GLUTAMIC ACID AND ITS SALTS IN *PETIT MAL* EPILEPSY.

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The following experiments on glutamic acid were carried out in view of the conflicting reports of Price, Waelsch and Putnam (1943), Waelsch and Price (1944), and Goodman *et al.* (1948) on its effect in epilepsy. A number of preliminary experiments were made which suggested that there was an apparent difference between the effects of glutamic acid and sodium glutamate. Such a difference does not appear to have been considered by most other investigators. It was decided therefore to try to determine whether a possible reason for the difference was the effect of the sodium ion on water balance, since this is known to be related to the tendency to seizures (McQuarrie *et al.*, 1932, Swinyard *et al.*, 1946, and Weinland, 1949). For comparison potassium glutamate was given in a way to be described below. The experiments will be reported under the following headings:

1. The acute E.E.G. and clinical effects of intravenous sodium glutamate.
2. The short term (one week) E.E.G. and clinical effects of glutamic acid, its sodium and potassium salts and a placebo.
3. Longer term clinical effects in out-patients.
4. Biochemical studies of the blood and urine levels of glutamic acid by paper chromatography of 7 epileptic patients and 5 non-epileptic control subjects, including salt and water balance studies of patients and controls.

For all these experiments patients were chosen who had *petit mal* seizures with or without *grand mal* attacks and whose E.E.G. records contained spike and wave activity.

1. The Effects of Intravenous Sodium Glutamate.

For the intravenous experiments 20 per cent. L (+) glutamic acid was neutralized with sodium hydroxide to exactly pH 7 and sterilized by filtration.

Intravenous sodium glutamate has a number of unpleasant side-effects (cf. Mayer-Gross and Walker, 1949), and it was necessary to prevent the almost immediate vomiting which occurred by a preceding injection of $\frac{1}{100}$ gr. atropine intramuscularly. The effect of atropine itself was tested on a preliminary 10 minute E.E.G. with hyperventilation and then sodium glutamate given. Even when covered with atropine there are a number of unpleasant side effects—a sense of heat and oppression in the chest, thumping in the head and ears and increased pulse-rate which can probably be ascribed to sudden intense autonomic stimulation (cf. Weil-Malherbe, 1950). All these effects passed

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off in ½–1 minute after the injection was stopped, and by slow and frequently interrupted injections about 15–20 ml. could be given in 10 minutes. The number of seconds of the record occupied by spike and wave in 10 minutes was then counted.

Owing to its unpleasant nature the intravenous experiment could be performed only 6 times in 3 subjects. In one subject who showed delta activity as well as spike and wave there was a definite decrease in this slow activity. On four occasions a 10-minute period was obtained after the injection when spike and wave could be counted and the results are shown in Table I. In every case there is a reduction in the amount of epileptic activity.

TABLE I.

	Before I.V. sodium glutamate.		After I.V. sodium glutamate.	
	No. of bursts of S. and W. in 10 minutes.	Total period of S. and W. in 10 minutes.	No. of bursts of S. and W. in 10 minutes.	Total period of S. and W. in 10 minutes.
Subject 1	8	39 seconds	1	2 seconds
,, 1	5	12 ,,	4	10 ,,
,, 2	2	22 ,,	1	13 ,,
,, 3	4	80 ,,	1	19 ,,

On the other two occasions hyperventilation was done immediately after the finish of the injection, and it took 12 and 10 seconds respectively more overbreathing than before to produce a burst of spike and wave—a doubtfully significant increase.

2. Effects of Oral Glutamic Acid and its Salts.

In some preliminary experiments of this series reported to the British Branch of the International League against Epilepsy in December, 1949, it was shown that sodium glutamate tended to increase the amount of spike and wave in the E.E.Gs. of *petit mal* patients and to increase the number of clinical attacks. It was shown in one patient that this effect was reversed if the unneutralized glutamic acid was given. In the dosages employed in these experiments (16–24 gm. glutamic acid per day) the neutralized salts represented considerable quantities of sodium ingested. This is well known to tend to produce corresponding water retention, and this in turn is equally well known to increase E.E.G. and clinical epileptic activity.

