LXXXIII. THE INFLUENCE OF SMALL QUANTITIES OF POTASSIUM IODIDE ON THE ASSIMILATION OF NITROGEN, PHOSPHORUS AND CALCIUM IN THE GROWING PIG.

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THE thyroid plays a significant part in the mechanism of growth and development, its secretion being "the most powerful stimulant of body metabolism known" [Sharpey-Schafer, 1924].

Baumann [1895] discovered that iodine is normally present in the thyroid gland and Kendall obtained from the gland a substance, thyroxin, in pure crystalline form which contains over 60 % of iodine and has been shown to possess most of the properties of thyroid extract [Kendall, 1919, 1, 2].

The notable work of Marine [1923] and his colleagues, on the beneficial use of iodine in the treatment of endemic goitre in the human subject is well known. Clinical investigators report pathological changes in the thyroid glands of children who had died in a "marasmic" condition and note the beneficial effects accruing from thyroid extract treatment [Simpson, 1910].

Examples of thyroid diseases occurring in domestic animals are given by Ennis Smith [1917] who describes the condition known as "hairless pig malady," and by Kalkus [1920] who gives an account of goitre and associated conditions occurring in horses, cattle, pigs and sheep in certain districts of America. Both these workers emphasise the value of potassium iodide as a therapeutic agent in the conditions they describe.

Numerous workers have dealt with the action of thyroid extract and of thyroxin but there is little experimental work which measures in a quantitative manner the effect of simple iodine compounds on metabolism. A summary of the experimental work on the action of iodine or iodides is given by Barbour [1924], who refers to work on the influence of iodides on basal metabolism, the results of which were negative, and to work by Christoni who states that iodides may increase the excretion of urea, total nitrogen, uric acid, purine bases and chlorides.

In recent years Orr and his co-workers have been carrying out an extensive study of the mineral requirements of animals. Special attention has been paid by Husband, Godden and Richards [1923] to the influence of certain oils on

the absorption and retention of nitrogen, calcium and phosphorus in growing pigs. Their results seem to indicate that cod-liver oil (which contains iodine) exercises a beneficial effect on the nitrogen as well as on the retention of calcium and phosphorus. Further unpublished data afford evidence that this beneficial effect on the nitrogen retention may be due, to some extent at least, to the iodine content of the cod-liver oil.

From the foregoing considerations it has been assumed that iodine is an essential constituent of every well-balanced diet, and it was decided to add small quantities of potassium iodide to normal cereal rations and observe the effect on the mineral metabolism of the growing animal with special reference to nitrogen, phosphorus and calcium.

EXPERIMENTAL.

Young male pigs from 2-4 months old were used. In each separate experiment the experimental and control pig were from the same litter and were comparable as regards weight and general condition. The methods, described by Husband, Godden and Richards [1923], for feeding the animals and for collection of excreta were followed throughout each experiment.

The urine and faeces were collected over 48-hour periods and duplicate analyses of nitrogen, phosphorus and calcium were made on each of those 2-day samples.

Four experiments were carried out. It was the aim to divide each into a "pre-period," feeding basal ration only, an "iodine-period" with basal ration plus potassium iodide, and a "post-period" during which the potassium iodide was withdrawn.

A control pig, on the basal ration only, was carried on simultaneously with each experimental pig, except in the case of Exp. 4. The average length of each period was 14 days.

Total nitrogen was determined by the Kjeldahl method; calcium by precipitation as oxalate and titration with $N/10$ $KMnO_4$; phosphorus by the Pemberton-Neumann method as described by Richards and Godden [1924].

Basal Ration.

The basal ration used for all pigs consisted of oatmeal, maize, blood-meal and either barley-meal (Exps. 1 and 2) or sharps (Exps. 3 and 4). The following figures show the average composition of the foodstuffs and the proportions in which they were used.

	Proportions	Average composition %		
		Total N	P ₂ O ₅	CaO
Oatmeal	10 parts	2.08	1.09	0.080
Maize	10 "	1.45	0.69	0.009
Barley-meal or	10 "	1.29	0.82	0.062
Sharps	10 "	2.50	1.72	0.077
Blood-meal	1 part	13.58	0.35	0.147

The above ration is deficient in calcium and it has been the experience here that growing pigs break down if fed on this ration alone. Therefore, in order to supply calcium adequate to the need of a growing pig, powdered chalk or a solution of calcium chloride, or both were added to the ration in the amounts shown along with the data for each separate experiment. Olive oil was added to assist regular defaecation, and, where calcium chloride was used, 10 g. sugar were given to mask the bitter taste. Distilled water was given to drink *ad lib*.

