LXXXIX. METABOLISM STUDIES IN TETANY.

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A DISTURBANCE in chlorine metabolism has long been associated as an etiological factor in the production of certain forms of tetany. MacCallum and his co-workers [1920] attributed the onset of tetany in cases of pyloric obstruction to the loss of the gastric hydrochloric acid by the vomitus with the consequent production of an alkalosis. Grant [1922] found in one of six cases of adult tetany a marked reduction in the blood-chlorine. Iversen and Hansborg [1922] showed that after thyroidectomy sodium chloride was retained in the tissues to an abnormal extent although the amount of chlorine in the blood was reduced. Parhon, Ballif and Derevici [1926] also reported a fall in the serum-chlorine. Rockemann [1923] found that tetany following injection of sodium dihydrogen phosphate was accompanied by decreased excretion of urinary chloride.

The present investigation was undertaken primarily to study the changes in chlorine metabolism during conditions of tetany not associated with vomiting. Much work, however, has already been done indicating that in many forms of tetany there is a profound disturbance in calcium metabolism. Numerous experimental studies by Berkeley and Beebe [1909], Cooke [1911] and others showed that after parathyroidectomy there occurs a definite increase in the output of nitrogen, while Burns [1917] recorded a similar finding following guanidine injection. The first section of this paper accordingly deals with the effect of tetany on chlorine metabolism, while succeeding parts describe the alterations in nitrogen and mineral metabolism.

Methods.

Tetany was induced in cats by removal of the parathyroids and in rabbits by injection of guanidine. The parathyroids were first removed under chloroform anaesthesia; this usually produced a condition of latent tetany indicated by sluggishness and the other characteristic manifestations. A second operation of complete thyroidectomy led to the development of active tetany. The effect of guanidine was investigated by the subcutaneous injection of a 6 % solution of guanidine carbonate. 5 cc. were used in each case except rabbit 2

where the dose was 7 cc. An interval of 6 days elapsed between succeeding injections. The food was weighed and aliquot portions of each article of diet were analysed. The unused residues of the diet were kept, thoroughly mixed and analysed. Accordingly the intake during each period of the experiment was accurately known. The rabbits were fed on a mixture of equal parts of oats, bran and linseed, while the cats received oatmeal porridge and milk. Urine and faeces were collected separately. The urine was analysed daily while the faeces for each period were collected, dried on a steam-bath and analysed. The methods of analysis employed were: chloride [Van Slyke, 1923]; calcium [McCrudden, 1911]; phosphorus, Neumann, total nitrogen, Kjeldahl; purines, modified Camerer method [Cathcart *et al.*, 1925], creatine and creatinine, Folin; ammonia, Folin aeration method; amino-acids, Sørensen.

CHLORINE.

Results.

A. *Urine* (Table I). It is clear that the urinary output of chlorine was diminished after removal of parathyroids or injection of guanidine much more than can be accounted for by the decreased intake. Accordingly there

Table I. *Showing intake, output and retention of chlorine in mg. daily.*

Cat	Period	Intake	Output	Re- tention	% re- tention
1	1. Normal	790.6	672.5	118.1	14.9
	2. Latent tetany	718.7	496.0	222.7	30.9
	3. Recovery	830.4	529.4	301.0	36.3
	4. Active tetany	194.2	Nil	194.2	100.0
	5. Recovery	706.0	1267.0	Negative	Negative
2	1. Normal	919.0	906.7	12.3	1.3
	2. Latent tetany	1000.0	642.0	358.0	35.8
3	1. Normal	707.4	583.6	123.8	17.5
	2. Latent tetany	528.0	157.4	370.6	70.1
	3. Active tetany	676.3	148.4	527.9	78.0
	4. Recovery	707.4	564.0	143.4	20.2
4	1. Normal	400.7	379.6	21.1	5.2
	2. Latent tetany	400.4	260.4	140.0	34.9
5	1. Normal	431.4	372.7	58.7	13.6
	2. Latent tetany	430.0	287.0	143.0	33.2
Rabbit					
1	1. Normal—7 days	30.6	30.1	0.5	1.63
	2. Guanidine—5 days following 1st injection	18.2	8.6	9.6	52.7
	3. Guanidine—5 days following 2nd injection	8.55	3.0	5.55	64.9
	4. Guanidine—10 days following 3rd injection	7.1	1.4	5.7	80.2
2	1. Normal—7 days	28.4	31.3	12.9	—
	2. Guanidine—5 days after 1st injection ...	7.1	4.04	3.06	43.1
3	1. Normal—7 days	42.6	41.2	1.4	3.3
	2. Guanidine—5 days following 1st injection	16.05	13.33	2.72	16.9
	3. Guanidine—5 days following 2nd injection	10.2	4.76	5.44	53.3
	4. Guanidine—10 days following 3rd injection	14.2	5.1	9.1	64.1
4	1. Normal—7 days	44.4	42.9	1.5	3.4
	2. Guanidine—5 days following 1st injection	8.66	4.54	4.12	47.5
	3. Guanidine—5 days following 2nd injection	7.1	2.44	4.66	65.6
	4. Guanidine—10 days following 3rd injection	8.6	2.40	6.20	72.1