It was decided therefore to compare the effects of potassium and sodium salts with glutamic acid, as in this way it was hoped to be able to see what part was played by the specific effect of the sodium ion on water and electrolyte balance.

The Latin square shown in Table II was designed to eliminate any effect purely due to the period of hospitalization, and to any "carry-over" effect from one treatment to another. This is possible if it is assumed firstly that the "carry-over" effect from a previous treatment is the same for each patient, and secondly, that treatments other than the immediately previous one do not enter into the "carry-over."

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TABLE II.

Weeks.	Patient. 1.	2.	3.	4.
1	P	NaGl	KGl	G.A.
2	NaGl	KGl	G.A.	P
3	G.A.	P	NaGl	KGl
4	KGl	G.A.	P	NaGl

G.A. = glutamic acid.
NaGl = sodium glutamate.
KGl = potassium glutamate.
P = placebo.

For this experiment four patients were admitted to the wards who showed frequent spikes and waves in their records. They were kept under steady but not measured conditions of diet, exercise and rest. Two were females, and their ages ranged from 7 to 13 years. During the course of the experiments the patients were taken for E.E.G. every morning, fasting, at approximately the same time after waking on 5 or 6 mornings of each week. A timed 10-minute record was taken in one position on every occasion—a 3-channel bipolar recording with electrodes along the left sides of the head in the anterior-posterior plane. Hyperventilation was done until a clinical attack occurred or a prolonged burst of spike and wave. A capillary blood sugar was done on every occasion and estimated by the method of Hagedorn and Jensen. In each record the following points were noted:

1. The number and duration in seconds of spike and wave bursts occurring during the 10 minutes.
2. The number of seconds of overbreathing before a clinical attack occurred.

In one or two patients the number of spikes and waves occurring in 5 or 10 seconds were counted to see if glutamic acid had any effect on their frequency, but as nothing significant emerged this measure will not be further discussed.

The dose of glutamic acid (neutralized or unneutralized) was either 8 gm. *t.d.s.* or (on some days in connection with water and electrolyte studies) 12 gm. in the morning and 8 gm. in the afternoon, the morning dose always being given one hour before the E.E.G. This time was chosen on the basis of studies of the rate of absorption described below. Breakfast was not given until at least 1½ hours after the dose so as not to interfere with absorption. The placebo was coloured and flavoured water. The potassium and sodium salts are very soluble but had to be flavoured to be tolerable; the unneutralized acid was given as a sludge in water.

Table III shows the average number of seconds of spike and wave in the standard 10-minute period over each week (5 E.E.Gs.) with a different treatment.

Statistical analysis of the raw daily scores shows that there is a difference at the 1 per cent. level between treatments and between patients, but not between days or weeks (i.e., there is no systematic error simply due to the period of hospitalization or to the method of measuring spike and wave).

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TABLE III.—*Seconds of Spike and Wave in the Daily* 10-*minute Period.*

Week on—	Patient. 1.	2.	3.	4.	Daily mean.	Daily s.d.*
Placebo	12	14	29	52·2	26·80 seconds	25·56
NaGl	38·4	59·9	53	53·8	51·25 ,,	21·53
KGl	32·2	26·4	33·8	84	44·10 ,,	16·41
G.A.	13	13·2	15	35·4	19·05 ,,	19·26

* A test for homogeneity of variance was carried out and the four variances were found to be homogeneous. The best estimate of the s.d. is therefore 22·23.

Analysing the difference between treatments it is shown that there is no significant difference between sodium and potassium glutamate. For both these treatments the number of seconds of spike and wave are significantly higher than the amount of spike and wave during the placebo period. Although the amount of spike and wave under the glutamic acid treatment was the lowest of all four treatments, the difference from the placebo is not significant. However, glutamic acid and the placebo would differ significantly at the 1 per cent. level of significance if the same difference (i.e., 7·75 seconds) were obtained in a group of 20 patients.

In four other patients not included in this Latin square but tested under the same conditions, there was a similar non-significant decrease in the amount of spike and wave with glutamic acid and an increase on the salts.

Table IV shows the average number of seconds of overbreathing required to produce a clinical attack. There were no significant differences between treatments, patients, days or weeks.

