CCIV. HEART BLOCK IN PIGEONS, CURATIVE FACTOR.

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A CONDITION of sinus bradycardia and heart block, which develops in pigeons fed on a diet of polished rice, was recently described by Carter and Drury [1929]. It was shown that the cardiac irregularity manifested itself at an earlier period after the commencement of rice feeding than head retraction, and, apart from loss of weight, was in fact one of the earliest indications of dietary deficiency in the pigeon. It was also observed that the irregularity was completely abolished by vagal section, or by atropine, and the suggestion was made that it was due to an over action of the vagus nerve.

The present work was undertaken with a view to elucidating the factor or factors, the absence of which from the diet of polished rice gives rise to heart block.

EXPERIMENTAL.

In order to have a standard for comparison, the heart rate has been recorded in a number of normal pigeons, using the stethoscope for this purpose. This method has been found to be satisfactory when compared with records obtained with the electrocardiograph.

Buchanan [1909] found the heart rate in 3 normal pigeons to be 141, 186, and 225 per minute respectively.

My own observations have confirmed the variability in the heart rate not only as between different individuals, but in the same bird examined under the same conditions from day to day. This is true even when disturbing factors such as excitement or slight muscular movement are excluded. Table I shows the heart rate of 7 normal birds, chosen at random, examined on different days.

Table I.

Bird	Heart rate per minute					6 days
	1	2	3	4	5	
1	232	232	264	200	182	—
2	260	288	240	288	280	—
3	240	264	212	216	212	212
4	224	216	224	220	198	212
5	216	188	208	212	208	170
6	160	166	158	192	188	188
7	212	184	182	186	192	—

In the experiments to be described only birds whose normal heart rates exceeded 170 per minute have been employed. When placed on a diet of polished rice, there is a progressive slowing of the heart rate (80–130 beats per minute), and in the majority of cases irregularity of rhythm is present at some stage. In some of these the irregularity is succeeded by a slow regular rhythm in which there is complete dissociation between auricle and ventricle, as can be demonstrated by the electrocardiograph. During exercise the irregularity disappears but during an ensuing period of rest it reappears, to be followed in some cases by a period of slow regular rhythm.

Exp. 1. It was thought that deficiencies in the protein or inorganic salt content of polished rice might be responsible for the development of heart block, and with a view to eliminating these possibilities a group of 4 birds was placed on a synthetic diet having the following composition:

Glaxo "casein" (vitamin B-free)	...	...	15 %
Rice starch	...	...	75
Fresh butter	...	...	5
McCollum's salt mixture	...	...	5

Regular daily doses of cod-liver oil were given in addition in order to ensure an adequate supply of fat-soluble vitamins. The powdered diet was mixed with water to give a granular consistency and was given freshly prepared each day. The birds readily ate the food supplied although in the later stages, as in the case of rice feeding, the appetite rapidly deteriorated. By the end of the 21st day all the birds had developed a well marked heart block, and death occurred in each case within 35 days. No head retraction was observed, but in one bird wing drop developed on the 21st day. Table II shows the data for one bird typical of the group.

Table II.

No. of days on diet	Weight g.	Heart rate	Remarks
0	412	240	Regular rhythm
5	387	216	"
10	363	180	Dropped beats
22	305	132	Irregular
25	290	136	"
31	267	132	"
33	—	—	Dead

It is evident from this experiment that any deficiency of protein, fat, or inorganic salts in a basal diet of polished rice is not related to the onset of heart block, since a diet complete in these respects does not prevent or delay its appearance. Moreover, the condition appears in its typical form even when an adequate supply of the fat-soluble vitamins is consumed.

A further series of experiments was undertaken with a view to ascertaining whether lack of one or more of the factors of the vitamin B complex played any part in the development of heart block. Both curative and protective tests were employed for this purpose. In some experiments birds were fed on

a polished rice diet until heart block was well established. The diet was then supplemented with daily doses of a fraction containing one or more vitamin factors, given by mouth or by injection. Observations of body weight and of the rhythm and frequency of the heart were recorded daily. In some experiments the protective test was employed, the birds being fed on a polished rice diet which was supplemented from the beginning of the experiment with test doses. The source of vitamin B_1 employed was the concentrate prepared according to the method of Kinnersley and Peters [1927]. Vitamin B_2 was given in the form of marmite heated at p_H 9.0 at 115° for 1 hour. In some experiments untreated marmite was used. This has been shown by Reader [1930] to contain a factor B_4 , which is not identical with the Williams-Waterman factor B_3 , in addition to vitamins B_1 and B_2 .

