dyes, paper and rubber are included. This publication is for all college, university, public and special libraries containing any chemical material.

THE Georgia Power Company has made a gift of $100 to the Alumni Foundation of the Georgia Institute of Technology at Atlanta. The fund will be used largely to buy equipment to further electrical research at the school.

SPECIAL ARTICLES

ORAL ADMINISTRATION OF PENICILLIN[1]

ALTHOUGH it was originally assumed that penicillin could not be administered orally because of its rapid destruction by gastric acid,[2] a number of investigators have reported effective blood levels when relatively large doses of penicillin by mouth were given by various methods (Libby[3]; Charney *et al.*[4]; McDermott *et al.*[5]; György *et al.*[6]; Little *et al.*[7]; Burke *et al.*[8] and Moses[9]). In a recent review of some of these investigators[10] it was stated that although oral penicillin was therapeutically effective when given either as a suspension in a digestible oil or when accompanied by one of the mild antacids, the most favorable vehicle had not yet been determined. McDermott and his collaborators[5] found no significant difference between the administration of penicillin by the oral route when it was given (*a*) in corn oil; (*b*) in water; (*c*) in water preceded by a buffer; and (*d*) in peanut oil and 4 per cent. beeswax. The authors, however, stated that the height of the penicillin concentrations in the blood two hours after ingestion of the oil and oil in beeswax preparations suggested that the duration of penicillin activity may be prolonged by the use of these vehicles by mouth in a manner similar to the prolongation which, as Romansky[11] showed, follows the intramuscular injection of penicillin in oil and beeswax. Selection of the best oral method from those previously reported is difficult because of the lack of an adequate number of blood level determinations in the same subjects with the various procedures.

In this communication the results of administration of penicillin mixed with aluminum hydroxide are compared with the results of administration of penicillin in water. When aluminum hydroxide was given one-half hour before ingestion of penicillin and not mixed with it, no significant advantage was detected by blood level curves. A few tests of penicillin by mouth with other procedures have been included in the graphs. The importance of using the same subject with different methods is revealed by the large individual variation with the same dose of penicillin. Thus, a man weighing 200 pounds would be expected to have a lower blood level than one weighing 100 pounds, irrespective of age. The factor of relationship to eating was kept relatively constant in this study. Most of the observations were made one to two hours after breakfast or lunch.

METHODS

The penicillin was dissolved in tap water, either (1) by inserting 4 cc of water into the 100,000 unit ampoule by a hypodermic syringe, withdrawing the contents and rinsing the remaining penicillin solution in the ampoule with an additional 4 cc of water, or (2) by removing the metal band and rubber cork from the bottle and dissolving the 100,000 units of penicillin in a teaspoonful of water and then rinsing

[1] This investigation was aided by grants from the Josiah Macy Jr. Foundation and the Foundation for the Investigation of Chronic Pulmonary Diseases. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutic and Other Agents of the National Research Council. The aluminum hydroxide used in this investigation was largely supplied to us by Wyeth, Inc.

[2] E. P. Abraham, E. Chain, C. M. Fletcher, A. D. Gardner, N. G. Heatley, M. A. Jennings and H. W. Florey, *Lancet*, 2: 177, August 16, 1941.

[3] R. L. Libby, SCIENCE, 101: 178, February 16, 1945.

[4] J. Charney, H. E. Alburn and F. W. Bernhart, SCIENCE, 101: 251, March 9, 1945.

[5] W. McDermott, P. A. Bunn, M. Benoit, R. DuBois and W. Haynes, SCIENCE, 101: 228, March 2, 1945.

[6] P. György, H. N. Vandergrift, W. Elias, L. G. Colio, F. M. Barry and J. D. Pilcher, *Jour. Am. Med. Asn.*, 127: 639, March 17, 1945.

[7] C. J. H. Little and G. Lumb, *Lancet*, 1: 203, February 17, 1945.