was actually an increased retention of chlorine during both latent and active tetany periods although the intake was in most cases much less than that of the normal. If sufficient chlorine had been ingested the retention was more marked in the active stage.

B. *Blood* (Table II). The immediate effect of an injection of guanidine on the total chlorine content of the blood was with one exception (rabbit 11) a reduction of 8 to 18 milli-equiv. per litre. This reduction was followed within

Table II. *Showing total and volatile chlorine of blood in normal condition and active and latent tetany (m.-eq. per litre).*

Period	Cat 1		Cat 3		Cat 5		Cat 6		Cat 7		Cat 8	
	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl
Normal	102.6	14.6	101.8	11.4	96.2	10.4	98.6	11.8	104.7	12.2	98.0	10.0
	—	—	100.4	10.4	97.1	11.2	100.1	11.8	106.0	12.0	100.2	10.4
	—	—	—	—	—	—	—	—	106.2	11.7	100.3	10.5
Latent tetany	—	—	—	—	—	—	91.2	12.9	93.1	16.3	92.5	12.1
	122.1	19.8	—	—	109.5	20.4	110.5	18.1	113.2	17.4	112.6	14.6
	—	—	—	—	108.7	18.3	112.8	20.6	115.9	17.3	115.9	19.8
	—	—	—	—	110.5	12.3	112.8	20.3	113.8	20.0	115.4	19.2
Active tetany	—	—	—	—	110.0	0.2	—	—	102.8	0.0	107.5	1.0
Recovery	105.8	12.6	103.0	11.6	—	—	—	—	—	—	—	—

	Rabbit 1		Rabbit 2		Rabbit 3		Rabbit 4		Rabbit 5		Rabbit 6	
	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl
Normal	80.2	8.6	74.6	12.2	85.0	8.6	77.6	11.2	82.5	10.0	67.3	11.2
	80.0	10.2	75.1	12.6	84.8	10.4	78.9	10.8	80.6	10.0	67.4	11.5
1st day after 1st injection	70.3	0.0	75.5	0.7	76.8	0.8	62.5	3.6	70.3	2.1	50.8	3.5
4th day after 1st injection	81.8	17.4	80.4	15.3	88.2	19.3	80.9	20.0	80.6	17.8	75.5	16.3
1st day after 2nd injection	72.9	-0.1	—	—	75.8	2.3	70.7	2.2	68.9	4.5	58.8	5.1
4th day after 2nd injection	86.6	17.7	—	—	80.4	19.6	86.5	18.6	78.8	18.4	75.9	16.1
1st day after 3rd injection	78.8	-0.2	—	—	75.9	1.1	80.4	4.9	75.5	0.3	70.2	0.3
8th day after 3rd injection	73.0	12.6	—	—	73.0	9.6	78.1	13.3	67.7	7.2	75.5	10.7

3 to 4 days by a return to a normal or slightly super-normal figure except in the period following the third injection. In two cases after the third injection a return to normal was recorded while in the other three the total chlorine was still further reduced. The volatile chlorine of the blood almost vanished immediately after administration of guanidine, only to return 4 days after the injection to a value exceeding the normal figure.

Similar results were noted following the removal of parathyroids. The onset of latent tetany was accompanied by a decrease of the total chlorine of the blood with a rise in the volatile portion. As the state of latent tetany was prolonged the total chlorine rose to a value 10–15 % in excess of the normal, while the volatile chlorine became almost twice as great as in health. When active tetany was induced by a complete thyreo-parathyroidectomy the total chlorine still remained above normal in two of the three cases, while

the volatile form almost completely disappeared. In two cats in which as the result of treatment with saline there were no evident symptoms the blood-chlorine values were normal.

