CLXXVI. THE PHYSIOLOGICAL RÔLE OF VITAMIN B.

PART V. THE RELATION OF INANITION TO VITAMIN B DEFICIENCY IN PIGEONS.

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Prefatory Note.

Throughout this paper vitamin B refers to the accessory food factors present in yeast. We have satisfied ourselves that pigeons fed on a synthetic diet of the type used throughout this work but supplemented with 4 % of yeast extract that has been heated with alkali for 4 hours to destroy the "anti-neuritic" factor behave exactly as do those which receive the unsupplemented ration. The presence of the treated yeast extract, providing amongst other substances the heat-stable factor [Hassan and Drummond, 1927], does not ameliorate the condition, or retard the decline or the onset of nervous symptoms, at any rate in the case of birds feeding voluntarily.

Introduction.

In previous communications [Drummond and Marrian, 1926; Kon and Drummond, 1927] of this series it has been pointed out that a large proportion of the abnormalities exhibited by animals deprived of vitamin B is due to the inanition that results from the failure of appetite rather than to any specific effect of the deficiency itself.

From the studies of the rat and of the pigeon it appeared that the lowered body temperature and metabolism, the loss of weight and atrophy of most tissues, and the hyperglycaemia could be so regarded, but it was not certain from these studies or the researches of earlier workers how intimately the nervous manifestations and the hypertrophy of the adrenal glands were related to starvation.

The investigation reported in this paper was carried out with the object of throwing light on these two points.

Experimental.

In the first experiment the pigeons were divided into four groups in such a manner that the average weight of each group was as nearly as possible the same. All were deprived of food with the exception that ample supplies of water were available. It must be remembered that simple starvation may be considered as one form of vitamin B deficiency. The birds in groups A and C served to differentiate between the effects of withholding food in presence and absence of vitamin B, in that the latter received every day 10 cc. of an aqueous 10 % solution of yeast extract (marmite) administered directly into the crop by a rubber tube.

In addition there were two other groups, B and D, similar to A and C except that each bird received daily from 100 to 200 cc. of water introduced directly into the crop in two equal doses every morning and evening.

These two groups were studied in order to investigate the claims of Chamberlain, Bloombergh and Kilbourne [1911], Chamberlain and Vedder [1911] and of Eijkman and van Hoogenhuyze [1916] to have produced the characteristic nervous symptoms of vitamin B deficiency in fowls and pigeons by "washing out" the birds with large volumes of water during the course of starvation.

In the second experiment three groups of pigeons were fed on a diet deficient in vitamin B. An artificial diet of the type used by Randoin and Simonnet [1924] was used. The diet was composed as follows:

Rice starch	66 %	Butter	4 %
Caseinogen	16 %	Paper pulp	2 %
Agar-agar	8 %	Salt mixture (McCollum)	4 %

The birds in group F were allowed to feed voluntarily on the deficient diet. Those of group G were forcibly fed with about 20 g. of the diet daily, whereas those of group H were forcibly fed with about 15 g. of the deficient diet and in addition were given daily 1 g. of yeast extract, in order to serve as a control against the diet and the possible ill effects of the forcible feeding. The diet could be readily introduced into the crop in a coarsely powdered form by pouring it down a wide bore glass tube and regulating the rate of flow with a thin glass rod.

All the birds were starved for 24 hours before the "initial weight" was recorded, in order to eliminate errors due to a loaded crop.

General behaviour of the starving birds.