TABLE IV.—*Seconds of Overbreathing to Clinical Attack.*

On—	Patient. 1.	2.	3.	4.	Daily mean.	Daily s.d.*
Placebo	41	42	28	19	32·65 seconds	24·77
NaGl	12·4	49	35	33	32·65 ,,	20·18
KGl	28	53	42	27	37·50 ,,	37·54
G.A.	44	30·4	45	26	36·35 ,,	21·39

* The test for homogeneity of variance found a difference significant at the 5 per cent. level but not at the 1 per cent. level ($L_1 = \cdot 878$).

The blood-sugar values varied between 80 and 100 mgm. per cent. on practically every occasion. The average value during the placebo weeks was 85 mgm. per cent. and during the other weeks was 87 mgm. per cent., so that there was no correlation between the average values in any one week and the amount of spike and wave or the overbreathing time, a hardly surprising result in view of the comparatively small blood-sugar range.

That the E.E.G. effects are probably cumulative at least over the 24 hours was suggested by the results in one patient who had E.E.Gs. done under the standard conditions, but who did not receive the morning glutamic acid dose until after the E.E.G. There was approximately the same decrease in spike and wave as in the patients tested one hour after the glutamic acid dose.

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There did not appear to be any other significant change produced in the E.E.G. other than the reduction in spike and wave. Occasionally there appeared to be less slow activity such as might have been expected from the intravenous experiments.

As a further check on the acute effects of glutamic acid an attempt was made to remove the substance from the body. Ambrose, Power and Sherwin (1933) showed that phenyl-acetic acid is excreted in conjunction with the amide of glutamic acid, and that in this way the body can be made to excrete large quantities of the latter. A partially neutralized solution of about 7 gm. of phenyl-acetic acid to the fluid ounce was therefore administred suspended in mucilage and water and suitably flavoured to be palatable. It was given to one subject three times a day for a week without there being any change in the number of clinical attacks or the amount of epileptic activity in her E.E.G. on the usual daily recordings.

3. Longer Term Clinical Effects.

The in-patient experiments were too short to allow the observation of any possible long-term effects such as has been claimed by Zimmerman (1947) and others in mental defect. A longer trial of the clinical effects in out-patients was therefore undertaken. In the preliminary investigations, when sodium glutamate only was used, no improvement at all was obtained in any of ten patients who were given 8 gm. *t.d.s.* for a month. In fact in two patients who had *grand mal* as well as *petit mal* attacks the former were actually increased.

A total of 8 patients (other than those partaking in the in-patient investigations) have now had glutamic acid for periods of one to four months. They are all children or young adults, and included two who had previously had sodium glutamate. The dose given was usually 24 gm. per day, given in divided doses. Of the eight, five reported a decrease in the number of seizures but the effect tended to wear off after a few weeks. Two of the patients not improved suffered also from occasional *grand mal* seizures, which were actually increased in number in both.

There was spontaneous comment of improved behaviour by the parents of two of the children who had fewer fits.

The effects were in some ways comparable to that of amphetamine, but in two cases in whom this drug was given for a time simultaneously with the glutamic acid there was no evidence of any synergistic action, such as was suggested by Weil-Malherbe (1950). In no case was the improvement as dramatic as that normally obtained by tridione, and for this reason the experiments have not been continued.

4. Biochemical Investigations.

The first aim of the biochemical investigations was to study the absorption and excretion of the glutamic acid and its salts. No accurate chemical or microbiological method for estimating glutamic acid was readily applicable to our patients, but paper chromatographic studies of urine and plasma amino-

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acids were being carried out for other experiments, and this method was found to give useful data about the rate of absorption and excretion of glutamic acid, including a rough quantitative estimation of the actual amounts involved. The technique of two-way paper chromatograms using phenol and collidine as solvents follows in principle the methods of Consden, Gordon and Martin (1944 and 1947) and Dent (1948). The exact details of the method including both the experimental work and the quantitative assessment of results used by one of us are described elsewhere (Pond, 1950). It will be sufficient to say here that paper chromatograms carried out in duplicate on each specimen of desalted urine and plasma ultrafiltrate gave reliable and consistent results as regards the presence or absence of glutamic acid and glutamine and other normal amino-acid constituents of body fluids. It was also easy to detect large variations in concentration from the normal range, but we do not place much reliance on small quantitative variations, knowing that the error of quantitative assessment of results is about $\pm$ 30 per cent.