[8] F. G. Burke, S. Ross and C. Strauss, *Jour. Am. Med. Asn.*, 128: 83, May 12, 1945.

[9] C. Moses, *Jour. Am. Med. Asn.*, 128: 52, May 5, 1945.

[10] Editorial, *Jour. Am. Med. Asn.*, 127: 1129, April 28, 1945.

[11] M. F. Romansky and F. E. Rittman, SCIENCE, 100: 196, 1944.

the bottle with an additional one or two teaspoonfuls of water. The final 8 cc, or two to three teaspoonfuls of penicillin solution, were then mixed in a glass with one tablespoonful of aluminum hydroxide.[12] After thorough mixing with a spoon or fork, a quarter of a glass of water is added and the solution drunk in this form. When 50,000 units were administered the total amount from the ampoule was divided in two equal parts and one half the quantity ingested. When blood level determinations were made the first 2 cc of the 4 cc of solution instilled into the bottle were withdrawn accurately with a tuberculin or a two cc syringe. The serial broth dilution method of blood level analysis described by Hobby[13] was used.

RESULTS

The subjects consisted in the main of patients with bronchial asthma, bronchiectasis and pulmonary fibrosis, who were being treated with penicillin aerosol and oral penicillin. The total number of blood levels was 314, of which 250 were from patients and 64 from normal individuals. In Chart 1 the blood levels after administration of 50,000 units of penicillin mixed with aluminum hydroxide were compared to the results on the same subjects when penicillin was taken dissolved in water alone. As will be seen from the chart, a significantly higher blood level was present from ½ to 2 hours after ingestion of the drug mixed with aluminum hydroxide. The results of ingestion of 50,000 units of penicillin mixed with aluminum hydroxide in a miscellaneous group in which both the same and different subjects were used is revealed in Chart 2. It will be seen that the penicillin blood level curve with aluminum hydroxide was again higher, although this chart included patients who were not treated by all the various methods.

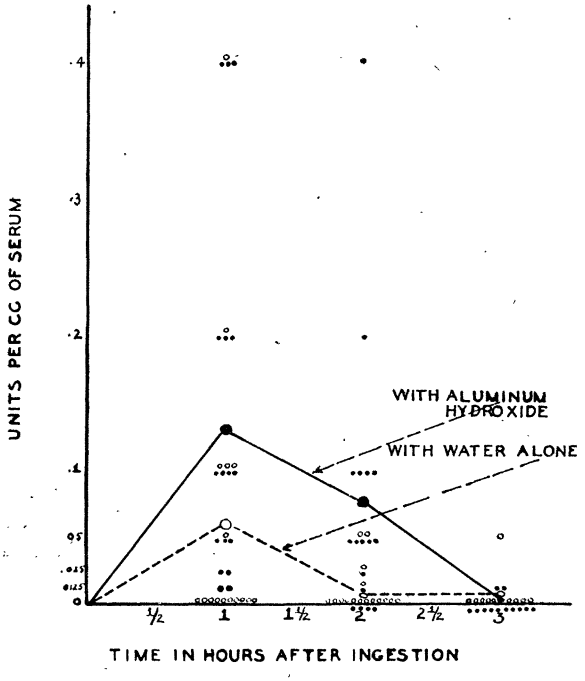

CHART 1. Comparison of penicillin blood levels on the same 14 patients after oral administration of 50,000 units of penicillin with (A) aluminum hydroxide and (B) water alone. The curves represent a total of 88 blood level determinations.

[12] A mixture of aluminum hydroxide and kaolin has been found to be better tolerated and at least as effective an adsorbent of penicillin as pure aluminum hydroxide. One tablespoonful of Kaomagma is mixed with 100,000 units of penicillin and stirred for a full minute or more. The quantity of water added has been increased to three-quarters of a glass in order to avoid local irritating effects, such as red tongue and pharynx, which are at times apparently produced by contact of the mucous membrane with concentrated solutions. A quarter to half a glass of water is also ingested afterwards.