Apart from a steady loss of body weight and an initial fall in body temperature the birds did not display any striking symptoms for the first few days. Later the feathers became ruffled and the birds seemed disinclined for movement of any sort, although they appeared to be quite strong when they desired to walk or fly. The final phase usually appeared with great suddenness and was characterised by rapid onset of muscular weakness and a sharp fall

in the body temperature, closely resembling the condition described in rats [Drummond and Marrian, 1926]. This dramatic collapse nearly always occurred in the very early morning hours, and we think it probable that nervous symptoms similar to those which we observed in the birds of all groups have escaped the attention of most investigators in the past because close observation of the animals during the whole 24 hours was not maintained. Perhaps the most characteristic behaviour of the birds in the pre-mortal phase of inanition, whether vitamin B extracts were given or not, was a slow dropping forward of the head followed by a step forward to readjust the balance of the body. This movement would go on rhythmically for several hours, interrupted sometimes by retrograde steps and in certain cases by more or less well-marked head retraction and cartwheel turning. To this last point we will again refer.

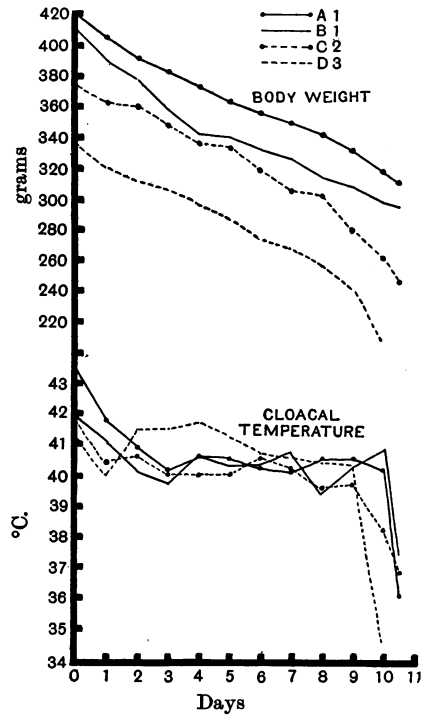

Fig. 1.

In Fig. 1 are drawn curves illustrating the weights and temperatures of birds in groups A–D. It will be seen that the loss of body weight is of the same order in all four groups, and that neither the rate of loss of body weight nor the course of the temperature curves is affected by the administration of amounts of yeast extract sufficient to supply the vitamin B requirements of the pigeon when feeding normally. These observations confirm in detail those that we have recorded for the rat.

General behaviour of the birds on the deficient diet.

For about the first week the birds in group F ate normally and the body weight was maintained. This period was followed by one showing progressively increasing fall in food intake, and a corresponding decrease in body weight. After about 30 days the birds usually showed the typical nervous symptoms of avian "beriberi," but in a few cases the pigeons failed to show any such symptoms and eventually died in a state of extreme weakness. In nearly all cases the birds by the time convulsions were observed had shown a loss of body weight of the same order as that shown by the starving birds, *i.e.* 30 to 40 % of the original weight.

The birds in group G behaved normally for about the first week, and appeared to be able to assimilate all the diet that was administered. Later, however, a small amount of the food was often vomited. A rough quantitative measure of the amount of rejected diet showed that at least 80 % of the diet fed was retained and digested. With no exception, the birds in this group developed violent convulsions within 20 days, at a period when the reduction of body weight was so slight as to be almost negligible.

In order to avoid errors in body weight due to a loaded crop, the food was removed quantitatively after the death of the bird, dried and the weight subtracted from the total weight of the bird before death.

Hypertrophy of the adrenal glands in inanition and vitamin B deficiency.

One of the most striking changes that have been observed in animals suffering from a deficiency of vitamin B is a well-marked hypertrophy of the adrenal glands [McCarrison, 1919, 1920; Kellaway, 1921; Findlay, 1921; Beznak, 1923; Lasowsky and Sumnitzki, 1926]. Changes of a similar order have also frequently been observed as a result of simple starvation [McCarrison, 1919; Vincent and Hollenberg, 1920, 1921; Findlay, 1921; Beznak, 1923]. It must, however, be borne in mind that complete deprivation of food also involves a deficiency of vitamin B, so that the fact that the adrenals hypertrophy as a result of starvation does not warrant the assumption that the enlargement is not specifically due to the deficiency of the accessory factors. Beznak [1923] indeed claims to have shown that no hypertrophy of the adrenal glands is exhibited by starving pigeons that are receiving ample supplies of vitamin B in the form of yeast extract.