Clinical Material.

Twelve cases were studied. Seven were in-patients forming a part of the series described above. Five were non-epileptic volunteer controls. All patients received urine investigation, but it was only possible to carry out plasma investigations on 4 patients and 2 controls. All investigations on in-patients were carried out on at least two or three different days during the week's investigation on each drug. Of the controls, only 2 were in-patients and investigated in exactly the same way, the out-patients being investigated on one occasion only. All the in-patients received glutamic acid, the sodium and potassium salts, but the 3 out-patient controls received sodium glutamate and glutamic acid only.

The specimens were collected at the following times: Urine was collected fasting and then 1, 2, 4, 6 and 8 hours after administration of the drug. Plasma was collected fasting and then $\frac{1}{2}$, 1, 2, 4 and 6 hours after administration. It was not always possible to collect a complete series of plasma specimens on the same day owing to the difficulty of repeated venepuncture on children. All drugs were given orally on an empty stomach morning and evening, meals being then withheld for $1\frac{1}{2}$ hours to prevent interference with absorption.

Results.

No difference of any kind was found between normal controls and epileptic patients and therefore their results are treated together.

Table V represents a specimen series of results, and the range and average values where sufficient results are available, of plasma ultrafiltrate levels following the oral ingestion of the three drugs.

Each of the three drugs when examined by this method appear as glutamic acid in the final picture, the sodium and potassium ions being removed in the desalting process. Hence they are easily comparable, and it is the comparison of the three series of results which is of the greatest value. No great accuracy

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TABLE V.—*Plasma Ultrafiltrate Levels (mgm./100 ml.) of Glutamic Acid after the Ingestion of the Acid, Sodium Glutamate and Potassium Glutamate.*

Time.	Drug given. Glutamic acid. Specimen series.	Range.	Average.	Sodium glutamate. Specimen series.	Range.	Average.	Potassium glutamate. Specimen series.	Range.	Average.
Fasting	1	1– 3	2	2	1– 3	2	1	Insufficient results	
½ hour	1	1	1	8	6– 8	7	6	,,	,,
1 ,,	4	3– 6	3	20	6–20	12	20	,,	,,
2 hours	10	1–11	6	22	4–22	12	11	,,	,,
4 ,,	4	3– 4	4	3	2– 3	3	1	,,	,,
6 ,,	3	—	—	1	1	1	1	,,	,,

is claimed for the actual figures, and there are wide variations in day-to-day values for similar experiments. This may be compared with reports by other workers—Prescott and Waelsch (1947), and Krebs, Eggleston and Hems (1949)—that glutamic acid values in plasma vary considerably from day to day and patient to patient, even when estimated by more accurate chemical methods. However, the following broad trends appeared: Firstly, the maximum blood levels occurred between 1 and 2 hours after the administration of sodium and potassium salts, a return to normal being complete in 4 hours. The response to glutamic acid administration tended to be less marked and to be spaced over a longer period, that is, between 1 and 4 hours after dosage.

The excretion of glutamic acid in the urine following administration of the drug followed a very standard pattern. Fasting urines showed occasional traces of glutamic acid and this was taken as normal (equivalent to not more than 20 μgm./ml.). Following the ingestion of glutamic acid there was occasionally a small rise in the excretion of glutamic acid, but more commonly there was no excretion of glutamic acid. The excretion of glutamic acid, if present, amounted to less that 30 mgm. in 8 hours following the dose (i.e. less than 0·05 per cent. of the dose given). However, sodium and potassium salts behaved quite differently from glutamic acid, though similarly to each other. In every case the quantities excreted in the first few hours after the dose were large compared with those after glutamic acid. The excretion on different days was variable, being approximately 0·25 to 0·75 gm., i.e., about 3 per cent. of the total dose given. The maximum excretion was always in the first two hours, excretion being complete in 6 hours. Table VI shows a series of typical results in which each urine has been examined in the chromatogram in an amount proportional to its specific gravity, therefore eliminating any changes in concentration due to the varying dilution of the urine.

