FULLER'S EARTH; ITS ADSORPTIVE POWER, AND ITS ANTIDOTAL VALUE FOR ALKALOIDS.*

BERNARD FANTUS, M. D.

For several decades fuller's earth (Parsons[1]) has been used extensively for the removal of coloring matter from oils. It owes this use to its capacity for adsorbing basic colors from solutions, which resides in the finest particles of the clay. The union between the basic substance and the earth is believed to be physical, as it can be easily broken up by use of proper solvents.

In 1910, John Uri Lloyd,[2] of Cincinnati, discovered that the addition of fuller's earth to alkaloids greatly diminished or almost abolished their bitter taste and that most alkaloids could be quantitatively removed from solutions by means of it. Further research revealed that this activity resided in the finest particles of the earth, which Lloyd separated by elutriation from the coarser portion and to which the name "Lloyd's reagent" has been applied.

In view of the theoretic interest as well as the practical possibilities inherent in this property of fuller's earth, this research was undertaken to determine, first, the relation of alkaloids to "Lloyd's reagent" and to various other specimens of fuller's earths; and, secondly, to see to what extent the action of various alkaloids may be modified by combination with these earths. Lloyd, Eli Lilly & Co., and various producers of fuller's earth have kindly supplied liberal quantitaties of material, by means of which the following data were obtained.

THE ALKALOID ADSORBING QUALITY OF VARIOUS SPECIMENS OF FULLER'S EARTH.

This was studied by briefly shaking accurately measured quantities of alkaloidal solutions with varying amounts of fuller's earth, filtering and then testing the filtrate for the alkaloid to determine the smallest amount necessary to remove the alkaloid from the solution. The figures given in Tables 1 and 2 show how many parts of fuller's earth had to be used to remove 1 part of alkaloid from solution. There is some difficulty in deciding on the end-point in these determinations, owing to the fact that water dissociates the combination to a slight extent, so that it is almost impossible to get rid of traces of the alkaloids in the filtrate. Therefore the smallest amount of fuller's earth that would remove the alkaloid as thoroughly as a larger amount was the quantity looked for.

In Table 1, the various earths have been arranged in order of their adsorptive power. It must be understood that the figures given in this table are only of relative value. Slight modifications in the technic of the test give quite different results. Nevertheless, when the same technic was applied to each of the differ-

* From the Pharmacologic Laboratory of the College of Medicine of the University of Illinois, through Journal A. M. A.

[1] Parsons, Charles L.: Fuller's Earth, Bull. 71, Mineral Technology, Dept. of the Interior, Bureau of Mines, October, 1913.

[2] Lloyd, John Uri: Lloyd's Reagent—Preliminary Announcement, Jour. Am. Pharm. Assn., May, 1914, iii, No. 5, p. 625.

ent specimens, their relative position in the table was well maintained. It must furthermore be realized that the adsorptive power of fuller's earth from various sources depends, to a certain extent, on the degree and uniformity of fineness of the specimen. Mere sifting raises the value, if a considerable amount of coarse particles be present; so does elutriation. Nevertheless there is a limit to which the adsorptivity of any one specimen may be raised by these means.

TABLE 1.—Adsorptive value and acidity of various specimen's of fuller's earth.*

Specimen	Morphin Sulphate, 0.5% sol.	Quinin Bisulphate, 0.5% sol.	Malachite Green 1%, with 0.25% Morphin	For 100 Gm. Earth Phenolphthalein, c.c. of Tenth Normal Sodium Hydroxid	Congo-red*
Colloidal portion of Lester Clay without drying.†	6.5	9	20	77	Purplish.
Lloyd's Reagent, Eli Lilly & Co.	8	10	80	155	Bluish purple.
General Reduction Co., Dry Branch, Ga.	20	30	60	175	Blue.
Olson Fuller's Earth, Benton, Ark.	26	44	70	20	Red with trace of blue.
Specimen F (source unknown)	28	50	75	215	Bluish purple.
Lester Clay Co. (xx F) Jacksonville, Fla.	36	60	100	25	Reddish purple.
Specimen D (source unknown)	52	74	105	30	Red with trace of blue.
Midway, Fla., Fuller's Earth	70	80	120	40	Bluish red.
Manatee (E x F) Ellenton, Fla.	80	104	115	15	Bluish red.
Atlantic Refining Co. (xxF) Ellenton, Fla.	110	140	130	5	Red with faint tr. of blue.
Specimen E (source unknown)	200	280	160	5	Red with faint tr. of blue.
Pear's Precipitated....	500	400	600	5	Red with faint tr. of blue.
Kaolin	600	600	1,000	0	Red.

* The figures in the first three columns indicate parts by weight of the respective earths required to remove from solution 1 part of the substance named at the head of the column. The figures in the fourth column indicate cc. of tenth normal sodium hydroxide needed to neutralize 100 gm. of fuller'se arth, phenolphthalein being used as indicator. The specimens are arranged in order of adsorptive power. Variations in adsorptive power of different specimens from the same source have been noted.

† Drying would reduce activity somewhat.

It will be noted that "Lloyd's reagent" is considerably more powerful than any one of the specimens of fuller's earth. It will also be seen that the specimens obtained from Ellenton, Fla., are quite deficient in this power. Pear's precipitated fuller's earth, a very fine white powder, is surprisingly inert. The activity of kaolin is practically nil. In view of the fact that the United States Dispensatory as well as the National Dispensatory quote "fuller's earth" as one of the synonyms of kaolin, it seems of importance to point out that there is a marked difference in the adsorptive power of these substances.

Kaolin as well as fuller's earth is considered to be essentially composed of hydrous aluminum silicate; the latter being merely less pure than the former. That this is the case can be readily seen by comparing the composition of kaolin (Watts[3]) with that of fuller's earth (Vaughan[4]) and of Lloyd's reagent (Waldbott[5]).