C. *Tissues* (Table III). Analysis of the tissues showed that in both the latent and active stages of tetany due either to parathyroidectomy or guanidine poisoning there occurred a marked increase of the total Cl of muscle, heart

Table III. *Showing total and volatile chlorine of tissues in normal condition and active and latent tetany (m.-eq. per litre).*

Cat	Condition	Muscle		Heart		Liver		Kidney		Lung	
		Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl	Total Cl	Vol. Cl
A	Normal	15.0	1.8	32.1	6.1	27.2	3.4	41.0	7.0	61.1	11.1
B	"	13.6	4.1	—	—	26.3	7.8	40.0	4.4	—	—
C	"	14.2	2.2	26.6	6.2	31.5	2.3	35.0	5.0	62.5	11.7
	Average	14.3	2.7	29.4	6.2	28.3	4.5	38.7	5.5	61.8	11.4
6	Latent tetany	51.0	28.2	67.0	36.4	34.5	19.7	51.2	9.2	57.7	22.0
2	Active tetany	63.6	2.1	77.8	0.0	62.2	0.1	56.3	0.0	42.0	0.2
5	"	63.8	3.1	86.0	0.7	66.0	0.0	63.3	0.0	51.2	0.0
7	"	54.0	0.2	85.0	0.1	40.0	1.7	64.0	0.0	57.2	1.1
8	"	76.5	0.7	48.4	0.4	60.4	0.2	40.8	0.8	55.9	2.9
	Average	65.0	1.5	74.3	0.3	57.2	0.5	56.1	0.2	51.6	1.1
1	Recovered	46.0	5.6	50.5	20.4	28.2	5.8	50.0	5.0	54.0	4.9
3	"	23.0	3.0	40.0	16.0	30.0	5.2	53.0	4.0	51.0	21.4
	Average	34.5	4.3	45.3	18.2	29.1	5.5	51.5	4.5	52.5	13.2
Rabbit											
7	Normal	7.3	3.7	34.2	9.9	27.6	3.5	—	—	48.8	16.2
8	"	11.0	3.9	36.0	9.6	22.0	2.0	48.6	14.1	50.0	15.9
9	"	15.6	4.7	34.8	8.5	23.0	5.1	53.8	19.6	49.2	13.0
	Average	11.3	4.1	35.0	9.3	24.2	3.5	50.7	16.9	49.3	15.0
3	Latent tetany	35.0	25.2	55.0	12.5	39.5	24.3	37.8	10.4	43.5	14.7
4	"	31.0	19.9	52.0	7.0	41.4	14.9	44.0	9.9	41.4	11.6
5	"	41.0	32.8	55.4	12.2	42.4	24.1	43.2	25.6	47.7	17.7
	Average	35.7	26.0	54.1	10.6	41.1	21.1	41.7	15.3	44.2	14.7
1	Active tetany	46.0	0.2	54.6	0.6	40.1	1.5	23.7	0.8	46.3	0.3
2	"	42.4	0.5	56.4	0.4	38.9	0.1	29.8	1.0	47.2	0.4
6	"	40.0	2.8	55.7	1.9	37.8	1.8	28.5	1.4	41.2	1.2
	Average	42.8	1.2	55.6	1.0	38.9	1.1	27.3	1.1	44.9	0.6

and liver. Following injection of guanidine the total Cl of kidney and lung was reduced, while after removal of the parathyroids the Cl was increased in the kidney but reduced in the lung. During the latent tetany stage the volatile Cl was increased markedly in muscle and liver and slightly in kidney in both series of experiments. In heart and lung the volatile portion was unchanged in the guanidine-treated group but definitely increased in the parathyroidectomy series. During active tetany in both groups there was almost complete disappearance of volatile Cl. Two cats, which were killed during a period of freedom from all manifest signs of tetany, showed a moderate increase in the total Cl content of heart and skeletal muscle but otherwise practically normal values.

Discussion.

Guanidine. From these results it is permissible to conclude that guanidine poisoning creates a demand for chlorine in the tissues. The early fall in the total chlorine content of the blood coupled with the diminution in the urinary excretion is clearly a consequence of the withdrawal of chlorine to the tissues. The subsequent rise of the blood-chlorine is in all probability the result of gradual repletion of the blood from the chlorine ingested.

It has already been shown that chlorine exists in part as a volatile organic compound which has the power of forming a complex with substances containing the amino-group [Morris and Morris, 1930]. When so combined the power of volatilisation at 100° is lost. The amount of non-volatile amino-chlorine complex depends on the proportion of volatile organic chlorine to amino-groups, closely following the adsorption formula. The changes in the content of volatile chlorine of blood and tissues are strongly suggestive of the formation of amino-compounds in the tissues. Within 24 hours of the injection of guanidine the volatile chlorine of the blood has completely disappeared while the non-volatile fraction remains practically unaltered in amount. As there is no excessive excretion of chlorine it must be concluded that the volatile chlorine has gone to the tissues. Four days after the injection the volatile chlorine in the blood has increased above its normal value. Meanwhile in order to satisfy the extra demands there is an excessive retention of the chlorine ingested. The results of tissue analysis during the latent tetany stage conform with this view. It is seen that during that period there is a great increase in the total chlorine, affecting in muscle and liver only the volatile form. Renal tissue, however, contains rather less chlorine in this period, the result probably of less chlorine having been carried to the kidney for excretion. It is possible that the increase of volatile chlorine is due to the presence of guanidine itself. If that were so it would be reasonable to expect either that it should be more or less uniformly distributed over the tissues or that excess should be found only in the liver, the chief seat of deamination. It is significant, however, that skeletal muscle, one of the chief centres of metabolic activity, shows equally with liver a marked increase in the amount of volatile chlorine.