In all investigations on both plasma ultrafiltrate and urine the other amino-acids were normal in pattern and concentration. Slight alterations of glutamine were sometimes observed, but they were considered too small to be of any significance. The possibility was considered that glutamine was easily "lost" during the experiment by acid hydrolysis, causing a relative increase of glutamic acid. By controlled experiments using known quantities of the pure substances, it was found that only a small loss (less than 10 per cent.)

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TABLE VI.—*Specimen Urinary Levels of Glutamic Acid after Ingestion of Glutamic Acid and Sodium and Potassium Salts. (Quantities examined proportionate to s.g. of urine specimen.)*

Time.	Drug given. Glutamic acid.	Sodium glutamate.	Potassium glutamate.
Fasting .	—	—	—
1 hour .	+	++++	++++
2 hours .	tr.	+++	
4 ,, .	—	+	+
6 ,, .	—	tr.	—
8 ,, .	tr.	—	—

— = no glutamic acid detected.
tr. = light " spots " equivalent to less than 2 mgm.
\+ = light " spots " equivalent to 3–10 mgm.
++ = medium " spots " equivalent to 10–40 mgm.
+++ = medium " spots " equivalent to 40–80 mgm.
++++ = heavy " spots " equivalent to over 80 mgm.
(Quantities examined were usually 25–100.)

occurred in this way if reasonable cooling precautions were taken during the desalting.

All other amino-acids were always normal with the occasional exception of aspartic acid. The normal fasting value of aspartic acid in the blood was found to be 0–1 mgm./100ml. Whenever the value of glutamic acid reached more than about 10 mgm./100 ml. of plasma ultrafiltrate, there was a corresponding rise of aspartic acid up to about 2 mgm./100 ml. The same was true of the urine: whenever there was a large excretion of the one (+++ or ++++) there was a relative increase in the excretion of the other.

In view of these findings the question of contamination of the glutamic acid used by aspartic acid was investigated by running chromatograms on ethanol solutions of the original substance. However, no aspartic acid was found, and therefore any rise demonstrated in the patients was due to an *in vivo* reaction.

It is to be noted that in common with all other investigators we have considered only the free glutamic acid in the urine. It is generally assumed that no significant variations occurred in the combined glutamic acid.

WATER-ELECTROLYTE STUDIES.

Measurements were taken on 7 patients of—

1. Daily weight.
2. Twenty-four-hour intake of fluid and output of urine.
3. The urinary chlorides on the twenty-four specimens and specimens passed 2, 4 and 6 hours after dosage three times each week.

For various reasons a full study proved an impossible aim and the records are very incomplete. Such measurments as were obtained were disappointing in that few conclusions can be drawn. The twenty-four-hour volumes and chloride content showed no significant variations during the whole experiment. Neither did daily weight charts suggest any water retention during sodium glutamate therapy, except in one patient who gained three pounds during the

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week on sodium glutamate, followed by a return to her previous weight the next week.

Furthermore, the fact that sodium and potassium glutamate had such similar E.E.G. effects, though the body deals with these two ions quite differently, suggests that it is doubtful whether the sodium ion and water retention could have played a significant part in the action of sodium glutamate in contrast to glutamic acid.

Chloride estimations of urine specimens passed for the first six hours after the drug showed suggestive changes in about half the cases investigated, the other half showing no change at all. The results in two patients summarized in Table VII below show a large increase in chloride excretion following potassium glutamate and a decrease following sodium glutamate as compared with glutamic acid. This suggests chloride retention following the sodium salt and chloride excretion following the potassium salt, but the results were not borne out in all patients. Accurate determination could not be carried out, as strict dietary control could not be instituted, and it was necessary to assume that an average value of three days' estimation would rule out some of the variation of salt content in a standard hospital diet.