In nearly all cases, the starving birds were killed during the final collapse which we have described previously. The vitamin B-deficient birds were killed immediately the first signs of convulsions appeared. Immediately after death the glands were dissected out and weighed. In a number of cases estimations of the adrenaline present were carried out by a modification of the Folin, Cannon and Denis method [Baker and Marrian, 1927]. Table I shows the results obtained from a number of normally fed pigeons.

Table I. *Normal pigeons starved 24 hours before experiment.*

Weight (g.)	Sex	Weight of adrenals (g.)	Weight of adrenals per kg. body weight	Adrenaline (mg.)	Adrenaline per 1 g. gland (mg.)	Adrenaline per kg. body weight (mg.)
372	♀	0·0195	0·0524	0·055	2·82	0·148
263	,,	0·0317	0·1206	0·106	3·34	0·403
331	,,	0·0196	0·0592	0·048	2·45	0·145
388	,,	0·0170	0·0438	0·045	2·65	0·116
334	,,	0·0191	0·0572	0·056	2·93	0·167
296	,,	0·0192	0·0648	0·044	2·29	0·148
326	,,	0·0270	0·0828	0·072	2·66	0·214
Average 330	—	0·0219	0·0687	0·061	2·73	0·191
320	♂	0·0244	0·0769	0·066	2·71	0·206
395	,,	0·0216	0·0547	0·067	3·08	0·169
309	,,	0·0270	0·0879	0·069	2·55	0·223
304	,,	0·0319	0·1049	—	—	—
386	,,	0·0211	0·0546	0·076	3·60	0·197
322	,,	0·0154	0·0478	0·052	3·37	0·161
344	,,	0·0302	0·0878	0·072	2·38	0·209
Average 340	—	0·0245	0·0735	0·067	2·95	0·194

It is evident from the figures in Table II that the adrenal gland is hypertrophied in the later stages of starvation and that this enlargement is not prevented by the administration of extracts rich in vitamin B. This is contrary to the conclusion reached by Beznak [1923], and we are unable to account for his results.

The birds in group F which were voluntarily feeding on the deficient diet also showed with one exception a definite but rather smaller hypertrophy (Table III). At first sight it might have appeared that this could be ascribed entirely to the complicating effects of inanition. However, the forcibly fed birds in group G, which only showed a very slight decrease in body weight, exhibited an enlargement of the glands of the same order as that shown by the birds in group F. The birds in group H showed no abnormalities of the adrenal glands. Both the weight of the glands and the adrenaline estimated were of the same order as for the normally fed pigeons.

There is considerable divergence of opinion as to whether the hypertrophy of the glands observed in vitamin B deficiency and starvation is medullary or cortical in origin. As a result of chemical determinations of the adrenaline content of the glands McCarrison [1920] is convinced that the hypertrophy is medullary. On the other hand Beznak [1923], adopting similar methods, could find no increase in the adrenaline content of the glands and concluded that the cortex alone hypertrophies. As a result of histological studies of the adrenals of pigeons fed on polished rice, Findlay [1921] and Lasowsky and Sumnitzki [1926] also concluded that the hypertrophy is cortical. Indeed Findlay claims to have shown that after curing a pigeon with yeast extract there is an immediate disappearance of a large amount of lipoid material from the cortex.

Our own results show that in all cases the total adrenaline present in the starving birds is considerably increased. In some instances this increase is proportional to the hypertrophy of the glands, from which it would seem

Table II.