	SiO_2	Al_2O_3	Fe_2O_3	CaO	MgO	Alkalies	Water
Kaolin	45.40	37.34	1.92	0.44	0.20	0.52	14.0
Fuller's Earth	57.26	18.33	1.87	2.58	1.06		18.4
Lloyd's Reagent	55.30	9.82	14.80	1.58			17.41

It is an interesting question, why such great difference in adsorptive power exists among these substances. The following theories present themselves: First, it might be due to a physical difference, namely, the amount of colloidal material present; secondly, it might be due to difference in reaction; thirdly, it might be due to difference in chemical composition.

[3] Watts, A. S.: Mining and Treatment of Feldspar and Kaolin, Bull. 53, Dept. of the Interior, Bureau of Mines, 1913, p. 37.

[4] Vaughan, T. W.: Fuller's Earth Deposits of Florida and Georgia, Bull. 213, Dept. of the Interior, U. S. Geo. Survey, 1902, p. 393.

[5] Waldbott, Sigmund: Precipitation of Alkaloids by Lloyd's Reagent, Jour, Am. Chem. Soc., June, 1913, p. 837.

THE AMOUNT OF COLLOID IN FULLER'S EARTH.

Ashley[6] believes that the power of adsorbing certain dyes by clay supplies a measure of the amount of colloid present. He selected malachite green as the best dye known for this purpose, as it is wholly non-colloidal. Colloidal dyes, even if as feebly colloidal as methylene blue, introduce complicating factors that vitiate results, as may be seen by comparing the figures for malachite green with those arrived at with methylene blue: of Specimen F 40 times the amount was required, of Specimen D 60 times, of Specimen E 50 times, of Midway, Fla., fuller's earth 60 times—figures the are very near together in spite of great difference in alkaloid adsorbing power of these various specimens. Ashley agitates the clay with the dye solution for an hour, by means of a small ball mill, permits the clay to settle over night, and determines the amount of malachite green adsorbed by comparison with dilutions of a standard solution of malachite green. He found that half an hour's settling gave results that were too erratic, in view of the slow sedimentation of some specimens of fuller's earth. It must be understood that colored colloidal material in suspension makes the solution appear darker, so that it would seem less color was adsorbed, leading to the judgment that that clay is less colloidal, when it would be actually more colloidal than another clay that settled readily. I believe I have hit on a much less troublesome, more rapid and probably as accurate method of estimating the adsorptive power of fuller's earth by means of malachite green. The addition of a small quantity of an alkaloid, for example, morphine, to a fuller's earth suspension produces immediate deflocculation. On the other hand morphine does not readily salt out the malachite green. I therefore used in the determination of the malachite green figures (Tables 1 and 2) a solution of the following composition:

Malachite green	1.0
Morphine sulphate	2.5
Distilled water to	1000

Filter after prolonged agitation.

The amount of fuller's earth needed to remove a certain quantity of malachite green from this solution, expressed in multiples of that quantity, is represented by the figures in Table 1. It will be noted that these figures run quite closely parallel to the figures indicating alkaloid adsorptive power. Other electrolytes, for example, sodium chloride, also produce deflocculation of suspended fuller's earth. However, considerably larger quantities of sodium chloride are needed to produce this result promptly: quantities that are capable of salting out the malachite green, thus interfering with the test.

From Tables 1 and 2 it will be seen that the adsorption of malachite green runs parallel with the adsorption of alkaloids, and is therefore presumably due to the same cause. To use this adsorption as a measure of the amount of colloid present, as is proposed by Ashley, merely rests on the assumption that it is due to colloid. It does not prove that this is the case. Inasmuch as other colloids experimented with, such as colloidal aluminum hydroxide, colloidal ferric hydroxide, colloidal silicic acid, mastic emulsion, do not have the power of adsorbing alkaloids to nearly the same degree as active fuller's earth, it is reasonable

[6] Ashley, Harrison Everett: The Colloidal Matter of Clay and Its Measurement, Bull. 388, U. S. Geol. Survey, 1909.

to assume that we have here a case of specific adsorption; and that, while no doubt the colloidal state is necessary for this effect, it is not the essential cause of it.

THE "ACIDITY" OF FULLER'S EARTH.

To determine whether the acid reaction generally displayed by fuller's earth is the cause of the effects observed, the degree of "acidity," or rather the power of the earth to adsorb bases, was determined for each specimen by titration of 2 gm. of the earth, suspended in 100 cc. of distilled water, with tenth normal sodium hydroxide, using phenolphthalein as an indicator. *A priori* one might expect that the power of adsorbing alkali would be proportionate to, or at least run parallel with, the power of adsorbing alkaloids. This, however, is not the case, as can be seen by a glance at Table 1. Nevertheless, specimens devoid or practically devoid of acidity, like kaolin or Pear's precipitated fuller's earth, fail to adsorb alkaloids and those of lowest acidity are lowest in the list of alkaloidal adsorbents. Hence the presence of "acidity" is necessary to enable fuller's earth to adsorb alkaloids; though its degree is by no means a measure of the degree of this power. It therefore appears there are at least two factors involved in the adsorption phenomenon under consideration: the one the "acidity," the other the colloidal state. Whether the reason for the comparatively high adsorptive power of "Olson" and "Lester" fuller's earth, in spite of their rather low "acidity," is due to a relatively higher content of colloid than is present in more acid earths of lower activity, or whether there are two different "acidities" involved, one of importance in adsorption of alkaloids and the other not, remains to be settled. Nor have I the data at hand, at present, to discuss with any degree of profit the other theory previously advanced. On work on these questions I hope to report in the near future.

The addition of Congo-red to fuller's earth enables one to determine roughly, but quickly, the presence and degree of "acidity." It will be seen (Table 1) that all the earths that gave a blue or purple color with Congo-red were found active, while with the inactive kaolin there was no change; the others produced intermediate tints.

TABLE 2.—Proportion of fuller's earth needed to remove one part of alkaloidal salt from solution.