[13] H. J. Greene and G. L. Hobby, *Proc. Soc. Exp. Biol. and Med.*, 57: 282, 1944.

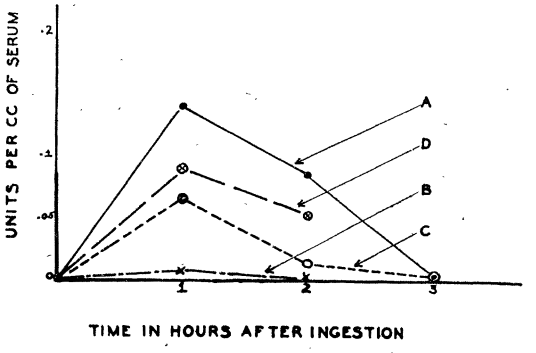

CHART 2. Comparison of penicillin blood levels on miscellaneous groups of patients after oral administration of 50,000 units of penicillin. (A) Mixed with aluminum hydroxide, 16 cases. (B) Aluminum hydroxide given previously, not mixed, 5 cases. (C) With water alone, 18 cases. (D) With $NaHCO_3$, egg and milk, 7 cases. The curves represent a total of 148 blood level determinations taken during 55 tests.

The results of ingestion of 100,000 units of penicillin mixed with aluminum hydroxide with comparative data on the same patients after 100,000 units were administered in water are illustrated in Chart 3. The blood level of penicillin when 100,000 units were given mixed with aluminum hydroxide was higher on the average than when given with water, but when different subjects were at times used for different tests, as shown in Chart 4, the penicillin blood level curves do not reveal the superiority of the aluminum hydroxide mixing method. This chart is evidence of the failure of the method of using different people for different tests, since when the same people are used for comparison, as shown in Charts 1 and 3, the aluminum hydroxide method showed a higher blood level. A more clear-cut difference was found when the smaller dose, 50,000 units, was given.

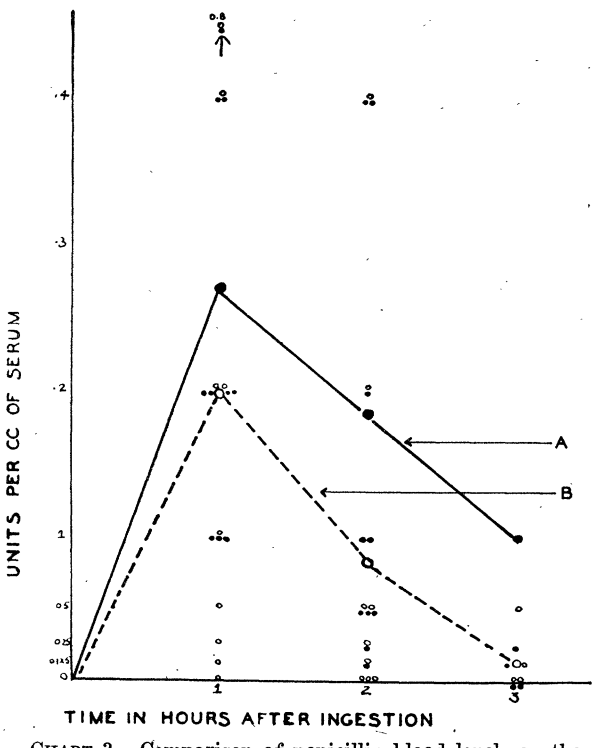

CHART 3. Comparison of penicillin blood levels on the same 9 patients after oral administration of 100,000 units of penicillin with (A) aluminum hydroxide; (B) water alone. The curves represent a total of 47 blood levels.