In the stage of active tetany the striking feature of the results of tissue analysis is the great diminution in volatile chlorine, which must be due to the presence of excessive amount of amino-compound. The total chlorine of all the tissues except kidney remains high as in the latent tetany stage.

Parathyroidectomy. The results show that chlorine metabolism was affected in almost the same manner as in guanidine poisoning. In several instances intraperitoneal injection of sodium chloride led to a rapid disappearance of the symptoms. This was shown by Paton and Findlay [1917] who attributed the beneficial action of the saline to a dilution of the poison. It seems from the present study more correct to refer the effect of administered

chloride to a neutralisation of the protein breakdown product by the formation of an amino-chlorine complex.

It appears justifiable, therefore, to conclude that the production of tetany by guanidine poisoning or by parathyroidectomy is the result of excessive proteolysis leading to the liberation of a large amount of amino-nitrogen which unites with the volatile chlorine. As long as the ratio of volatile chlorine to amino-nitrogen is maintained above a certain value manifest symptoms of tetany do not appear. When the liberation of amino-nitrogen proceeds apace and reduces this ratio the volatile chlorine disappears owing to the formation of a non-volatile complex, and active tetany ensues. Should the ratio again be raised by the parenteral administration of chlorine, owing to the rapid formation of volatile chlorine the symptoms again become latent. It is well known that the feeding of meat hastens the onset of tetany, a result to be expected in view of the increased amount of circulating amino-nitrogen. This view would explain the discordant results recorded of guanidine poisoning. Obviously the production of manifest tetany would depend on two factors, (a) the extent of protein breakdown and (b) the available supply of chlorine. The greater the supply of chlorine the larger would be the dose of guanidine necessary to produce symptoms. Further, the guanidine having itself an amino-group might conceivably be detoxicated before it could act on the tissues, provided there was available an abundance of chlorine.

Still further support is lent to our hypothesis by a consideration of gastric tetany. In this form there is a great loss of chlorine by the vomitus leading to a great deficiency in the tissues, which coincides with normal or slightly excessive liberation of amino-nitrogen. Further, it is of interest to state that in the idiopathic tetany of children there also occurs a marked retention of chlorine [Morris and MacRae, 1931].

NITROGEN.

The results noted in Table IV indicate that, following parathyroidectomy, in spite of decreased intake the urinary output of nitrogen was markedly increased so that the retention was greatly diminished, there being in four instances a net loss. The faecal nitrogen content varied but little. This is in accord with the numerous experimental studies previously recorded by Berkeley and Beebe [1909] and others for tetania parathyreopriva and by Burns [1917] for guanidine tetany. The partition of nitrogen in the urine is of importance in indicating the source of the excess nitrogen. The results heretofore recorded in the literature are conflicting. Berkeley and Beebe [1909] found an increase in the ammonia of the blood and urine and because of this and of the effectiveness of calcium therapy in parathyroid tetany and ammonia intoxication concluded that the excess of ammonia was the causal agent in the production of tetany. Falta and Kahn [1912] and Underhill *et al.* [1922] also found an increase in ammonia whereas Carlson and Jacobson [1911], Greenwald [1913], Albertoni [1914] could only show a slight rise in the ammonia