Effect of vitamin B_1 .

Exp. 2. A group of 7 birds was placed on a diet of polished rice, and each bird was given by mouth daily 0.1 cc. of the standard concentrate equivalent to 4 pigeon day doses of the antineuritic vitamin. The acid alcohol extract was heated for 2 minutes on a water-bath to remove the alcohol, carefully neutralised and diluted to 5 cc. before administration. The birds survived for varying periods up to 80 days and throughout the period of survival showed a gradual loss of weight. Within 13 days of the beginning of the experiment every bird showed typical heart block. Table III shows the data for this period of the experiment. In a number of cases prior to death the slow, irregular rhythm of the heart became very rapid and regular, indicating the sudden and final failure. The daily dose of the vitamin was at least twice the amount necessary to protect the pigeon against polyneuritis, but was without effect in protecting the bird against heart block.

Table III.

	Pigeon 64		Pigeon 58		Pigeon 69		Pigeon 66		Pigeon 110		Pigeon 115		Pigeon 122	
Day	Weight g.	Heart rate	Weight g.	Heart rate	Weight g.	Heart rate	Weight g.	Heart rate	Weight g.	Heart rate	Weight g.	Heart rate	Weight g.	Heart rate
1	382	204	390	224	440	220	432	204	390	200	452	174	380	208
7	350	144	360	124	410	160	400	170	370	162	430	170	364	156
13	326	98	342	110	364	132	384	100	332	90	396	128	312	128

The progressive fall of heart rate has become very marked by the 13th day. On the 7th day irregularity of rhythm was noted in 2 birds. By the end of the 13th day 5 birds exhibited marked irregularity.

In several birds which had been allowed to develop heart block the injection, intravenously or intramuscularly, of relatively enormous doses of antineuritic vitamin entirely failed to effect a cure. Table IV shows the absence of curative effect after the injection of 0.6 cc. of an antineuritic concentrate equivalent to 18 pigeon day doses repeated on three successive days.

In two birds which had developed heart block a cannula was tied into the jugular vein under urethane anaesthesia, and doses of vitamin B_1 , equivalent to 2 pigeon day doses and 6 pigeon day doses respectively, were injected, the

extract being washed into the vein with a small quantity of saline solution. Observations at short intervals over a period of 4 hours failed to reveal any improvement of the heart condition.

Table IV.

Date	Heart rate	Rhythm	Remarks
April 19. 11.12 a.m.	124	Regular	Bradycardia
6.5 p.m.	104	"	
" 20. 12.8 "	120	"	
12.15 "			Intramuscular injection 0.6 cc. vitamin B ₁
3.5 "	116	Dropped beats	Heart block
6.26 "	110	Regular	
" 21. 11.56 a.m.	116	"	
3.10 p.m.			Intramuscular injection 0.6 cc. vitamin B ₁
6.50 "	128	"	
" 22. 12.0 noon	128	"	
3.0 p.m.			Intramuscular injection 0.6 cc. vitamin B ₁
6.30 "	136	"	
" 23. 11.53 a.m.	134	"	
3.52 p.m.	124	Irregular	Heart block. No recovery

Effect of vitamins B₁ and B₂.

Exp. 4. A group of 11 birds was placed on a diet of polished rice which was supplemented by daily doses of vitamin B₂. The vitamin was supplied in the form of marmite suspended in water. This had been previously heated to a temperature of 115° for 1 hour at p_H 9.0, and was neutralised before administration. This treatment results in complete destruction of vitamin B₁ without serious destruction of vitamin B₂ [Reader, 1930].

Seven birds received a daily dose of 0.5 g. of the autoclaved marmite. Each bird received in addition a daily dose of cod-liver oil. The remaining 4 birds received daily 1.0 g. of the supplement, and cod-liver oil. By the end of the 13th day heart block was established in every bird.

Exp. 5. A group of 8 birds on a polished rice diet received daily 1.0 g. of marmite autoclaved as described above, together with 0.1 cc. standard vitamin B₁ concentrate, equivalent to 4 pigeon day doses of the antineuritic factor. Cod-liver oil was given in addition. Seven birds developed heart block at varying periods up to the 18th day; the remaining bird showed no cardiac abnormality up to the time of death, which occurred on the 49th day.