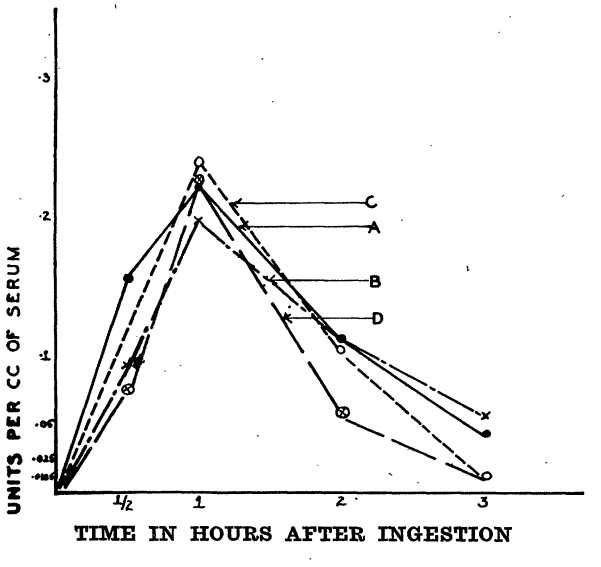

CHART 4. Comparison of penicillin blood levels on miscellaneous groups of patients after oral administration of 100,000 units of penicillin. (A) Mixed with aluminum hydroxide, 21 cases. (B) Aluminum hydroxide given previously, not mixed, 13 cases. (C) With water alone, 14 cases. (D) With $NaHCO_3$, egg and milk, 4 cases. The curves represent a total of 166 blood level determinations taken during 58 tests.

When the data were examined from the point of view of whether or not an effective blood level was found by the various methods, it was seen that in 43 of 44 cases in which aluminum hydroxide was mixed with penicillin a measurable blood level was obtained, whereas in 19 out of 58 cases in which the penicillin was dissolved in water and taken either with or without previous ingestion of aluminum hydroxide or sodium citrate, no penicillin was found in the blood.

The value of mixing penicillin with aluminum hydroxide is, therefore, indicated both by the frequency of effective blood levels and by the consistency with which a measurable blood level was obtained even with a dose as moderate as 50,000 units, which is less than that frequently used in other methods of oral administration in adults.

Although it has long been known that penicillin is destroyed in the large intestine, a recent report of Loewe[14] disclosed that large doses of penicillin administered in a suppository were followed by demonstrable blood levels. This stimulated us to try a series of 5 cases, dissolving 50,000 units of penicillin in 20 cc of water and introducing it by catheter and syringe into the rectum. No demonstrable blood level was found at the end of one, two or three hours in the five individuals tested in this manner. From these experiments it was evident that the administration of penicillin in aqueous solution by rectum was an inefficient and impracticable method.

DISCUSSION

Complete neutralization of gastric acid to prevent the destructive effect of hydrochloric acid on penicillin would require relatively large doses of alkaline medication. When penicillin is mixed with aluminum hydroxide a protective effect is apparently exerted by this colloidal substance due to adsorption of penicillin on aluminum hydroxide and due to its antacid effect on that portion of gastric acid with which the penicillin-aluminum hydroxide mixture comes in contact. No significant advantage was detected when aluminum hydroxide was used as an antacid prior to administration of penicillin, a finding which is consistent with the results of McDermott *et al.*[5]

In the clinical use of this procedure, nausea and indigestion have been encountered at times when one tablespoonful of aluminum hydroxide was administered at three-hour intervals, either with 50,000 or 100,000 units of penicillin. In these cases the dosage was lowered to two teaspoonfuls, which is generally well tolerated, either at three or, if desired, at two-hour intervals.[12] Further investigations in progress aim at the production of still higher blood levels than

[14] L. Loewe, E. Alture-Werber and P. Rosenblatt, *Jour. Am. Med. Asn.*, 128: 18, May 5, 1945.

those here reported. Had it been practical to give penicillin before breakfast and take the necessary blood levels for two- and three-hour periods under fasting conditions, better results would presumably have been obtained. However, since the clinical use of oral penicillin requires administration one or two hours after eating as well as before meals, these findings are applicable to the actual conditions of treatment. To provide optimal conditions for the absorption of penicillin, by mouth, the patient should be instructed to avoid fat in the diet in order not to delay the emptying time of the stomach, and also to take the penicillin one hour before eating and two hours after eating.