Alkaloidal Salt	Lloyd's Reagent	General Reduction Co	Olson Fuller's Earth	Lester Fuller's Earth
Morphin sulphate	5	20	26	36
Quinin bisulphate	10	30	44	50
Nicotin hydrochlorid	20	50	100	110
Cocain hydrochlorid	20	75	95	150
Aconitin nitrate	60	70	100	120
Strychnin sulphate	40	110	120	200
Colchicin hydrochlorid	130	160	200	
Malachite green	80	65	70	100

THE ADSORPTION OF VARIOUS ALKALOIDS BY FULLER'S EARTH

It will be seen from Table 2 that the various alkaloids differ in their relation to fuller's earth. For instance, a smaller quantity of an earth is needed to remove a morphine than a quinine salt; and less fuller's earth is needed to remove quinine bisulphate than strychnine sulphate. Colchicine needs the largest amount. As will presently be seen, these relations are significant in connection with the antidotal value of fuller's earth for these different alkaloids.

THE ACTIVITY OF ALKALOIDAL FULLER'S EARTH COMPOUNDS.

The alkaloidal fuller's earth compounds resist dilute acid; but are decomposed by alkalies, even as dilute as fiftieth normal sodium carbonate, which is approximately the alkalinity of the intestinal juice. When fuller's earth compounds of various alkaloids are treated with fiftieth normal sodium carbonate solution and the solution is acidified, it yields precipitates with Mayer's reagent, apparently in proportion to the solubility of the free alkaloid in water: the nicotine precipitate is much more copious than that obtained with cocaine; and the latter more abundant than the aconitine or the strychnine precipitate. Emetine yields only a trace. The concentration of the morphine solution obtained under these circumstances is below the threshold of distinct precipitation by Mayer's reagent, as is also a saturated solution of morphine in water; it yields, however, a copious precipitate with phosphomolybdic acid. Colchicine does not, of course, precipitate with Mayer's reagent, but does with tannic acid.

TABLE 3.—Effect on rabbits of small fatal doses of Strychnine Sulphate (5 mg. per Kilogram) given orally with and without fuller's earth and acid.

Rabbit		Dose			Effect	
No.	Weight Gm.	Strych. Mg.	Fuller's Earth	Acid	Symptoms	Result
A 1	624	0.0031	0	0	Convulsions in [illegible] min	Death in [illegible] min
A 2	1,190	0.006	0	0	Convulsions in 20 min.	Death in 25 min
A 3	800	0.004	0	0	Convulsions in 15 min.	Death in [illegible] min.
A 4	2,000	0.010	0	0	0	Recovery
A 5	650	0.0034	0	0	Convulsions in 72 min	Recovery
A 6	680	0.0034	0	0	Convulsions in 47 min	Recovery
B 1	794	0.004	0.400	0	Convulsions in 47 min	Death in 50 min.
C 1	1,021	0.005	1.500	1.600 tartaric	0	Recovery
C 3	1,190	0.006	0.600	0.600 tartaric	0	Recovery
C 4	794	0.008	0.800	0.800 tartaric	0	Death in [illegible] hrs
C1 1	680	0.0034	1.020*	1.020 tartaric*	0	Recovery
C1 2	737	0.0037	0.870*	0.870 tartaric*	Convulsions in 45 min.	Death in [illegible] min.
D 1	740	0.0037	1.110	2.220 NaH_2PO_4	0	Recovery
D 2	680	0.0034	0.340	1.020 NaH_2PO_4	0	Recovery
D 3	737	0.0037	0.870	0.740 NaH_2PO_4	0	Recovery
D 4	624	0.0031	0.310	0.310 NaH_2PO_4	0	Recovery
D 5	2,305	0.0115	1.150	1.150 NaH_2PO_4	0	Recovery
D1 1	740	0.0037	1.110*	1.110 NaH_2PO_4*	0	Recovery
D1 2	1,070	0.0054	1.600*	1.600 NaH_2PO_4*	0	Recovery
D1 3	1,640	0.0082	1.040*	1.640 NaH_2PO_4*	0	Recovery
D1 4	500	0.0025	0.750*	0.750 NaH_2PO_4*	0	Recovery
D1 5	570	0.0028	0.840*	0.840 NaH_2PO_4*	0	Recovery

* Five minutes later.

In view of this dissociability of the alkaloidal fuller's earth compounds by very dilute alkali, it is easy to understand why they become active in the animal body in spite of the fact, as Gordin and Kaplan[7] have shown, that the digestive ferments have no disrupting effect on these compounds. Being insoluble in acid liquids, even in the presence of pepsin, they pass through the stomach without acting on this viscus and without being acted on. On arriving in the intestine, they are gradually dissociated into their constituents, yielding the alkaloid to absorption. This explains why the general action of alkaloids, administered in this combination, is markedly delayed; and why a larger does is needed to obtain the same effect.

TABLE 4.—Effect on rabbits of large fatal doses of Strychnine Sulphate (10 mg. per Kilogram) given orally with and without fuller's earth and acid.

Rabbit		Dose			Effect	
No.	Weight Gm.	Strych. Mg	Fuller's Earth	Acid	Symptoms	Result
A 1	2,250	0.0225	0	0	Convulsions in 17 min	Death in [illegible] min
B 1	2,000	0.025	7.50	0	?	Death in 23 hrs
C 1	634	0.00634	1.25	1.25 tartaric	0	Recovery.
D 1	2,320	0.0232	2.32	2.32 NaH_2PO_4	0	Recovery.
D 2	570	0.0057	1.14	1.14 NaH_2PO_4	0	Recovery
D1 1	1,870	0.0187	5.60*	5.60 NaH_2PO_4*	Convulsions in 15 min.	Death in 17 min.
D1 2	1,570	0.0167	5.60*	5.60 NaH_2PO_4*	Convulsions in 15 min.	Death in 17 min.

* Five minutes later.