It is evident that vitamin B₂ is incapable of protecting the pigeon against the development of heart block when the bird is fed on a basal diet of polished rice, even when supplemented by the antineuritic factor. It may be noted that fall of body weight occurred under these conditions.

Effect of marmite.

Several experiments were performed in which untreated marmite was employed as a supplement to a polished rice diet. In one of these marmite was given by mouth in large doses (2.0–4.0 g. daily) over a period of a few days. In another experiment a smaller dose (1.5 g. daily) was given over a

period of many weeks. With daily doses exceeding 2.0 g. difficulty was experienced owing to the fact that in some cases part of the marmite was vomited, and in most cases diarrhoea was set up owing to its high salt content.

Exp. 6. A bird which had developed heart block on a diet of polished rice was given in addition 2.0 g. untreated marmite daily in 5.0 cc. water for 5 days. This dose of marmite is usually found to produce in an avitaminous pigeon an initial daily increase in weight of about 10 g. which diminishes steadily until after about 5 days the weight is again stationary. In the present case the heart condition failed to show any improvement. This is seen in Table V.

Table V.

Date	Heart rate	Rhythm	Remarks
April 18. 11.45 a.m.	176	Irregular	Heart block
5.55 p.m.	132	"	
" 19. 11.27 a.m.	128	Regular	
6.8 p.m.	120	"	2 g. marmite by mouth
" 20. 12.15 "	160	"	
6.42 "	140	"	2 g. marmite by mouth
" 21. 11.22 a.m.	216	Irregular	
6.32 p.m.	160	"	2 g. marmite by mouth
" 22. 12.40 "	176	"	
7.2 "	144	Regular	2 g. marmite by mouth
" 23. 12.40 "	160	"	
" 24. 12.40 "	156	Irregular	Heart block. No recovery, but some improvement in heart rate

Exp. 7. Six birds, after a preliminary period on polished rice, were given daily in addition 1.5 g. marmite by mouth, and 0.5 cc. cod-liver oil once weekly. This diet was continued for a period of 91 days, records of the heart condition and body weight being made at intervals of 2 or 3 days. Table VI summarises the data of this experiment in the case of 4 birds.

Table VI.

Day	Pigeon 3		Pigeon 47		Pigeon 76		Pigeon 152	
	Weight g.	Heart rate	Weight g.	Heart rate	Weight g.	Heart rate	Weight g.	Heart rate
0	250	104	318	120	322	92	228	100
17	268	108	346	148	322	120	264	188
30	302	188	346	184	347	168	272	164
64	300	142	352	196	364	180	292	232
85	318	152	380	232	379	184	316	304
Marmite discontinued. Whole wheat diet								
116	411	166	468	272	484	240	—	—

It will be seen that throughout the whole period of marmite feeding the recovery of body weight was gradual and incomplete, though it was noticeable that the general condition of the birds showed a very great improvement. Of the cases detailed in Table VI recovery of normal rhythm and frequency of the heart occurred in three birds within 60 days. On the other hand,

Pigeon 3 showed occasional periods of heart block up to the 85th day, and even on a whole wheat diet the heart did not recover its normal rate. The remaining two birds of this group died on the 22nd and 30th day respectively after commencing marmite feeding without showing any recovery from heart block. It is evident that marmite in doses of 1.5 g. has very little curative action on heart block even when administered for long periods.

Exp. 8. Three birds which had been fed for 2 weeks on whole wheat were placed on polished rice, supplemented by 1.5 g. marmite daily. This diet was continued for 36 days. The heart in all the birds remained normal both as regards rhythm and frequency throughout this period. Marmite appears to be effective in protecting the pigeon against the development of heart block though relatively inefficient as a curative agent.

Curative action of yeast.

Baker's yeast proved to be much more effective in the cure of heart block than marmite.

Exp. 9. Two birds were fed on polished rice for 18 days. Subsequently they received in addition daily doses of baker's yeast in amounts of 2 g. (dry weight 0.6 g.), and 6 g. (dry weight 2.0 g.) respectively. With the smaller supplement there was a definite response of the heart. The rate increased and phases of irregularity of rhythm were less frequent. The beneficial effect was, however, temporary and had more or less disappeared within 24 hours of giving the yeast. With the larger dose the curative action was more striking (Table VII).