In every case the iodine was added as a solution of potassium iodide. The exact intake of nitrogen, phosphorus and calcium is given along with the tables of experimental data (Tables I and II).

Exp. 1. The amount of iodine added daily to the ration of the experimental pig was 0.19 g. It was given in the form of 25 cc. of a 1 % solution of KI.

Number of pig	Weight in kg.	
	At beginning of experiment	At end of experiment
798 experimental	16.8	25.9
801 control	15.7	25.3

Daily ration fed to each pig.

Basal ration	775 g.
CaCl ₂	25 cc. of 20 % solution $\equiv$ 1.62 g. CaO
CaCO ₃	6 g. $\equiv$ 3.26 g. CaO

10 cc. olive oil and 10 g. sugar.

During the post-period the experimental animal had a tendency to eat its faeces, thus making the figures for that period somewhat unreliable.

Exp. 2. This experiment was similar to the first with the exception that the olive oil and calcium chloride were withdrawn. The amount of iodine added daily to the ration of the experimental pig was the same as in Exp. 1.

Number of pig	Weight in kg.	
	At beginning of experiment	At end of experiment
867 experimental	32.4	50.0
866 control	34.1	50.4

Daily ration fed to each pig.

Basal ration	1550 g.
CaCO ₃	10 g. $\equiv$ 5.68 g. CaO

As is shown in Tables I and II, it was clear from the first two experiments that the addition of iodine had some effect on the nitrogen and phosphorus metabolism. The generally positive nature of the results obtained in these two experiments made it desirable to test what effect a smaller dose of potassium iodide would have and to ascertain if possible what might be the minimum dose with which an effect could be obtained.

Exp. 3. In this experiment the amount of iodine added daily to the ration of the experimental pig was very much reduced. The amount was 25 cc. of 0.26 % KI solution $\equiv$ 0.005 g. iodine.

Number of pig	Weight in kg.	
	At beginning of experiment	At end of experiment
1358 experimental	36.8	58.9
1359 control	32.8	54.3

Ration fed daily to each pig.

Basal ration	1550 g.
CaCl ₂	50 cc. solution $\equiv$ 3.248 g. CaO
10 cc. olive oil and 10 g. sugar	

Exp. 4. This was a continuation of Exp. 3 and consisted in carrying on the control pig as an "iodine" pig. After this pig had acted as a control as far as the end of the iodine-period in Exp. 3, 0.003 g. iodine (as KI) was added daily for 12 days. No increase in the balances was observed so it was decided to double that amount (0.006 g. iodine). This still failed to produce any effect but maintained the balances at the same level. Again at the end of 10 days 0.5 g. KI (0.38 g. iodine) was added daily and this higher dose caused an immediate rise in all balances. There was no control in this case.

The experimental data relating to these four experiments are summarised in Tables I and II. Table I gives the data for the "iodine" pigs and Table II those for the corresponding controls.

DISCUSSION OF RESULTS.

It seems advisable in discussing these results to group the four experiments together and lay emphasis on the aggregate effect over four experiments, rather than to take each one individually. In the following table the average retention of nitrogen, phosphorus and calcium in the pre-period has been subtracted from that in the iodine-period in each of the four experiments, a plus sign indicating an increased retention in the iodine-period and a minus sign indicating a fall in that period. For the control pigs a similar procedure has been adopted, the averages for a period corresponding to the pre-period in the experimental pigs being subtracted from the period corresponding to the iodine-period. The average increase or decrease in retention per pig in the iodine-period is shown at the foot of each column. In Exp. 4, the retention during the 0.006 g. iodine-period is subtracted from that during the 0.38 g. iodine-period.

From a study of Tables I, II and III it is apparent that on adding iodine an increase in the retention of nitrogen and phosphorus is the rule rather than the exception, whereas in the control pigs without iodine a fall in these balances is more general. The effect on the calcium balance is more difficult to gauge.