Table IV. *Showing intake, output and retention of nitrogen in g. daily.*

Cat	Period	Intake	Output			Reten- tion	NH ₃	Total* crea- tinine	Amino- acid- N	Purine*- N
			Urine	Faeces	Total					
1	Normal	3.5200	1.2400	1.6209	2.8600	0.6592	—	167.40	101.52	3.478
	Latent	3.2700	1.9725	1.7100	3.6825	0.4125	—	50.20	359.56	31.500
	Active	0.7205	1.5170	0.0000	1.5170	0.7965	—	70.70	203.60	30.080
	Recovery	2.9100	0.8824	0.6911	1.5174	1.3926	—	124.40	172.02	3.500
2	Normal	5.7370	1.7130	3.5400	5.2530	0.4840	—	234.36	113.40	6.456
	Latent	5.7000	2.8180	3.7610	6.5790	0.8790	—	66.75	344.25	20.410
3	Normal	3.9000	0.6886	0.2781	0.9667	2.9333	0.1294	137.06	63.95	2.514
	Latent	1.3730	0.8770	0.0370	0.9140	0.4590	0.0346	39.36	301.25	37.829
	Active	0.7080	2.1443	0.0000	2.1443	1.4363	0.0239	53.96	302.00	105.148
	Recovery	3.9000	0.6540	0.2581	0.9121	2.9879	0.0681	110.92	62.83	9.201
4	Normal	3.5300	0.5960	0.2820	0.8780	2.6520	0.1074	220.32	43.38	1.538
	Latent	2.2800	0.8430	0.1280	0.9710	1.3090	0.0507	135.66	47.54	41.025
5	Normal	2.6140	0.7306	0.0900	0.8206	1.7934	0.1279	243.00	70.65	1.032
	Latent	2.0500	0.9512	0.0821	1.0333	1.0167	0.0515	157.00	60.13	44.600
Rabbit										
1	Normal	1.4301	0.7767	0.3240	1.1007	0.3294	0.0296	24.50	61.30	9.87
	1st injection	0.7322	0.3966	0.3329	0.7315	0.0007	0.0165	25.10	38.60	11.80
	2nd "	0.3000	0.2310	0.2225	0.4535	-0.1535	0.0014	4.90	82.10	31.72
	3rd "	0.2860	0.3137	0.2005	0.5142	-0.2282	0.0004	—	131.40	33.87
2	Normal	1.1072	0.5997	0.2490	0.8487	0.2585	0.0370	24.50	22.00	12.04
	1st injection	0.2860	0.2460	0.1380	0.3840	-0.0980	0.0086	25.00	53.40	12.01
3	Normal	1.7875	0.8857	0.6000	1.4857	0.3018	0.0096	17.46	27.75	12.90
	1st injection	0.6464	0.3852	0.2082	0.5934	0.0530	0.0076	18.05	17.58	10.20
	2nd "	0.4118	0.3148	0.1071	0.4219	-0.0101	0.0018	5.18	41.84	30.70
	3rd "	0.5720	0.5839	0.1109	0.6948	-0.1228	0.0008	—	174.40	25.40
4	Normal	1.8000	0.8420	0.5850	1.4270	0.3730	0.0113	13.53	20.00	9.87
	1st injection	0.3489	0.1870	0.1800	0.3670	-0.0181	0.0123	13.00	16.08	10.00
	2nd "	0.3000	0.3201	0.1075	0.4276	-0.1276	0.0068	5.80	81.00	24.27
	3rd "	0.3000	0.4333	0.1069	0.5402	-0.2402	0.0016	—	152.80	22.89

* The figures for creatinine, amino-acid-N and purine-N are in mg. daily.

excreted in the urine and no excess in the blood. Carlson and Jacobson [1911] also showed that there is a difference in the therapeutic actions of calcium salts in ammonia poisoning and tetany. Wilson, Stearns and Thurlow [1915] found a lowering of the ammonia coefficient during latent, but a rise during active tetany. MacCallum and Voegtlin [1911] on the other hand obtained a definite increase immediately after parathyroidectomy. Cooke [1910] and Palladin and Grilliches [1924] reported in tetania parathyreopriva an increase in the total creatinine output whereas Burns [1917] obtained the opposite result after parathyroidectomy but a slight increase in guanidine tetany. Esau and Stoland [1930] concluded that the initial effect of parathyroidectomy is on tissue metabolism, the substance chiefly affected being phosphagen. Justschenko [1913] found an increase in the output of amino-acids, while Falta and Kahn's [1912] results indicated no change in the excretion of amino-acids but a rise in the peptide-nitrogen of the urine. Burns [1917] reported a slight rise in the output of amino-acids after one injection of guanidine.

Our results demonstrate the following points.

Total creatinine. After removal of the parathyroids there was a definite decrease in the amount of total creatinine during latent and active tetany with a tendency to return to normal in the recovery stage. After the first

injection of guanidine, however, the output was unchanged or slightly increased but following the later injections it was markedly diminished. After the third injection creatinine could not be detected in the urine.

Ammonia. The amount excreted was diminished, the decrease becoming more marked as the tetany became more manifest.

Amino-acids. After parathyroidectomy the amino-acid content of the urine was markedly increased in all the tetany periods except two (in one it was practically unchanged and in the other somewhat reduced). Following the first injection of guanidine there occurred except in rabbit 2 a decrease in the amount of amino-acid excreted. The later injections of guanidine led to a marked increase in the output.