This modification of the action of alkaloids is of toxicologic, of pharmacodynamic, and of therapeutic interest. The diminution of taste, for instance, obtained in this manner has made it possible to produce perfectly pleasant sweet tablets of strichnine (Fantus[8]) for administration to children. The absence of effect on the stomach might be of value in connection with some of the alkaloids. Though, in case of ipecac, the removal of the emetic action by means of fuller's earth also seems to destroy action on certain infusoria, as I have found in as yet unpublished experiments. The delayed absorption might increase the effect on the intestine and its contents; for example, the quinine combination might exhibit

[7] Gordin and Kaplan: Jour. Am. Pharm. Assn., December, 1914, iii, 1656.

[8] Fantus, Bernard: Tabellae Dulces, Sweet Tablets for Children's Medication, Jour. Am. Pharm. Assn., **May, 1914, p. 656.**

amebicidal action in the intestine. The delayed absorption of cocaine may make the cocaine combination of value as an antipruritic in weeping skin disease. Work on some of these questions is being carried on at present.

THE NAMING OF THE ALKALOIDAL FULLER'S EARTH COMPOUNDS.

Inasmuch as some of these alkaloidal fuller's earth compounds are likely to prove of therapeutic value, it might be well to discuss the terms that have been applied to them. Lloyd named these "alcresta" alkaloids. It is under this title that Eli Lilly & Co. propose to place them on the market. The name is unfortunately not descriptive of the nature of the compound.

TABLE 5.—Effect on dogs of fatal dose of Strychnine Sulphate (2 mg. per Kilogram) given orally with and without fuller's earth and acid.

Dog		Previous Adm. of Morphin. 5 Mg per Kg.	Dose				Effect	
No.	Weight, Gm.		Strych. Sulph., 2 Mg. per Kg.	Accomp. (+) or Followed	Fuller's Earth	Acid	Symptoms	Resu...
A 1	8,500	0	0.017	....	0	0	Convulsions in 12 minutes	Death in 26 minutes.
A 2	9,500	0	0.019	....	0	0	Convulsions in 10 minutes	Death in 11 minutes.
A 3	7,000	0.035	0.014	....	0	0	Convulsions in 100 minutes	Death in 135 minutes.
A 4	7,300	0.037	0.0146	....	0	0	Convulsions in 25 minutes	Death in 40 minutes.
A 5	14,000	0.070	0.028	....	0	0	?	Death in 24 hours.
A 6	8,150	0.040	0.014	....	0	0	Convulsions in 7 hours.	Death in 20 hours.
B 1	8,000	0	0.016	+	4.80	0	Convulsions in 30 minutes lasting for 6:30 hours	Recovery.
C 1	19,500	0	0.039	+	12.00	12.0 Tart.	Emesis + Conv. 0	Recovery.
C 2	9,000	0	0.018	+	5.4	5.4 Tart.	Emesis (?) Conv. 0	Recovery.
C 3	5,000	0	0.010	+	3.0	2.0 Tart.	Convulsions in 2:30 hours	Death in 2:45.
C 4	9,000	0	0.018	+	5.4	1.8 Tart.	Convulsions in 1:30 hours	Recovery
C1 1	8,500	0	0.019	5 min. later	5.7	5.7 Tart.	Convulsions in 14 minutes	Recovery
C1 2	12,500	0	0.025	5 min. later	7.5	7.5 Tart.	Emesis in 20 minutes	Recovery.
C1 3	6,500	0	0.013	5 min. later	3.9	3.9 Tart.	?	Death in 20 hours.
C1 4	16,000	0	0.032	5 min. later	9.6	9.6 Tart.	0	Recovery.
C1 5	7,500	0	0.015	10 min. later	4.5	4.5 Tart.	Convulsions in 10 minutes	Death in 20 minutes.
D 1	15,500	0	0.031	+	9.3	18.6 NaH_2PO_4	Emesis, slight	Recovery
D 2	14,500	0	0.029	+	8.7	17.4 NaH_2PO_4	Defecation	Recovery
D 3	12,000	0	0.024	+	7.2	14.4 NaH_2PO_4	Emesis	Recovery
D 4	8,500	0	0.019	●	5.7	5.7 NaH_2PO_4	Convulsions in 78 minutes	Death in 130 minutes.
D1 1	7,000	0	0.014	5 min. later	4.2	8.4 NaH_2PO_4	Emesis, convulsions (?)	Death in 20 hours.
D1 2	15,500	0	0.031	5 min. later	9.3	18.6 NaH_2PO_4	Convulsions in 4 hours. ..	Death in 20 hours
D1 3	4,000	0.020	0.008	5 min. later	2.4	2.4 NaH_2PO_4	0	Recovery
D1 4	[illegible]	0.042	0.017	10 min. later	5.1	5.1 NaH_2PO_4	Convulsions, slight	Recovery
D1 5	6,350	0.0325	0.0127	10 min. later	3.8	3.8 NaH_2PO_4	0	Recovery
D1 6	6,800	0.035	0.014	15 min. later	4.2	4.2 NaH_2PO_4	0	Recovery
E 1	4,125	0	0.00825	+	2.475	5.0 Potas. Bitart	Convulsions (?)	Death in 5 hours

McGuigan[9] has applied the name "colloidal" strychnine to the strychnine compound with fuller's earth; a name I believe to be erroneous, as the moment the combination between the colloid and the alkaloid occurs, the colloidal state is destroyed and a coarse suspension results, as may be shown by the readiness with which morphine produces deflocculation of a fuller's earth sol or gel. It appears to me that the best name to apply to the strychnine compound would be "strychninated fuller's earth"; to the morphine compound "morphinated fuller's earth"; to the cocaine compound "cocainated fuller's earth," etc.; terms analogous to "chlorinated lime" and "sulphurated potash."