Table VII.

Date	Heart rate	Weight g.	Remarks
Pigeon 1:			
May 1. 10.50 a.m.	104	—	Slow heart rate. Rhythm regular
„ 2. 12.17 p.m.	108	256	
12.30 „	—	—	2 g. yeast by mouth
3.0 „	108	—	No change in heart
„ 3. 12.15 „	232	—	Recovery
12.20 „	—	—	2 g. yeast by mouth
„ 4. 12.0 noon	128	262	Slow rate. Dropped beats.
12.5 p.m.	—	—	2 g. yeast by mouth
„ 5. 10.38 a.m.	180	—	Recovery
„ 6. 10.45 „	152	268	
3.15 p.m.	116	—	Relapse to slow rate with occasional irregularity
Pigeon 2:			
May 1. 11.15 a.m.	104	258	Slow heart rate. Rhythm regular
11.30 „	—	—	6 g. yeast by mouth
„ 2. 11.15 „	400	262	Recovery, heart rate very rapid
„ 4. 11.0 „	136	264	Relapse to slow rate
„ 4. 11.10 „	—	—	6 g. yeast by mouth
„ 5. 10.30 „	312	271	Recovery

Brewer's yeast was found to be as effective as baker's yeast in restoring normal function of the heart.

Exp. 10. A group of 6 pigeons, after a depletion period on polished rice varying from 11 to 25 days, were given subsequently daily doses of brewer's yeast of 6.0 g. (dry weight 2.1 g.). There was a rapid improvement in the heart, and normal function was restored in 1-6 days. In two of these the recovery took place within 24 hours. Table VIII gives the data for these birds.

Table VIII.

Days on rice		Bird 1	Bird 2	Bird 3	Bird 4	Bird 5	Bird 6
0	Heart rate	180	196	192	208	216	188
	Weight (g.)	432	445	410	411	394	448
5	Heart rate	160	184	156	160	176	196
	Weight (g.)	390	411	370	328	332	381
11	Heart rate	140*	144*	120*	—	—	184
	Weight (g.)	323	361	312	—	—	336
13	Heart rate	134	140	136	144	176	—
	Weight (g.)	350	370	345	291	268	—
14	Heart rate	184	144	152	136*	—	—
	Weight (g.)	341	365	342	284	—	—
15	Heart rate	—	164	170	190	—	—
	Weight (g.)	—	368	345	305	—	—
16	Heart rate	208	170	190	192	140	—
	Weight (g.)	342	370	342	287	253	—
17	Heart rate	—	—	—	—	124*	—
	Weight (g.)	—	—	—	—	248	—
18	Heart rate	200	—	196	176	174	—
	Weight (g.)	354	—	353	320	270	—
24	Heart rate	—	—	—	200	—	96
	Weight (g.)	—	—	—	363	—	275
25	Heart rate	198	188	196	—	232	80*
	Weight (g.)	379	392	375	—	297	267
26	Heart rate	—	—	—	—	—	152
	Weight (g.)	—	—	—	—	—	280
32	Heart rate	216	196	198	192	232	160
	Weight (g.)	371	391	381	372	321	327

* Doses: 6.0 g. brewer's yeast given daily thereafter.

Curative action of wheat.

Exp. 11. Following a preliminary period of 18 days on polished rice a group of pigeons was fed daily supplements of 2, 4, 10 and 20 g. of whole wheat. All birds exhibited definite heart block before administration of wheat. The birds receiving rations up to 10 g. daily of wheat showed no improvement of

Table IX.

Pigeon 1			Pigeon 2		
Date	Heart rate	Remarks	Date	Heart rate	Remarks
April 18	128	Irregular rhythm 12 g. wheat daily	April 21	112	Heart block
" 19	128		" 21	—	20 g. wheat daily
" 20	148		" 22	152	No recovery
" 21	144		" 23	192	Recovery
" 22	132		" 24	188	
" 23	160	Irregular rhythm	" 25	208	
" 24	140				
" 27	170	Definite improvement			
" 28	160				

the cardiac condition over a period of 6 days. A supplement of 12 g. daily of wheat produced some improvement by the end of 8 days. Birds fed daily doses of 20 g., constituting about 60 % of the daily food intake, showed complete recovery of the heart in about 3 days. Table IX shows the data for two of these birds.