Purine-nitrogen. In all cases the output of purine-nitrogen was definitely increased.

From these results it seems fair to conclude that an immediate and important effect of parathyroidectomy and guanidine poisoning is an excessive tissue catabolism. It also seems that the effect on nitrogen metabolism is roughly parallel with the degree of tetany produced. This is more apparent in the guanidine series where it is evident that the effect of guanidine is dependent on the dosage. The second and third injections produced more marked effects.

MINERALS.

It is clear that comparison between the retentions of calcium and phosphorus in the various periods is difficult owing to the difference in intakes. Accordingly we have estimated the retention as a percentage of the intake. In calculating the difference in the amount of calcium or phosphorus excreted we have calculated the expected excretion of the normal period on the same calcium or phosphorus intake as that of the tetany period. This admittedly is not satisfactory, but the fact that we obtain such close correlation between the excess calcium calculated on this basis and the excess amino-acids seems to afford some justification for this method of computation. The only other course is to withhold food entirely during all the periods. Such a procedure is open to the very serious objection that ketosis with all its concomitant metabolic effects complicates the picture.

Calcium.

Our results (Table V) may be summarised as follows.

After removal of the parathyroids the urinary output of calcium was increased in the stage of latent tetany and still more in the active period, the faecal output was decreased but not markedly so and the retention of calcium calculated as a percentage of the intake was decreased.

After the first injection of guanidine there occurred a decrease of urinary calcium. The second and still more the third administration of guanidine led to a rise in the amount of calcium in the urine. The percentage retention was

Table V. *Showing intake, output and retention of calcium and phosphorus in g. daily.*

Cat	Period	Calcium						Phosphorus					
		Intake	Output			Retention		Intake	Output			Retention	
			Urine	Faeces	Total	Total	%		Urine	Faeces	Total	Total	%
1	Normal	0.3309	0.0311	0.1034	0.1345	0.1964	59.3	0.4107	0.1545	0.1325	0.2870	0.1237	30.1
	Latent	0.2512	0.0388	0.0878	0.1266	0.1246	49.6	0.3678	0.1667	0.0876	0.2543	0.1135	30.8
	Active	0.0765	0.0410	0.0000	0.0410	0.0355	46.4	0.1824	0.1210	0.0000	0.1210	0.0614	33.9
	Recovery	0.1960	0.0354	0.0512	0.0866	0.1094	55.9	0.1900	0.0800	0.0438	0.1238	0.0662	82.7
2	Normal	0.3417	0.0620	0.1450	0.2070	0.1347	39.4	0.4715	0.2017	0.2200	0.4217	0.0498	24.7
	Latent	0.3635	0.1480	0.1076	0.2556	0.1079	29.7	0.4300	0.2250	0.1302	0.3552	0.0748	33.2
3	Normal	0.2030	0.0140	0.1322	0.1462	0.0568	28.0	0.2933	0.1090	0.1972	0.3063	0.0130	—
	Latent	0.1270	0.0113	0.1021	0.1134	0.0136	10.9	0.1530	0.0792	0.0831	0.1623	0.0093	—
	Active	0.0570	0.0640	0.0000	0.0640	0.0070	—	0.1100	0.1628	0.0000	0.1628	0.0528	—
	Recovery	0.2030	0.0100	0.1411	0.1511	0.0519	25.0	0.2933	0.0705	0.2324	0.3029	0.0096	—
4	Normal	0.2010	0.0068	0.1021	0.1089	0.0921	45.8	0.2830	0.0925	0.1001	0.1926	0.0904	31.9
	Latent	0.1650	0.0113	0.0786	0.0899	0.0751	45.5	0.2500	0.1074	0.0625	0.1699	0.0801	32.0
5	Normal	0.1690	0.0089	0.0885	0.0974	0.0716	42.4	0.2280	0.0935	0.0870	0.1805	0.0475	20.8
	Latent	0.1350	0.0085	0.0614	0.0699	0.0651	48.2	0.1650	0.0910	0.0390	0.1300	0.0350	21.2
Rabbit													
1	Normal	0.0904	0.0094	0.0304	0.0398	0.0506	56.0	0.9010	0.5737	0.1555	0.7292	0.1718	19.0
	1st injection	0.0474	0.0046	0.0151	0.0197	0.0277	58.4	0.4500	0.2870	0.0780	0.3650	0.0850	18.9
	2nd "	0.0242	0.0041	0.0085	0.0126	0.0116	47.9	0.2002	0.1403	0.0295	0.1698	0.0304	15.2
	3rd "	0.0185	0.0092	0.0061	0.0153	0.0032	17.3	0.1802	0.1413	0.0188	0.1601	0.0201	11.1
2	Normal	0.0700	0.0073	0.0236	0.0309	0.0391	55.8	0.6660	0.3000	0.1270	0.4270	0.2390	35.9
	1st injection	0.0201	0.0022	0.0070	0.0092	0.0109	54.2	0.1800	0.1168	0.0464	0.1182	0.0618	34.3
3	Normal	0.1140	0.0120	0.0401	0.0521	0.0619	45.7	1.1340	0.7632	0.2195	0.9827	0.1513	13.3
	1st injection	0.0380	0.0039	0.0128	0.0167	0.0213	56.0	0.3868	0.2608	0.0740	0.3348	0.0480	12.4
	2nd "	0.0282	0.0047	0.0096	0.0143	0.0139	49.3	0.2600	0.2015	0.0325	0.2340	0.0260	10.0
	3rd "	0.0370	0.0201	0.0122	0.0323	0.0047	12.6	0.3600	0.2888	0.0408	0.3296	0.0304	8.4
4	Normal	0.1135	0.0289	0.0305	0.0594	0.0541	47.6	1.1409	0.7856	0.1740	0.9596	0.1813	15.9
	1st injection	0.0224	0.0060	0.0054	0.0014	0.0110	49.0	0.2196	0.1380	0.0444	0.1824	0.0462	21.0
	2nd "	0.0242	0.0118	0.0070	0.0188	0.0054	22.3	0.2002	0.1478	0.0286	0.1764	0.0238	11.9
	3rd "	0.0242	0.0181	0.0066	0.0247	0.0005	—	0.2002	0.1563	0.0205	0.1768	0.0234	11.7