Lloyd first hoped that his reagent would prove a universal antidote for alkaloids and he describes it as one of the bitterest disappointments of his life when it was shown by Dr. Felter, in 1911, that the combination of Lloyd's reagent with strychnine was still capable of killing a dog in convulsions. Lloyd suggested to me that the addition of tartaric acid or of stearic acid to his reagent might raise its anti-

[9] McGuigan, Hugh: A Colloidal Compound of Strychnine and Its Pharmacology, The Journal A. M. A., November 28, 1914, p. 1933.

dotal value. It will presently be seen that this is indeed the case with tartaric acid. Experiments with the stearic acid combination proved negative.

The experiments recorded below were undertaken primarily to study the toxic action of alkaloidated fuller's earth It soon became apparent, however, that fuller's earth did possess antidotal value against certain alkaloids, while it had little value against others, as will be shown by the following data.

ANTIDOTAL VALUE IN STRYCHNINE POISONING.

The antidotal value of fuller's earth in strychnine poisoning in the rabbit may be estimated from Tables 3 and 4. It will be seen in Table 3 that 5 mg. per kilogram is invariably convulsive and frequently fatal for small rabbits; that, on the other hand, a large rabbit (A 4) showed no effect from such a dose. Eliminating, therefore, the only other large rabbit in this series (D 5) from consideration, we find that fuller's earth alone is not antidotal to strychnine. The addition of tartaric acid or of sodium dihydrogen phosphate to the fuller's earth renders it, however, capable of preventing convulsions and of saving life in small rabbits, even if administered five minutes after the poison has been given. The sodium dihydrogen phosphate showed itself superior to the tartaric acid by having this effect invariably, while with the tartaric combination convulsions and deaths have occurred. The dose of 10 mg. per kilogram (Table 4) is invariably fatal; and yet the addition of tartaric acid or of sodium dihydrogen phosphate to fuller's earth has enabled it to prevent effects, if administered at the same time; but not, if administered five minutes later. Against 15 mg. per kilogram, fuller's earth with sodium dihydrogen phosphate has been useless so far as saving of rabbits is concerned; but it, no doubt, postponed the effects to a considerable degree, as will be seen from the following observations:

TABLE 6.—Effect on rabbits of fatal doses of Morphine given orally with and without Fuller's earth.

Rabbit		Dose			Effects	
No	Weight Gm	Morphin Sulph per Kg	Administration followed	Fuller's Earth	Symptoms	Result
A [illegible]	[illegible]	1 gm		0	Depr. Conv. in 2 hrs.	Death in [illegible] hrs.
B 1	[illegible]	1 gm	*	[illegible]	Some depression	Recovery
B 2	[illegible]	1½ gm	*	[illegible]	Some depression	Recovery
B 3	[illegible]	2 gm		[illegible]	Some depression	Recovery
[illegible] 1	[illegible]	1 gm	[illegible] min. later	[illegible]	Some depression	Recovery
[illegible] 2	[illegible]	1 gm	15 min. later	[illegible]	Some depression	Recovery
[illegible] 3	[illegible]	1 gm	30 min. later	[illegible]	Depr. Conv. in 30 min.	Death in [illegible] hrs.
[illegible] 4	[illegible]	1 gm	20 min. later	[illegible]	Depr. Conv. in [illegible] hrs.	Death in [illegible] hrs.

Rabbit D 10, weighing 907 gm. was given 0.015 gm. strychnine with 4.50 gm. each of fuller's earth and of sodium dihydrogen phosphate. Death occurred in four hours and thirty minutes.

Rabbit D 11, weighing 2,660 gm. was given 0.040 gm. of strychnine with 13.3 gm. each of fuller's earth and sodium dihydrogen phosphate. Death occurred in thirty-two hours.

Table 5 shows that a dose of 2 mg. per kilogram is invariably fatal to dogs. The addition of fuller's earth saved life, but did not prevent convulsions. The addition of tartaric acid and of sodium dihydrogen phosphate frequently prevented convulsions and generally saved life. However, emesis was so frequently produced as to vitiate the results. Therefore morphine was given about one hour before the administration of the poison. This preliminary administration of morphine, of course, produced vomiting and often defecation within the hour, followed by a depression of the vomiting center, so that the doses were now regularly retained. Experiments A 3 to A 6 (Table 5) show that the morphine does not save the life of the animal, though it delays results. Experiments D 3 to

D 6 show that fuller's earth and sodium dihydrogen phosphate are capable of saving life, even though no emesis takes place. The fact that it was possible to save the life of morphinized dogs, even if the antidote was given five, ten and fifteen minutes after the poison, while the antidote failed to produce such result without the morphine, is most interesting and requires further study. Possibly it is due to delayed evacuation of the stomach.

A dose as large as 4 mg. per kilogram makes demands on the antidote that it is not able to meet, as will be seen from the following experiments:

Dog C 6, weighing 9 kg., was given, at 9:15 a. m., 0.036 gm. strychnine with 5.4 gm. each of fuller's earth and tartaric acid. It was found dead next morning, no convulsions having been observed.

Dog C 7, weighing 13.5 kg., was given at 9:30 a. m. 0.108 gm. strychnine with 9.1 gm. each of fuller's earth and of tartaric acid. There was slight emesis at 11 a. m. The animal was found dead next morning, no convulsions having been observed.

ANTIDOTAL VALUE IN MORPHINE POISONING.

Table 6 shows that the antidotal value of fuller's earth is much greater for morphine than it is for strychnine. This is probably due to the fact, shown in Tables 1 and 2, that morphine is much more readily removed from solutions by fuller's earth than are any of the other alkaloids, as well as to the slight solubility of the alkaloid morphine and the large dose needed to produce death in these animals. It will be noted that the mere addition of fuller's earth saved rabbits from as much as twice the fatal dose of morphine, and that fuller's earth was still capable of saving life, if given ten and fifteen minutes later, but not if given twenty minutes later. The administration, at intervals, of fuller's earth in morphine poisoning in human beings, even after hypodermic administration of the poison or evacuation of the stomach, appears indicated; as the morphine excreted into the stomach would be absorbed by the clay and its reabsorption prevented or at least delayed.