Group	No. of bird	Sex	Initial weight (g.)	Final weight (g.)	Initial wt / Final wt	Weight of adrenals (g.)	Weight of adrenals per kg. body weight: Initial (g.)	Weight of adrenals per kg. body weight: Final (g.)	Total adrenaline present (mg.)	Adrenaline per 1 g. gland (mg.)	Adrenaline per kg. body weight: Initial (mg.)	Adrenaline per kg. body weight: Final (mg.)	Days starving	Remarks
A	38	♀	280	174	1·61	0·0388	0·1385	0·2229	—	—	—	—	11	Complete collapse
	35	,,	320	193	1·66	0·0374	0·1169	0·1938	0·108	2·88	0·337	0·559	12	
	2	,,	358	242	1·48	0·0275	0·0768	0·1136	—	—	—	—	10½	Quite strong and steady
	3	,,	330	215	1·54	0·0602	0·1824	0·2800	—	—	—	—	10½	Complete collapse. Slight head retraction just before death
	4	,,	325	228	1·42	0·0457	0·1407	0·2005	—	—	—	—	7½	Not very weak. Loss of equilibrium after swinging
	5	,,	295	191	1·54	0·0329	0·1115	0·1722	—	—	—	—	10	Cartwheels and head retraction
Average		♀	318	207	1·54	0·0404	0·1278	0·1972	—	—	—	—		
	33	♂	380	226	1·68	0·0530	0·1394	0·2345	0·117	2·21	0·308	0·518	13½	Very weak. Slight head retraction just before death
	1	,,	405	310	1·31	0·0274	0·0676	0·0884	—	—	—	—	10½	Quite strong and steady
	6	,,	328	210	1·56	0·0610	0·1859	0·2905	—	—	—	—	• 8½	Loss of equilibrium after swinging
Average		♂	371	249	1·52	0·0471	0·1310	0·2045	—	—	—	—		
B	3	♀	323	220	1·47	0·0193	0·0590	0·0880	—	—	—	—	10½	Quite strong and steady
	1	♂	390	295	1·32	0·0455	0·1166	0·1542	—	—	—	—	10½	Quite strong and steady
	2	,,	364	253	1·44	0·0360	0·0989	0·1423	—	—	—	—	9½	Very weak. Cartwheels and head retraction
	4	,,	330	227	1·45	0·0384	0·1164	0·1691	—	—	—	—	8	Complete collapse
	6	,,	275	199	1·38	0·0530	0·1927	0·2660	—	—	—	—	6	Loss of equilibrium after swinging and head retraction
Average		♂	340	244	1·39	0·0432	0·1312	0·1829	—	—	—	—		
C	42	♀	310	208	1·49	0·0320	0·1032	0·1490	0·100	3·12	0·322	0·480	11	Very weak
	43	,,	330	211	1·56	0·0451	0·1366	0·2157	0·096	2·13	0·291	0·455	17	Weak
	1	,,	315	205	1·54	0·0448	0·1422	0·2185	—	—	—	—	7½	Loss of equilibrium after swinging
	4	,,	352	247	1·43	0·0480	0·1362	0·1943	—	—	—	—	10½	Disturbed by swinging. Head retraction and convulsions just before death
	5	,,	323	229	1·41	0·0512	0·1585	0·2236	—	—	—	—	9½	Very weak. Head retraction for short periods
	6	,,	286	200	1·43	0·0442	0·1545	0·2210	—	—	—	—	6½	Loss of equilibrium after swinging
Average		♀	319	217	1·47	0·0442	0·1385	0·2037	0·098	2·63	0·307	0·467		
	41	♂	340	210	1·62	0·0692	0·2353	0·3295	0·107	1·84	0·315	0·509	13	Marked head retraction. A tendency to turn cartwheels
	40	,,	330	207	1·59	0·0436	0·1321	0·2106	0·104	2·39	0·315	0·502	14½	Very weak
	39	,,	360	213	1·69	0·0577	0·1603	0·2709	0·099	1·72	0·275	0·465	15	
	2	,,	363	246	1·47	0·0428	0·1179	0·1739	—	—	—	—	10½	Quite strong and steady
Average		♂	348	219	1·59	0·0533	0·1614	0·2462	0·103	1·88	0·302	0·492		
D	3	♀	320	213	1·50	0·0444	0·1387	0·2084	—	—	—	—	10	Very weak
	6	,,	291	210	1·39	0·0449	0·1543	0·2138	—	—	—	—	8	Very weak. Slight tendency to head retraction
Average		♀	306	212	1·44	0·0447	0·1465	0·2111	—	—	—	—		
	1	♂	375	274	1·36	0·0479	0·1277	0·1748	—	—	—	—	7½	Cartwheels and head retraction
	2	,,	351	276	1·27	0·1144	0·3259	0·4144	—	—	—	—	7	Very weak. Slight tendency to head retraction
	4	,,	341	242	1·41	0·0334	0·0983	0·1384	—	—	—	—	9	Very weak
	5	,,	290	209	1·39	0·0552	0·1903	0·2641	—	—	—	—	6	Very weak
Average		♂	339	250	1·36	0·0628	0·1856	0·2479	—	—	—	—		