Table I. *Average daily excretions and balances in g.*¹

EXPERIMENTAL PIGS																	
Period	Days	Average daily weight faeces	Nitrogen (N)				Phosphorus (P ₂ O ₅)				Calcium (CaO)						
			Intake	Urine	Faeces	Total	Balance	Intake	Urine	Faeces	Total	Balance	Intake	Urine	Faeces	Total	Balance
Pig No. 798, Exp. 1																	
Pre-period	12	510	15-80	5-41	4-80	10-21	5-59	6-74	0-13	3-80	3-93	2-81	5-27	0-48	2-77	3-25	2-02
KI-period	12	425	15-80	5-57	4-17	9-74	6-06	6-74	0-12	4-02	4-14	2-60	5-27	0-87	2-06	2-93	2-34
Post-period	10	285	15-80	5-50	3-30	8-80	7-00	6-74	0-22	2-72	2-94	3-80	5-27	0-87	1-45	2-32	2-96
Pig No. 867, Exp. 2																	
Pre-period	14	631	31-77	11-30	8-91	20-21	11-56	13-85	1-51	7-50	9-01	4-84	6-50	0-16	3-38	3-54	2-96
KI-period	14	587	31-77	11-34	8-12	19-46	12-31	13-85	1-81	6-61	8-42	5-43	6-50	0-16	2-71	2-87	3-63
Post-period	14	585	31-77	12-24	8-08	20-32	11-45	13-85	2-02	6-84	8-86	4-99	6-50	0-19	2-97	3-16	3-34
Pig No. 1358, Exp. 3																	
Pre-period	16	580	35-87	14-45	8-61	23-06	12-81	17-83	5-04	10-42	15-46	2-37	4-18	0-10	3-04	3-14	1-04
KI-period	16	495	35-87	14-80	7-22	22-02	13-85	17-83	5-24	9-76	15-00	2-83	4-18	0-09	2-28	2-37	1-81
Post-period	12	463	35-87	16-40	6-82	23-22	12-65	17-83	5-51	9-47	14-98	2-85	4-18	0-10	2-00	2-10	2-08
Pig No. 1359, Exp. 4. (Control pig from Exp. 3 continued as an experimental pig.)																	
Q-003 I ₂ -period	12	600	35-87	15-51	7-47	22-98	12-89	17-83	5-17	10-73	15-90	1-93	4-18	0-11	2-09	2-20	1-98
Q-006 I ₂ -period	10	636	36-73	16-59	7-51	24-10	12-63	18-53	4-83	11-64	16-47	2-06	4-31	0-10	2-44	2-54	1-77
0-5 g. KI-period	10	620	36-73	16-48	6-73	23-21	13-52	18-53	4-36	10-09	14-45	4-08	4-31	0-09	2-14	2-23	2-08

¹ In averaging, the first 2 days of the KI-period are included in the pre-period and the first 2 days of the post-period are included in the iodine-period.

¹ In averaging, the first 2 days of the KI-period are included in the pre-period and the first 2 days of the post-period are included in the iodine-period.

Table II. *Average daily excretions and balances in g.*

CONTROL PIGS.																	
Period	Days	Average daily weight faeces	Nitrogen (N)			Phosphorus (P ₂ O ₅)			Calcium (CaO)								
			Intake	Urine	Faeces	Total	Balance	Intake	Urine	Faeces	Total	Balance					
			Pig No. 801, Exp. 1														
	12	391	15-80	5-71	4-51	10-22	5-58	6-74	0-09	3-81	3-90	2-84	5-27	0-66	2-34	3-00	2-27
Pre-period corresponding to KI-period	12	342	15-80	5-85	4-01	9-86	5-94	6-74	0-08	3-69	3-77	2-94	5-27	0-71	2-16	2-87	2-40
Post-period	10	353	15-80	6-02	3-90	9-92	5-88	6-74	0-09	4-07	4-16	2-58	5-27	0-69	1-84	2-53	2-74
			Pig No. 866, Exp. 2														
	14	600	31-77	11-07	8-58	19-65	12-12	13-85	1-58	7-40	8-98	4-87	6-50	0-23	3-46	3-69	2-81
Pre-period corresponding to KI-period	14	680	31-77	11-41	9-23	20-64	11-13	13-85	1-36	7-70	9-06	4-79	6-50	0-16	3-00	3-16	3-34
Post-period	14	650	31-77	11-72	9-03	20-75	11-02	13-85	1-43	7-67	9-10	4-75	6-50	0-14	2-50	2-64	3-86
			Pig No. 1359, Exp. 3														
	16	631	35-87	14-10	9-13	23-23	12-64	17-83	4-96	10-10	15-06	2-77	4-18	0-14	2-73	2-87	1-31
Pre-period corresponding to KI-period	16	622	35-87	15-21	8-05	23-26	12-61	17-83	5-18	10-62	15-80	2-03	4-18	0-12	2-19	2-31	1-87
Post-period ^a	12	600	35-87	15-51	7-47	22-98	12-89	17-83	5-17	10-73	15-90	1-93	4-18	0-11	2-09	2-20	1-98
^a This is also the 0-003 g. iodine-period in Exp. 4.																	