TABLE 7.—Effect on dogs of fatal doses of Cocaine with and witout Morphine and fuller's earth.

Dog		1 Hour Prev. Hypo. of Morphin, 5 Mg. per Kg.	Dose		Effects	
No.	Weight, Gm.		Cocain, Gm.	Fuller's Earth	Symptoms	Result
A 1	7,250	0	0.1 per kg.	0	Convulsions in 25 min.	Death in 90 min.
A 2	8,000	0	0.1 per kg.	0	Convulsions in 15 min.	Death in 20 hrs.
A 3	3,800	0	0.2 per kg.	0	Convulsions in 7 min.	Death in 16 min.
A 4	7,500	0.040	0.1 per kg.	0	Whining occ.	Recovery.
A 5	6,646	0.025	0.1 per kg.	0	Depr., later excit.	Recovery.
A 6	6,850	0.035	0.2 per kg.	0	Convulsions in 220 min.	Death in 260 min.
A 7	7,140	0.035	0.2 per kg.	0	Convulsions in 16 min.	Death in 30 min.
A 8	4,700	0.030	0.2 per kg.	0	Depression......	Death in 20 hrs.
B 1	6,000	0	0.1 per kg.	60.0	Emesis in 35 min.	Recovery.
B 2	12,000	0.600	0.1 per kg.	120.0	0	Recovery.
B 3	6,800	0.035	0.2 per kg.	135.0	0	Recovery.
B 4	4,800	0.025	0.2 per kg.	96.0	0	Recovery.
B 5	3,740	0.030	0.2 per kg.	76.0	0	Recovery.

ANTIDOTAL VALUE IN COCAINE POISONING.

In view of the local anesthetic quality of cocaine, it is of interest to note that the dog B 1 (Table 7), that received it together with fuller's earth, vomited. Evidently the compound produced by fuller's earth with cocaine is not decomposed in the stomach, which is entirely in accord with the general tendency of the alkaloidal fuller's earth compounds not to give up the alkaloid to an acid solution. This made it necessary again to use hypodermic injections of morphine, one hour previously, to prevent the emesis. However, inasmuch as morphine is an antagonist to cocaine, as will be seen by comparing the result in A 1 and A 2 with A 4 and A 5, it was necessary to use a large fatal dose of cocaine (0.2 gm. per kg.) in order to have a fatal does in the presence of morphine. The antidotal value of fuller's earth under these circumstances is demonstrated by the uniformly fatal results in experiments A 6, A 7 and A 8, as compared with the uniformly negative results in Experiments B 3, B 4 and B 5. Evidently fuller's earth is an antidote to cocaine, and it does not need acid to produce this effect, at least in the presence of morphine, which probably enhances the antidotal effect of fuller's earth by delaying the emptying of the stomach.

ANTIDOTAL VALUE IN NICOTINE POISONING.

Rabbits are killed within twenty minutes by 0.20 gm. nicotine per kilogram, as will be seen from Table 8. The addition of fuller's earth to such a dose is followed by recovery. A dose of 0.40 gm. per kilogram is fatal even when fuller's earth and sodium dihydrogen phosphate are added. If the antidote is given five minutes after the poison was administered, it is unable to save life. Evidently nicotine acts too rapidly to admit of any interval between the giving of the poison and of the antidote.

ANTIDOTAL VALUE IN IPECAC POISONING.

Emetic Dose.—If two dogs of similar size and with empty stomachs are chosen, and one of these is given, by means of the stomach tube, 0.3 cc. per kilogram of fluidextract of ipecac mixed with ten times the volume of water, while the other receives the same dose with the addition of 3 gm. of active fuller's earth per cubic centimeter of fluidextract used, the first dog will vomit profusely and many times—usually not until after half an hour, but within one hour—and soon afterward may have bowel evacuations, which sometimes become bloody. The other dog will show no effects whatever excepting perhaps, occasionally, a looseness of the bowels on the next day.

Fatal Dose.—A dose of 1.5 cc. of fluidextract of ipecac per kilogram has been found uniformly fatal in dogs, as will be seen from the following experiments:

Dog. A, weighing 15.5 kg. was given 23.25 cc. of fluidextract of ipecac, diluted with 232.5 cc. of water, at 9:42 a. m. Formed bowel movement occurred at 11:25; vomiting at 12, and again at 12:15; semi-liquid bowel movement at 12:30. Several other attacks of emesis occurred during the afternoon, the animal refusing food, but drinking water freely. The next day it was found that the animal had bloody bowel movements; and on this day it died at 10 a. m. Necropsy showed hemorrhagic gastro-enteritis. The urine obtained from the bladder contained albumin and a few red blood corpuscles, but no casts.

Similar results were obtained in three other dogs. A different result was obtained in Dog E. This dog, weighing 7.25 kg. was given 10 cc. of fluidextract of ipecac diluted with 100 cc. of water. Within half an hour, the dog showed marked depression, salivation, and had a fluid defecation, but did not vomit. The animal died within five hours after the administration of the poison, without having had emesis or bloody purging. On post-mortem examination, performed twenty hours later, the gastro-intestinal tract was found pale and without gross evidence of inflammation. Death had evidently occurred too soon for inflammation to have developed.