reasonable to suppose that in such cases the hypertrophy is medullary. In other cases, however, low figures for the adrenaline per g. of the gland were obtained although the total adrenaline present was above normal. This may either represent an approach to exhaustion of the adrenaline reserves of the gland in the last stages of inanition, or else an additional hypertrophy of the cortex.

The results obtained on the forcibly fed pigeons are of considerable interest, since in every case the total adrenaline present was either normal or slightly low, and in every case the adrenaline per g. of gland was definitely low (Table III). Since all these birds were killed at the first sign of convulsive symptoms, and at a time when they were muscularly strong, it does not seem possible that an exhaustion of the adrenaline in the gland had occurred. A possible explanation of these results would be to suppose that in "beriberi" uncomplicated by the effects of inanition only the cortex undergoes hypertrophy, and that in starvation, and "beriberi" associated with starvation, the hypertrophy is mainly medullary, but no decision can be reached without further experiments.

Blood-sugar of pigeons during inanition.

It is a clearly established fact that pigeons showing typical symptoms of "beriberi" may often show a distinct hyperglycaemia [Funk and Schönborn, 1914; Funk, 1920; Randoin and Lelesz, 1925; Collazo, 1923]. Kon and Drummond [1927] carefully controlled a series of pigeons against the complicating factors of starvation by feeding a second group of birds with the same amounts of food as were being voluntarily consumed by those receiving the deficient diet, at the same time administering excess of vitamin B in the form of yeast extract. The blood-sugars of these two groups were identical and they concluded that the hyperglycaemia observed during vitamin B deficiency is wholly attributable to inanition.

Blood-sugar determinations carried out on samples removed from the wing vein on our own two groups of starving pigeons (A and C) tend to support this conclusion (Table IV) and clearly show that the feeding of yeast extract during starvation had no effect on the blood-sugar. Except in the last stages of inanition both groups show a slight but distinct hyperglycaemia compared with the control group of normally fed birds.

The normal control birds were starved for 24 hours previous to the determinations in order that the blood-sugar should fall to the resting level.

A series of estimations of blood-sugar made during the course of the experiment shows that the slight hyperglycaemia which appears after the first day or two of deprivation of food and which persists for several days is followed by a marked hypoglycaemia (Fig. 2). The fall in the concentration of blood-sugar occurs very suddenly and is contemporary with the fall of temperature which characterises the pre-mortal phase. This picture is similar in all respects to that we have described in the case of the rat [Drummond and Marrian, 1926].

Table III.