² This is also the 0-003 g. iodine-period in Exp. 4.

Table III. *The average increase or decrease (in g.) in retention of nitrogen, phosphorus and calcium during the iodine-period.*

Exp.	Experimental pigs.			Control pigs.		
	Nitrogen	P ₂ O ₅	CaO	Nitrogen	P ₂ O ₅	CaO
1	+0.47	-0.21	+0.32	+0.36	+0.10	+0.13
2	+0.75	+0.59	+0.67	-0.99	-0.08	+0.53
3	+1.04	+0.46	+0.77	-0.03	-0.74	+0.56
4	+0.89	+2.02	+0.31	No control		
Total	+3.15	+2.86	+2.07	-0.66	-0.72	+1.22
Average	+0.78	+0.71	+0.52	-0.22	-0.24	+0.41

Nitrogen Balance.

That the action of iodine on the nitrogen metabolism has an immediate rather than a gradual effect will be seen from a consideration of Table IV.

Here the figures for the nitrogen balances are given in greater detail. The retention over the last 8 days of the pre-period is contrasted with the retention over the first 8 days of the iodine-period, figures for separate 2-day analysis periods being shown. It is clear that the increase in retention takes place almost immediately on the introduction of iodine. In Exp. 4 the last 8 days of the 0.006 g. iodine-period are compared with the first 8 days of the 0.38 g. iodine-period.

Table IV. *Average daily retention of nitrogen in g.*

	Exp. no.			
	1	2	3	4
Pre-period, last 8 days	5.50	10.75	14.37	13.29
	5.26	11.77	13.37	13.24
	5.64	13.09	12.49	11.63
	5.47	10.46	10.94	12.39
Iodine-period, first 8 days	6.00	12.30	12.56	13.73
	6.16	13.04	14.57	13.47
	5.28	11.36	14.12	13.52
	6.60	12.21	13.94	12.81

NOTE. —→ indicates introduction of iodine.

Exps. 2 and 3 are the only ones in which a consideration of the post-period is legitimate. The post-period in Exp. 1 is not considered since during this period the animal had a tendency to eat its faeces thus rendering the results unreliable; and in Exp. 4 no post-period without iodine was studied.

It will be seen from Table I that, on the removal of iodine in Exps. 2 and 3, the average retention of nitrogen in the post-period fell back almost to the same figure as the average retention in the pre-period.

Undoubtedly one of the functions of the thyroid gland is intimately connected with the capacity of the animal for proper growth, though the mechanism of this process is as yet unknown. The increased retention of nitrogen after the addition of iodine, observed in all these experiments, is an index of the inducement of better growth probably due to the stimulation of the thyroid gland by the iodine. Schafer [1912] has shown that addition of small amounts of thyroid tissue to the normal dietary of growing rats causes an acceleration

of growth and retention of nitrogen in the body. Though this is an experiment not strictly comparable with the feeding of iodine *per se*, the similar results obtained for the nitrogen balances in the experiments described show that no doubt the action of the thyroid tissue is in part due to its iodine content. Hesse [1924] from some 30 metabolism experiments on dogs found that on feeding sodium iodide increased excretion of nitrogen in the urine could always be produced. From Table I it will be seen that our results, in the main, confirm this finding. Hesse concludes from this that body protein is broken down, and that analyses of urine showing increased elimination of nitrogen are sufficient evidence for stating that there is a general decrease in the retention of nitrogen in the body. This may be so in full-grown animals, but it is unfortunate that no analyses of faeces are given by Hesse for without them erroneous conclusions are apt to be drawn.

Many other workers refer to the growth-promoting effects of feeding alkali iodides or iodine in organic form; though these observations, made without actual measurement, are less precise.

Hunziker [1920] noted a marked difference in the height of children given iodine from that of children not exposed to its influence. Horses suffering from lymphangitis when fed on sea-weed, which is rich in iodine, put on weight remarkably and were restored to normal health [Adrian, 1918].

In a feeding experiment on calves carried out on the farm at this Institute it has been found that a group of 12 calves getting potassium iodide in their ration gained, in the same time, three and a half hundredweights more than a similar group which had no iodine.

In our experiments the periods are too short to admit of a comparison between rates of growth or increase in weight in one period over another, but it is significant that throughout the whole experiment the "iodine" pigs grew generally better than the controls with the exception of those in Exp. 1.

Table V shows the total increase in weight during the entire experiment. It will be seen that in two cases the "iodine" pigs put on an average of 1 kg. more than the controls in the same time.