SUMMARY

A convenient, practical and effective procedure of administering penicillin by mouth consists of mixing the drug with one tablespoonful of aluminum hydroxide. Substantially higher blood levels are obtained following a 50,000 and a 100,000 unit dose of penicillin with this method than after administration of the drug dissolved in water, either with or without previous ingestion of a mild antacid, such as aluminum hydroxide. Adsorption of penicillin on aluminum hydroxide appears to exert a local protective effect against that portion of gastric acid with which it comes into contact.

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ON THE FORMATION OF ACETYLCHOLINE IN THE NERVE AXON

THE high concentration of choline esterase in the axon and its exclusive localization at the neuronal surface is one of the essential facts in favor of the concept that the release and the removal of acetylcholine is an intracellular process generating flow of current, the action potential.[1] Nachmansohn and Rothenberg[2, 3] have recently shown that the esterase of the nerve axon is specific for acetylcholine: if the enzyme activity is tested on a number of esters, a typical pattern is obtained distinctly different from that of other unspecified esterases. This specific choline esterase is found, either exclusively or predominantly, in all nerve tissue whether taken from mammalian brain or electric organ of fish, from vertebrate or invertebrate, from gray matter containing cell bodies and synaptic regions or from axon only.

The presence of a specific and highly active enzyme mechanism for the removal of acetylcholine in the axon indicates that the ester is metabolized there at a high rate and suggests therefore the possibility that acetylcholine may be formed in the axon as well as at the synapse.

Direct evidence is now offered for the formation of acetylcholine in the axon. As shown by Nachmansohn and Machado[4] acetylcholine is synthesized by choline acetylase, an enzyme system extracted by them from brain but not found in other organs. This enzyme forms acetylcholine in cell-free extracts, in the presence of adenosinetriphosphate, under strictly anaerobic condition.[5, 6, 7] Choline acetylase has now been found in the axon as shown in Table 1. The

TABLE 1

FORMATION OF ACETYLCHOLINE IN THE NORMAL AND DEGENERATING SCIATIC OF RABBIT

	Normal			Degenerated	
Exp. number	wt used mg	ACh formed μg/g/hr	Time after section (hours)	wt used mg	ACh formed μg/g/hr
1	395	60.0	0	392	61.0
	322	59.0	(control)	328	50.0
2	380	19.0	64	620	4.9
3	558	20.0	72	564	2.6

methods used were the same as described previously. The sciatics of 6 rabbits were used for each experiment. The amount formed per gram per hour is about 50 μg as compared with about 100–150 μg in guinea pig brain. The amount of acetylcholine formed in the axon as compared with that at synaptic regions thus appears to have about the same ratio as previously found for choline esterase activity at these two places.

Following section of the nerve the enzyme activity decreases. Two days after section nearly the total initial activity is still found. At that period conduction is still possible. The observation is consistent with the concept that the release of acetylcholine is responsible for conduction of the impulse. Three days after section, when conductivity had disappeared, the enzyme activity had lost only a part of the initial value. The results and conclusions are in

[1] D. Nachmansohn in R. S. Harris and K. V. Thimann, *Vitamins and Hormones*, New York, 3, 1945. In press.
[2] D. Nachmansohn and M. A. Rothenberg, SCIENCE, 100: 454, 1944.
[3] *Idem, Jour. Biol. Chem.*, 158: 653, 1945.
[4] D. Nachmansohn and A. L. Machado, *Jour. Neurophysiol.*, 6: 397, 1943.
[5] D. Nachmansohn, H. M. John and H. Waelsch, *Jour. Biol. Chem.*, 150: 485, 1943.
[6] D. Nachmansohn and H. M. John, *Proc. Soc. Exp. Biol. and Med.*, 57: 361, 1944.
[7] *Idem, Jour. Biol. Chem.*, 158: 157, 1945.