TABLE VII.—*Average Values of Three Estimations of Urinary Chlorides Excreted in 6 hours Following Glutamic Acid and its Salts (Volhard's Method).*

	Drug given.		
	Sodium glutamate.	Potassium glutamate.	Glutamic acid.
Patient 1 .	2·14 gm.Cl.	6·9 gm.Cl.	4·5 gm.Cl.
Patient 2 .	2·55 ,,	6·9 ,,	4·2 ,,

In two other patients alkali reserve and plasma chlorides were taken between one and two hours after each drug without any significant changes being detected.

DISCUSSION.

There appears to be some fairly definite evidence that glutamic acid can decrease the amount of spike and wave and the number of attacks in patients with *petit mal*. However, the effect is slight and probably only transitory. As a therapeutic measure it can hardly be considered worth while, and for this reason no further experiments were undertaken in an effort to elucidate its mechanism of action.

Some of our experiments were designed to investigate the apparently simpler problem of the difference between glutamic acid and its salts. The factor of deficient absorption in the cases of the salts may be considered ruled out by the high blood and urine levels obtained after these salts. In fact, the salts appear to be absorbed more quickly and completely than the acid itself, probably due simply to their solubility. Other possible reasons for the difference are that the acid is in some way more quickly and easily metabolized in the tissues, thus accounting for the lower blood and urine levels than appear with the salts; or, the beneficial effect of the glutamic acid is counteracted by

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the absorption at the same time of large quantities of sodium and potassium (2·4 and 3·9 gm. respectively per 20 gm. salt). The former seems doubtful on the present insufficient evidence, and the latter was not borne out by any salt-and-water balance studies carried out. The greater excretion of glutamic acid after the salts, although twenty times greater than that of the glutamic acid after the unneutralized acid, is still negligible in explaining the failure of the salts to produce a comparable effect, since it amounts to only 3 per cent. of the total dose given and is probably a simple overflow mechanism. Hence no explanation of the differences between glutamic acid and its salts can be satisfactorily given, although the fact that this difference exists has been undeniably shown.

The many possible modes of action of glutamic acid in the metabolism of the brain have been recently reviewed by Waelsch (1948) and Weil-Malherbe (1950). From the experiments of the latter on the effects of glutamic acid in hypoglycaemic coma, it is possible that the positive effects of glutamic acid may be equally non-specific in *petit mal* epilepsy. It is even by no means certain that the site of action is in the brain, since its concentration there does not increase following intravenous injection of glutamic acid (Klein and Olsen, 1947), though Waelsch (1949) finds the brain glutamine level does rise. It certainly does not appear to depend on the plasma level, as this returns to normal in 6–8 hours and the positive effect seems to last up to 24 hours.

Nor is there evidence that there are significant variations in the other amino-acid levels in the plasma, such as, for example, Waelsch (1949) reports in the glutamine and glutamic acid ratio. The small changes in aspartic acid levels with very high blood and urine glutamic values are consistent with the findings of Cohen (1940) and Awapara and Marvin (1949), and the postulated reaction involving glutamic aspartic transaminase, converting glutamic to aspartic acid via oxaloacetic and α-ketoglutaric acids.

The marked, predominantly sympathetic, autonomic reaction produced by the intravenous injection is in line with Weil-Malherbe's suggestion that glutamic acid acts as a relatively non-specific adrenergic agent. However, no similar effects were seen with oral dosage. Our data threw no light on the various other possibilities such as changes in the permeability of neuronal membranes to potassium (Krebs and Eggleston, 1949).

Summary.

The clinical and electroencephalographic effects of glutamic acid and its sodium and potassium salts in a total of 16 epileptics were investigated. The sodium salt was given intravenously in a few experiments, and orally in longer experiments in comparison with the acid and potassium salt. It was shown that the salts given orally significantly increased the amount of epileptic activity in the E.E.G. and the acid produced a decrease, but not at a statistically significant level. No consistent clinical changes were demonstrated, although 5 out of 8 patients given glutamic acid over a month reported a temporary decrease in the number of seizures. Biochemical investigations on some of the epileptics and a comparable number of controls (blood and urine

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glutamic acid levels by chromatography and other studies) failed to demonstrate any obvious mechanism for these differences. However, differences in the rates of absorption and between the acid and salts were demonstrated and discussed.

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