Entirely different is the result when the total dose of fluidextract of ipecac is mixed with fuller's earth, 3 gm. per cubic centimeter, as may be seen from the protocol of experiment on Dog J. This animal, weighing 9.5 kg., was given 14.25 cc. of fluidextract of ipecac diluted with 142.5 cc. of water, to which 42.75 gm. of fuller's earth were added. There was no effect whatever, excepting that the animal refused food and drink for several hours afterward. During the succeeding days the animal was perfectly normal. Its bowel movements were hard and clay-colored lumps. Its urine was free from albumin. The animal was chloroformed five days afterward. Its gastro-intestinal tract was found normal. Identical results were obtained in three other dogs. On the other hand, one dog whose stomach was full of food vomited shortly after administration of the dose, probably from over-distention of the stomach. Two other dogs recovered from twice the surely fatal dose of fluidextract of ipecac, namely, 3 cc. of the fluidextract per kilogram, diluted with ten times the amount of water to which a proportionate amount of fuller's earth had been added. Both dogs had a single emesis soon after injection, probably from over-distention of the stomach, for the bulk of the dose is considerable; but developed no further results of any importance and recovered completely, as may be seen from the protocol of one of these experiments:

A dog, weighing a little less than 12 kg., was given 35 cc. of fluidextract of ipecac with 350 cc. of water and 14 gm. of Lloyd's reagent. The dose was administered at 9:50 a. m. Shortly afterward, profuse salivation appeared and lasted for over an hour. Twenty minutes after the injection a single emesis occurred, the vomit consisting of thin watery fluid with a small amount (3 gm.) of the injected preparation. There was no further emesis. A fine muscular tremor appeared at 12 m., and lasted about an hour. Complete recovery took place.

Evidently fuller's earth is a powerful antidote to ipecac. To test its practical value in case of poisoning, the antidote was administered at varying intervals of time after the introduction of the poison with results that might best be shown by tabulation.

It will be noted (Table 9) that, when fuller's earth was given mixed with the poison, no damage occurs.

When the fuller's earth was given ten minutes afterward, the animal was seriously affected by the poison, but recovered. Fuller's earth was incapable of saving animals when administered twenty minutes or longer after the poison; but it rendered the picture of intoxication milder and postponed death in inverse proportion to the length of time that elapsed between the administration of the poison and of the antidote.

TABLE 8.—Effect on abbits of fatal doses of Nicotine given orally with and without fuller's earth and acid.

Rabbit		Dose				Effects	
No	Weight, Gm	Nicotin per kg	[illegible] (+) or Foll	Fuller's Earth	Acid	Symptoms	Result
A 1	1,500	0.10		0	0	0	Recovery
A 2	904	0.20		0	0	Convulsions in 15 min	Death in 20 min
A 3	500	0.20	.	0	0	Convulsions in 12 min	Death in 30 min
A 4	1416	0.20	.	0	0	Convulsions in 10 min.	Death in 15 min
B 1	740	0.20	+	18.0	0	0	Recovery
B 2	800	0.20	+	16.0	0	Depression in 30 min	Recovery in 60 min
B 3	570	0.40	+	25.0	0	Depression.	Death in 120 min
B1 1	740	0.20	5 min	18.0	0	Convulsions in 11 min	Death in 30 min.
D 1	900	0.20	+	16.0	5.0 NaH_2PO_4	0	Recovery
D 2	680	0.40	+	13.0	6.8 NaH_2PO_4	?	Death within 20 hrs.

ANTIDOTAL VALUE IN ACONITINE POISONING.

Table 10 shows that fuller's earth has some antidotal value in this condition also. It is difficult, however, to arrive at a definite judgment as to the degree of its value. It produces emesis even after the previous administration of morphine. That the emesis does not save life, will be seen from the fact that all the dogs that died vomited. They generally vomited more profusely than the dogs that recovered. Therefore emesis was probably not a factor in those cases in which recovery took place. It will be noted that in practically all the animals that did recover rather marked symptoms occurred: emesis generally the next day, and in several of them bloody defecation, which in one case lasted for several days. The death of the animal D 5 may not have been due to the poison, as the animal was sick before it was subjected to the experiment, as was discovered subsequently. In another series of animals, in which the alkaloid aconitine (crystalized) was used—not the salt—death occurred in every case, even when fuller's earth or fuller's earth with acid were added, the fatal result being postponed for from twenty-four to forty-eight hours. Evidently the free alkaloid does not combine with fuller's earth as readily as does the salt.

TABLE 9.—Results of administration of fatal dose (1.5 cc. per Kilogram) of Fluidextract Ipecac with and without fuller's earth at varying intervals.

Dog	Administration	Emesis		Defecation	Result	Post-Mortem Examination
		Onset, Min	Times			
A	Ipecac.......	138	5	Bloody..	Death in 24 hours.	Violent gastro-enteritis.
E	Ipecac............	...	0	Liquid not bloody.	Death in 5 hours.	Gastro-intestinal tract pale.
F	Ipecac and fuller's earth 40 minutes later.	...	0	Liquid not bloody.	Death within 20 hours.	Gastro-enteritis.
G	Ipecac and fuller's earth 30 minutes later.	65	6	Bloody.....	Death in 25 hours.	Gastro-enteritis.
H	Ipecac and fuller's earth 20 minutes later.	70	1	Bloody.....	Death within 44 hours.	Less severe gastro-enteritis.
I	Ipecac and fuller's earth 10 minutes later.	22	13	Bloody.....	Aborted 5 fetuses. Lived for 8 days.	Gastro-intestinal tract showed evidences of past enterocolitis.
J	Ipecac and fuller's earth mixed.	...	0	Hard, clay-colored.	Recovery....	Gastro-intestinal tract normal.

TABLE 10.—Effect on dogs of fatal dose of Aconitine Nitrate, Crystallized, Merck (4 mg. per Kilogram) given orally with and without fuller's earth and acid.

Dog		Morphin Sulph., 5 mg. per kg. Hypo. 1 Hour Prev. Gm.	Dose			Effects	
No.	Weight, Gm.		Aconitin	Fuller's Earth	NaH_2PO_4	Symptoms	Result
A 1	6,850	0.032	0.0254	0	0	Profuse emesis in 5 min.	Death in 50 min.
A 2	6,906	0.025	0.0204	0	0	Conv., emesis in 4 hours.	Death in 5 hrs.
B 1	8,000	0.043	0.0344	17.20	....	0	Recovery.
B 2	10,600	0.066	0.0432	21.00	...	Emesis next day	Recovery.
B 3	4,700	0.025	0.0190	7.60	....	Emesis (slight) in 6 hours.	Death in 24 hrs.
D 1	9,500	0.048	0.0380	19.00	19.00	Emesis next day	Recovery.
D 2	9,000	0.045	0.0362	18.10	18.10	Emesis next day. Bloody defecation.	Recovery.
D 3	8,600	0.043	0.0344	13.76	13.76	Emesis, clear in 2:30 hours.	Recovery.
D 4	6,570	0.033	0.0263	13.14	13.14	Bloody defecation next day	Recovery.
D 5	7,250	0.036	0.0290	14.50	14.50	Emesis in 1:30 hours.	Death in 44 hrs.