Table V. *Total increase in weight (kg.) during each entire experiment.*

	Exp. no.		
	1	2	3
Experimental pigs	9.1	17.6	22.1
Control pigs	9.6	16.3	21.5

Phosphorus Balance.

Corresponding with the nitrogen figures there is an increase in the retention of phosphorus on the addition of iodine to the ration. This is not so marked as in the case of nitrogen, but that it is none the less definite is seen when one compares the phosphorus balances in the "iodine" pigs with those of the controls. Leaving out Exp. 4, where the rise in the phosphorus balance seems abnormally high, we find that in experimental pigs there is an average increase

in retention of 0.28 g. in the iodine-period over that in the pre-period, whereas, in the controls, with the exception of Exp. 1, for a corresponding period a decrease in retention took place. The average retention of phosphorus in the post-period, in Exp. 2, fell back to a figure comparable with that in the pre-period, whilst in Exp. 3 no such drop was apparent, the retention being maintained as in the iodine-period.

Calcium Balance.

In every case the calcium balance throughout the entire experiment was on the ascendant in both "iodine" and control animals, thus making any further increment, which might possibly be due to iodine, difficult to observe. On the average, however, as seen in Table III, the increased retention during the iodine-period in the experimental pigs was higher than the increase for a corresponding period in the controls.

Amount of Iodine required to give a Positive Result.

The daily amount of potassium iodide used in these experiments varied from 0.5–0.0039 g. (from 0.38–0.003 g. iodine). In Exps. 1 and 2 the amounts of actual iodine used were equivalent to 0.025 % of the ration, and in Exp. 3 to 0.00032 %. In Exp. 4 a dose equal to 0.00019 % of the food failed to produce an effect. This was doubled and fed for 10 days, but it was not until the percentage was raised to 0.025 g., as in Exps. 1 and 2, that an effect became apparent. Sufficient experiments using varying amounts have not been carried out to enable us to state definitely what is the least amount with which one can obtain an effect. The animals used in these experiments had not been fed with any iodine-rich food (such as fish-meal) before they were used for the present study and in considering the results it must be borne in mind that in some cases the iodine store in the thyroid gland might not be so high as in others.

Uncompleted studies on the iodine content of thyroid glands of pigs show marked variation in the amounts stored; and in the present experiments it is legitimate to assume that individual animals would react differently to different doses, those with a depleted initial store requiring only a minute dose to give an effect, whilst exceedingly healthy animals, such as the pig used in Exp. 4, seem to require a relatively large dose before any change becomes apparent. No toxic symptoms due to iodine were observable in any of the animals used.

These results point to the necessity for ensuring that a sufficiency of iodine is present in synthetic rations which are presumed to contain all the known essential constituents of food. This precaution, which apparently has not been taken in some experimental work published in recent years, is of special importance when cod-liver oil and green food are being used. The physiological effects of the unknown constituents of cod-liver oil are being widely investigated at the present time; and the experiments described in this paper seemed

desirable when one considers that this oil is relatively very rich in iodine, containing on an average 0.001 %. Weight for weight this is 1000 times more than is usually present in the commoner foodstuffs such as cereals where, as a rule, it is present only in traces [Forbes, 1916]. Green vegetables occupy an intermediate position between cod-liver oil and cereals as regards their iodine content, and Forbes concludes that they are the most important source of iodine in the human dietary. They contain about one-hundredth of the amount usually present in cod-liver oil, though Fellenberg [1923] estimates the iodine content of some green vegetables at more than a thousandth of that amount.

McCarrison [1920], in certain of his experiments on deficiency diseases, describes the effect of onions in restraining the tendency to thyroid hyperplasia in pigeons which were fed on a deficient diet. He states that this effect may have been due to the enrichment of the dietary in iodine which onions may have afforded, though he is not inclined to support that view. It is significant, however, that onions stand fairly high among vegetables in their iodine content [Forbes, 1916]. It is, of course, recognised that the well-known effects on nutrition of cod-liver oil and green food cannot be attributed entirely to iodine; but it is suggested that when these substances are added to iodine-free rations the possible effect of their iodine content should be considered.

SUMMARY.

1. Small amounts of iodine, as potassium iodide, added to the cereal rations used, led to an increased assimilation and retention of nitrogen and phosphorus in young growing pigs. Though the nitrogen and phosphorus retentions ran parallel to each other the effect of iodine was usually more marked in the case of nitrogen.

2. There was also some evidence of an increased retention of calcium, but this was less definite.

3. The amount of iodine required to obtain this result varies with individual animals, and probably depends on the type of diet fed previous to the experiment.

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