Group	No. of bird	Sex	Initial weight (g.)	Final weight (g.)	Initial wt / Final wt	Weight o adrenals (g.)	Weight of adrenals per kg. body weight: Initial (g.)	Weight of adrenals per kg. body weight: Final (g.)	Total adrenaline (mg.)	Adrenaline per 1 g. gland (mg.)	Adrenaline per kg. body weight: Initial (mg.)	Adrenaline per kg. body weight: Final (mg.)	No. of days on diet
F*	328	♀	303	208	1·45	0·0516	0·1703	0·2481	0·142	2·75	0·468	0·682	33
	329	♂	357	233	1·53	0·0414	0·1159	0·1776	0·093	2·25	0·261	0·399	26
	326	,,	349	250	1·39	0·0192	0·0550	0·0768	0·041	2·13	0·117	0·164	27
	39	,,	452	362	1·24	0·0446	0·0986	0·1232	0·075	1·68	0·166	0·207	29
	32	,,	387	286	1·35	0·0395	0·1020	0·1381	0·084	2·13	0·217	0·293	30
	46	,,	389	285	1·34	0·0434	0·1116	0·1523	0·139	3·20	0·357	0·488	34
Average		♂	387	283	1·37	0·0376	0·0972	0·1328	0·086	2·28	0·224	0·310	
G*	839	♀	301	245	1·23	0·0370	0·1229	0·1510	0·039	1·05	0·129	0·159	19
	3302	♂	411	406	1·01	0·0376	0·0915	0·0926	0·069	1·83	0·168	0·169	15
	718	,,	352	321	1·09	0·0546	0·1551	0·1701	0·072	1·32	0·204	0·224	13
	749	,,	394	390	1·01	0·0519	0·1317	0·1331	0·068	1·31	0·172	0·174	12
	25	,,	347	326	1·07	0·0400	0·1149	0·1227	0·038	0·95	0·109	0·117	16
Average		♂	376	361	1·05	0·0460	0·1233	0·1296	0·062	1·35	0·163	0·171	
H	994	♀	337	364	0·93	0·0284	0·0843	0·0780	0·062	2·18	0·184	0·170	17
	734	,,	332	357	0·93	0·0276	0·0831	0·0773	0·058	2·10	0·175	0·163	17
Average		♀	335	361	0·93	0·0280	0·0837	0·0777	0·060	2·14	0·180	0·167	
	872	♂	278	254	1·09	0·0260	0·0934	0·1024	0·070	2·69	0·252	0·275	17
	924	,,	317	323	0·98	0·0236	0·0744	0·0731	0·075	3·18	0·237	0·232	17
Average		♂	298	289	1·04	0·0248	0·0839	0·0878	0·073	2·94	0·245	0·254	

* All the pigeons in groups F and G showed typical convulsions.

We are inclined to attach importance to the fact that all birds showing head-retraction simulating "beriberi" convulsions were passing through this pre-mortal phase.

Table IV.

Normal. Blood-sugar %	Group A. Starving 4–9 days. Blood-sugar %		Group C. Starving 4–9 days. 1 g. yeast extract daily. Blood-sugar %	
0·174	A 1	0·174	C 1	0·206
0·176	A 2	0·202	C 2	0·160
0·186		0·210	C 3	0·242
0·190	A 3	0·224	C 4	0·234
0·178		0·242	C 5	0·186
0·191	A 4	0·214	C 6	0·236
0·171	A 5	0·186	C 39	0·209
0·183	A 6	0·210	C 40	0·202
—		0·226	—	
—	A 38	0·215	—	
—	A 33	0·202	—	
Average 0·181 %		0·209 %		0·209 %

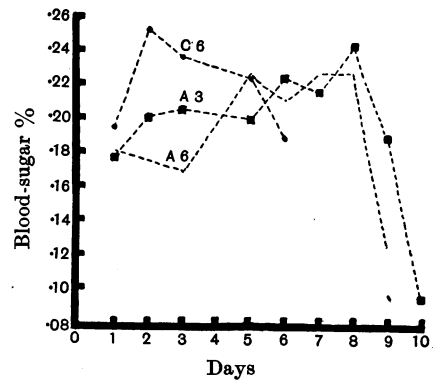

Fig. 2.