Exp. 12. A group of 4 birds was placed on a diet of wheat which had been previously heated at 100° for 5 hours in a steamer. This treatment involved some destruction of the antineuritic factor, since three of the birds developed head retraction on the 60th, 65th and 76th day respectively. The birds received cod-liver oil at regular intervals. During the first 15 days there was only slight loss of weight, but later this loss became rapid. By the end of the 22nd day all birds had developed heart block. Table X shows the data for one of these birds.

The substance responsible for the curative effect on the heart which is present in wheat is therefore destroyed by this treatment.

Table X.

Days on steamed wheat	Weight g.	Heart rate	Remarks
0	520	240	Normal heart action
13	486	156	Irregular rhythm. Heart block
16	486	140	
22	480	88	
46	315	160	No recovery

Exp. 13. Powdered wheat was thoroughly extracted with ether five times. Three birds were placed on polished rice until heart block had become well established at the end of the 18th day. Two of the birds were then fed daily on the extracted wheat, which was moistened with water to give a granular consistency. There was an immediate rapid increase in weight together with a great improvement in the general condition of the birds. The heart became normal in rhythm and frequency within 3 days. The third bird was given daily doses of the dark yellow oil obtained on extraction of the original wheat, containing the fat-soluble vitamins A, D, and E. The bird continued to lose weight and developed head retraction on the 23rd day. No improvement occurred in the condition of the heart. It is evident that extraction with ether does not remove the curative substance from wheat (Table XI).

Table XI.

Pigeon 1				Pigeon 2			Pigeon 3			
Date	Weight g.	Heart rate	Remarks	Weight g.	Heart rate	Remarks	Date	Weight g.	Heart rate	Remarks
Nov. 22	308	92	Heart block	272	92	Heart block	Nov. 20	300	80	Heart block
„ 22	—	—	Ether-extracted wheat	—	—	Ether-extracted wheat	„ 20	—	—	1 cc. ethereal wheat extract daily
„ 25	351	172	Recovery	306	192	Recovery	„ 22	294	108	
„ 30	432	196		388	272		„ 25	—	148	
							„ 27	260	120	Head retraction. No improve- ment in heart action. Died

DISCUSSION.

The experiments described in this paper indicate that whole wheat and yeast contain a factor, or factors, essential for the normal metabolism and nutrition of the pigeon, the absence of which from polished rice leads to the development of heart block, among other disorders.

The evidence here presented would appear to indicate that the well-known deficiencies of the basal constituents of polished rice are not related to the development of heart block. A diet complete in respect of its content of protein, fat, carbohydrate and inorganic salts, even when supplemented by cod-liver oil, fails to protect the pigeon against this disorder.

It is clear also that the disorder of metabolism which manifests itself in heart block is not identical with that underlying the onset of polyneuritis. The administration of vitamin B₁ in a dose more than sufficient to clear up signs of polyneuritis, even when this is repeated daily for several weeks, is without effect on the heart. This is true also when vitamin B₂ is given in addition. The fat-soluble vitamins A, D and E, present in the ether-soluble material extracted from whole wheat, and in cod-liver oil and butter, are incapable of clearing up an established heart block, or of preventing its development.

Williams and Waterman [1928] described a factor present in wheat and in yeast which is essential for the normal nutrition of the pigeon but not for the rat. Until it has been found possible to obtain this factor free from the other constituents of the vitamin B complex it will be impossible to decide whether this is identical with the substance present in wheat and yeast on which the normal function of the heart depends. The similarity in the distribution of these substances and their thermolability may, however, be noted. Drury and Harris have recently reported a condition of sinus bradycardia without bundle block in rats fed on a vitamin B-free diet. In the extensive literature on the cardiac manifestations of human beri-beri there is no evidence of heart block even when electrocardiographic records have been taken of the heart [Aalsmeer and Wenkebach, 1929; Keefer, 1930].

In conclusion I wish to express my sincere thanks to Prof. Peters for his continued interest and advice and for the opportunity afforded me of making use of his antineuritic preparations. I am also indebted to Dr A. N. Drury for certain electrocardiographic records and for his assistance with some of the operations.

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