unchanged or slightly increased after the first injection of guanidine but diminished after the second and third doses.

Cybulski [1906], Haskins and Gerstenberger [1909] and Salvesen [1923] found a decreased retention of calcium in tetany, the increased output being both by urine and faeces. Cooke [1910] failed to obtain an increase of calcium either in the urine or faeces and maintained that tetany was produced by an altered salt equilibrium brought about by accumulation of acid. Greenwald [1929] although he upholds the low calcium theory of the causation of tetany, found with Hastings and Murray [1921] a retention of calcium. Several investigators have mentioned the possibility of acid substances being involved in the increased loss of lime. Thus Salvesen attributed the loss of lime to the high phosphate content of the blood. Table VI shows the close relationship between the excess excretion of total calcium and that of amino-acids. The excess amino-acid/excess calcium ratio in the parathyroidectomy series varied from 10.3 to 10.8 in all but one instance and in all but two of the guanidine series from 9.5 to 11.0. In the exceptions it will be noted that there was an actual increase in the retention of calcium and a reduction in the output of amino-acids. The other results which show such a close correlation, seem to

Table VI. *Calcium and amino-acid excretion.*

Cat	Period	Excess Ca over normal excretion in g.	Excess amino-acid over normal excretion in g.	Amino-acid Calcium
1	Latent	0.0245	0.25804	10.53
	Active	0.0099	0.10210	10.31
2	Latent	0.0220	0.23805	10.82
3	Latent	0.0220	0.23730	10.78
	Active	0.0230	0.23805	10.35
4	Latent	0.0004	0.00416	10.4
5	Latent	-0.0080 (retention)	-0.01052 (retention)	1.32
Rabbit				
1	1st injection	-0.0058	-0.0227	3.91
	2nd "	0.0020	0.0208	10.4
	3rd "	0.0071	0.0701	9.9
2	1st "	0.0031	0.0314	10.1
3	1st "	-0.0007	-0.01017	14.5
	2nd "	0.0014	0.01409	10.6
	3rd "	0.0154	0.14665	9.5
4	1st "	-0.0004	-0.00392	9.8
	2nd "	0.0061	0.06100	10.0
	3rd "	0.0120	0.13280	11.0

indicate that there is some etiological relationship between the excess production of amino-acids and the decreased retention of calcium. These findings lead one tentatively to suggest that the decalcification of the bones which has been shown radiologically to occur after parathyroidectomy [Erdheim, 1911] may be due to the formation of amino-acids in excessive amounts.

Phosphorus.

Greenwald [1922] found a decreased retention of phosphorus during the latent stage following parathyroidectomy and a marked increase during the active period. Recently Greenwald [1929] concluded that the only two constant changes following parathyroidectomy were a fall in serum-calcium and a retention of phosphorus and maintained that the phosphorus is precipitated in the tissues as calcium phosphate. The increase in blood-phosphorus he attributed to a breakdown of lipoids and proteins containing phosphorus. Esau and Stoland [1930] have elaborated this theory on the basis of the recent work carried out on the relationship of phosphocreatine to muscle metabolism.