Head-retraction in pigeons during inanition.

Chamberlain, Bloombergh and Kilbourne [1911] and Chamberlain and Vedder [1911] reported that they were able to produce the typical nervous symptoms of "beriberi" in birds by "washing out" the tissues by administering large volumes of water during starvation. These results were confirmed by Eijkman and van Hoogenhuyze [1916] who showed that these symptoms could be cured by the administration of vitamin B notwithstanding starvation, and concluded that "polyneuritis" occurring as a result of feeding on a vitamin B-deficient diet cannot be caused by inanition.

It will be observed on referring to Table II that in each of the two groups A and B there were several cases of pigeons that had quite definite head-retraction. Pigeons A 5 and B 2 displayed extremely well-marked "polyneuritic" symptoms. In addition to showing a definite head-retraction, these birds turned "cartwheels"; their general appearance being indistinguishable

from that of those suffering from true vitamin B deficiency. In many other instances less marked but quite definite head-retraction was observed. By disturbing the equilibrium of all the birds these symptoms could be accentuated. It must be pointed out that these symptoms only occurred during the final pre-mortal phase, and that they were of considerably shorter duration than those observed in vitamin B deficiency.

The appearance of these typical "beriberi"-like symptoms in several of the birds in group A seems to indicate that flushing with water is an unnecessary procedure.

We were surprised to observe several cases of head-retraction in groups C and D which were receiving yeast extract daily. Pigeons C 4, C 5 and D 6, D 2 all showed slight but definite head-retraction for a short period before death, while C 41 and D 1 displayed more definite symptoms which were quite as well marked as any in groups A and B.

As these birds had been receiving yeast extract every day and had been given a dose within a few hours of the appearance of the convulsions, we have found it hard to reconcile our observations with those of Eijkman and van Hoogenhuyze that the convulsions exhibited by starving birds may be cured by administration of vitamin B[1].

Discussion.

Before we had carried out the experiments on the pigeons that received the food deficient in vitamin B forcibly we were convinced that the hypertrophy of the adrenals in ordinary vitamin B deficiency was due merely to inanition and was unrelated specifically to the absence of the vitamin. Obviously this view could be held no longer when enlarged glands were exhibited by the birds whose body weight had been more or less satisfactorily maintained by forcible administration of the food deficient in vitamin B. Moreover, the fact that the control birds, which received in addition to their ration of food a supplement providing an ample supply of vitamin B showed normal glands ruled out the possible explanation that hypertrophy might be caused by the actual process of forcible feeding.

As we have pointed out, our results could be explained on the rather improbable hypothesis that inanition produces medullary hypertrophy whilst deficiency of the factor B tends to cause enlargement of the cortical tissue.

We prefer to make no further comment at this stage of the enquiry on the results we have obtained. Further work is in progress which may throw light on the curious facts we have observed.

Regarding the appearance in the starving birds of convulsive seizures

[1] Dr R. R. Williams very kindly placed the manuscript of his paper [1927] in our hands whilst we were preparing the results of our work for publication. It is interesting that he noted that birds which exhibited nerve symptoms on diets containing ample supplies of vitamin B had lost from 30 to 40 % of their original body weight, a loss of the order of that shown by our starving birds at the time of onset of symptoms.

similar in general character to those exhibited by birds fed on diets deficient in vitamin B, it must be admitted that when the case of those which received a daily ration of yeast extract is considered the whole question becomes a much broader one than was originally raised by the experimental results of Chamberlain and his colleagues and Eijkman and van Hoogenhuyze.

In the first place we are not entirely satisfied that the symptoms shown by the birds "flushed" with water by Chamberlain were due to the washing out of vitamin B from the tissues as they suggested, because in our experience there was just as marked a tendency for the convulsions to occur in birds whose consumption of water was limited to the very small quantity they drank voluntarily. Secondly, we find it difficult to reconcile our observations with the statement of Eijkman and van Hoogenhuyze that they could cure "polyneuritis" in starving water-flushed birds with extracts of vitamin B.