TABLE 11.—Effect on dogs of fatal doses of Colchicine (2 mg. per Kilogram) given orally with and without fuller's earth and acid.

Dog		Dose				Effects	
No.	Weight.	Preliminary Morphin. 0.005 per Kg.	Colchicin.	Fuller's Earth	Acid	Symptoms	Results
A 1	19,500	0	0.039	0	0	Vomiting in 1:30 hours. Bloody defec. in 4:30 hours.	Death with violent gastritis and colitis within 20 hrs.
A 2	7,700	0.0375	0.0155	0	0	Vomiting and bloody defec. next day.	Death with violent gastritis and colitis in 30 hours.
D 1	9,300	0.050	0.0186	5.60	5.60 NaH_2PO_4	Bloody defec. next day.	Death with less severe colitis in 68 hours.

ANTIDOTAL VALUE IN COLCHICINE POISONING.

The antidotal value of fuller's earth against colchicine poisoning is, no doubt, very slight, even though the number of experiments on this point, as shown by Table 10, may be insufficient. With the comparative indifference, however, of colchicine toward fuller's earth, as shown in Table *2*, a different result could hardly be expected.

PERSONAL EXPERIMENTS WITH METHYLENE BLUE AND FULLER'S EARTH.

To put the question to an approximate test whether fuller's earth would be likely to act in human beings as it does in the lower animals, I and one of my colleagues took doses of methylene blue with and without fuller's earth with the following results:

When a dose of 0.010 gm. of methylene blue is taken a dark green color appears in the urine within a short time and disappears within twenty-four hours. If 1.0 gm. of fuller's earth is added to 0.010 gm. of methylene blue in solution, the urine acquires a faint greenish tint for twenty-four hours; the difference between the two specimens of urine being striking.

The results of larger doses might probably best be presented as in Table 12. It will be noted that fuller's earth alone postponed the appearance of the discoloration, lessened the duration of intense discoloration, but not the duration of slight discoloration. The addition of a small amount of sodium dihydrogen phosphate did not increase very greatly the effect of fuller's earth. The addition of a larger dose that acted on the bowel within an hour and thirty minutes markedly lessened the period and amount of discoloration. It seems safe to conclude that *fuller's earth, especially when combined with a laxative dose of sodium dihydrogen phosphate, is capable of greatly lessening in the human the absorption of substances that are readily adsorbed by fuller's earth.*

CONCLUSIONS.

1. Alkaloidal fuller's earth compounds do not act on the stomach; but are gradually dissociated in the intestine, producing a delayed and milder general action.

2. Fuller's earth has antidotal value in morphine, cocaine, nicotine, and ipecac poisoning. It has less value in strychnine and in aconitine poisoning, though even in these conditions it is capable of saving life, when combined with sodium dihydrogen phosphate. In colchicine poisoning it is of little value.

3. The power of adsorbing alkaloids is strongly developed in some fuller's earths and very feebly in others. The adsorptive value of commercial fuller's earths should be stated by the dealers; and pharmacists should demand specimens of high activity. Lloyd's reagent possesses this power to the highest degree.

4. Fuller's earth is not synonymous with kaolin, as the United States Dispensatory and the National Dispensatory would lead one to infer. It is a substance with markedly different properties.

TABLE 12.—Results of doses of Methylene Blue with and without fuller's earth and Sodium Dihydrogen Phosphate.

Experiment	Dose	Effect
1	0.050 gm. methylene blue	Urine green in 1 hr. 25 min., lasting for 2½ days
2	0.050 gm. methylene blue 2.500 gm. fuller's earth .	Urine green in 9 hrs., lasting for 24 hrs. Traces of discoloration occasionally for 2 days longer
3	0.050 gm. methylene blue 2.500 gm. fuller's earth . . 2.500 gm. NaH_2PO_4	Urine green in 10 hrs. 30 min., lasting for 17 hrs. Traces of discoloration occasionally for 2 days longer.
4	0.050 gm. methylene blue 2.500 gm. fuller's earth 6.000 gm. NaH_2PO_4.	Bluish brown liquid defecation in 1 hr. 30 min. Urine light green in 10 hrs. Urine green in 14 hrs., lasting for 7 hrs. Traces of discoloration occasionally for 12 hrs. longer

ORIGIN OF URIC ACID.

The uric acid excreted in the urine is not by any means exclusively derived from alimentary purines; a part of it is formed in the organism. Probably the whole of this endogenous uric acid is not derived from nucleo-albumins, but from other albuminoids. When a subject is submitted to a purine-free diet or one deficient in nitrogen it is difficult to reduce the uric acid below 0.005 gm. per kilo, body weight. Probably a part of this 0.005 gm. comes from the body nucleins or other albuminoids. At any rate, they are of endogenous origin. With purine-free diet given in excess of the requirements for nutriment the amount of urinary uric acid increases. This increase is probably also endogenous. When an excess of purine-containing diet is taken, the increase in uric acid excreted is still greater than can be derived from the food. Here, again, endogenous formation must occur. A part at least of this endogenous uric acid is formed shortly after a meal. More certain knowledge of the physiological role of uric acid excretion would be obtained by the systematic study of the other nitrogenous constituents of urine. In superalimentation with nitrogenous diet the uric nitrogen does not represent a tenth part of the total nitrogen excreted.—*E. Maurel* (*L'Union pharm,* 1914, 55, 337, *through Pharmaceutical Journal.*)