The results in connection with phosphorus metabolism are given in Table V. They indicate that after parathyroidectomy there is but slight change in the retention of phosphorus. After injection of guanidine the percentage retention of phosphorus is diminished, the diminution becoming more marked after succeeding injections. Owing to the marked reduction in the intake it may be urged that the decrease in the percentage is a result not of abnormal metabolic processes but simply of the smaller amounts ingested. In rabbit No. 4, however, the intake of phosphorus was increased in the periods following the second and third injections and despite this the absolute amount of phosphorus retained was appreciably less. This lends support to the

view that there is an increased catabolism of phosphorus-containing substances as a result of guanidine poisoning.

In view of the diminished retention of calcium and the fact that four-fifths of the calcium of the body is united with phosphorus it seems at first glance strange that the phosphorus retention should not run parallel with that of calcium. It has to be remembered, however, that whereas practically the sole *dépôt* of calcium is bony tissue, considerable amounts of phosphorus are also found in combination with lipoids and nitrogenous substances.

On the basis of the results recorded here it seems possible to formulate a hypothesis as to the chemical pathogenesis of tetany produced either by parathyroidectomy or by injection of guanidine. The primary effect in both cases is to produce an abnormal protein catabolism resulting in the formation of some toxic amino-compound which immediately combines with an organic chlorine compound. Simultaneously there occurs an excessive catabolism of phosphorus-containing substances and formation of large amounts of amino-acids. The effect on calcium and phosphorus suggests that the excess amino-acid carries away calcium from the bone leaving phosphorus either to be excreted or to form a phosphocreatine compound. Whether the extra phosphocreatine formed in the body is the result of excessive guanidine formation following parathyroidectomy we have no means of deciding from the data presented here. It is certainly suggestive that injection of guanidine produces metabolic results bearing a striking resemblance to those following removal of the parathyroids.

There is not the same gradation in the results observed following guanidine injection as there is after parathyroidectomy. It must be remembered, however, that in the latter case the abnormality produced leads either to continuous production of some abnormal substance or to an equally continuous process of excessive protein breakdown. In guanidine poisoning under the conditions of the experiment there is but one massive injection of poison. If this dose is too great death is likely to ensue, whereas if the body is able to deal with it a return to normal is likely to follow provided a second injection is not given too quickly. The fact that chlorine is retained in such large amount after even a single injection of guanidine, and this despite the fact that there is comparatively little upset of nitrogen metabolism, suggests that guanidine is detoxicated by a chlorine compound. If the available chlorine is sufficient to detoxicate the guanidine there will be but little disturbance. This would explain the variability in the results recorded of guanidine injection. The immediate effect at any rate seems to depend not simply on the amount of guanidine injected but on the amount of available chlorine. The fact that succeeding doses of guanidine of the same amount as the first produce effects quite out of proportion to the first indicates that the amount of available chlorine progressively decreases.

The actual onset of active tetany, if this hypothesis be correct, does not occur until the amount of toxic substance exceeds the amount of available

chlorine. As already mentioned this would explain the conditions of so-called tetania chloropriva. Furthermore, the carrying away of the calcium by the excess amino-acids would account for the low serum-calcium. The rise in inorganic phosphorus which tends to occur could be explained by the extra production of acid-soluble phosphorus resulting from abnormal nucleoprotein catabolism.

SUMMARY.

Following parathyroidectomy or injection of guanidine there occur the following metabolic disturbances.

A. *Chlorine*. There is a marked retention of chlorine in the tissues. In the latent tetany stage there is an increase of volatile chlorine both in the blood and tissues while in the active period there is almost complete absence of volatile chlorine.

B. *Nitrogen*. There is an increased catabolism of tissue protein associated with a rise in the urinary output of total nitrogen, amino-acids and purine-nitrogen and a fall in creatinine and ammonia.

C. *Calcium*. The percentage retention is decreased as a result of relative excess in the urinary excretion. There is a correlation between the excess of calcium and amino-acids excreted.

D. *Phosphorus*. The retention is either slightly diminished or unchanged.

It is suggested (1) that the primary effect in both parathyroidectomy and guanidine poisoning is an abnormal breakdown of tissue proteins and that the changes in calcium, phosphorus and chlorine are secondary to the disturbance in nitrogen metabolism, and (2) that the appearance of active tetany is in part at any rate due to a relative deficiency of chlorine compared with some toxic amino-compound occurring in the course of protein breakdown.

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