We have described the onset of typical "beriberi" symptoms in starving pigeons which have been receiving daily an ample dose of vitamin B, and somewhat similar observations are recorded by Williams [1927] (see footnote to p. 1345).

The problem that faces us is not only to reconcile these conflicting views, but to provide an explanation of the curious fact that whereas pigeons feeding voluntarily on a ration deficient in vitamin B will usually show "beriberi" symptoms at about the 30th day, those forcibly fed on this diet do so at about the 16th day, and those deprived of food altogether at about the 9th.

We do not wish to commit ourselves to any definite opinion on these obviously difficult questions at present. For the time being we are, as we have already remarked, inclined to attach importance to the fact that whilst the nervous manifestations in the "beriberi" pigeon that is receiving food often appear at a time when the body temperature is not markedly subnormal and when the sugar concentration in the blood is usually slightly above the normal level, we have never observed the convulsions in starving birds except in the pre-mortal phase when the blood-sugar is very greatly reduced and the temperature is falling rapidly.

This difference raises in our minds the query whether the changes in the nervous system that are responsible for the convulsions may not be brought about by a variety of agents. This view is strengthened by reference to the work of Hess, which we have ourselves confirmed, and which showed that a condition closely simulating "beriberi" in pigeons can be produced by sublethal doses of cyanides. If this view be regarded as reasonable it attracts attention to the conception, many times expressed in the literature of experimental beriberi, that in vitamin B deficiency the underlying cause of the convulsions is a toxic substance, of which either the production is suppressed or the poisonous action is neutralised when vitamin B is administered. Dr Williams strikes the same note in the concluding paragraph of his discussion [1927, p. 1351].

In the investigations we are now reporting a considerable amount of

additional evidence was obtained from the histological examination of the peripheral nervous system of the pigeons. It all served to confirm the opinion previously expressed [Woollard, 1927] that the minor changes observed are attributable solely to inanition and are in no way directly related to vitamin B deficiency.

SUMMARY.

(1) The administration of extracts rich in vitamin B does not prevent the hypertrophy of the adrenal glands in pigeons that are deprived of food. This is contrary to the conclusion of Beznak.

(2) In most cases the adrenaline content of the glands of starving pigeons, whether receiving vitamin B or not, is increased proportionately to the hypertrophy. This tends to confirm the opinion of McCarrison that the hypertrophy is medullary.

(3) A slight but definite hyperglycaemia is observed in pigeons during most of the course of inanition. It is followed by a marked fall in the amount of blood-sugar coincident with the pre-mortal fall in body temperature. The administration of extracts rich in vitamin B has no effect on the blood-sugar levels of such birds.

(4) Nervous symptoms similar to those observed in pigeons suffering from vitamin B deficiency were observed in a number of starving birds. The incidence of such symptoms was not increased by the daily administration of large volumes of water.

These convulsions cannot be due to a vitamin B deficiency resulting from starvation since several cases were observed in birds receiving daily administration of vitamin B.

(5) The symptoms observed in starving birds always occurred during the period just before death when body temperature and blood-sugar were much reduced. This is in contrast to the established fact that nervous manifestations in pigeons nourished on rations deficient in vitamin B usually appear when the temperature is but slightly reduced and the blood-sugar level is, if anything, above normal.

(6) By forcibly feeding pigeons on larger quantities of a diet deficient in vitamin B than they would voluntarily consume, typical nervous symptoms of beriberi were produced in about 16 days, at a time when the loss of body weight was almost negligible.

(7) The adrenal glands of the forcibly fed pigeons were hypertrophied to a considerable extent, although no corresponding increase of the adrenaline content was observed. At present no satisfactory explanation of this is forthcoming.

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