

THE THYMUS GLAND IN BERIBERI¹

By R. R. WILLIAMS and B. C. CROWELL

(From the Laboratory of Organic Chemistry and the Biological Laboratory,
Bureau of Science, Manila, P. I.)

Funk and Douglas² have shown that, among the changes which take place in pigeons suffering from polyneuritis as a result of an exclusive white-rice diet, a marked diminution in size occurs in the glands of internal secretion. Microscopically there is a marked degenerative change of the cells with higher functions. In most cases the marked atrophy is due to a disappearance of the cells, the framework of the gland alone remaining. The most marked change is in the disappearance of the thymus; microscopically no thymus could be seen in any of the beriberic pigeons examined.

Following these observations, a theory that a severe change in the glands of internal secretion occurs in beriberi has been proposed by Funk on the a priori grounds that the vitamins of the food have a close relationship to the glands of internal secretion.

Funk and Douglas omitted to mention the age of the pigeons used in their work, and it seems that this is a factor of supreme importance. In human beings the thymus gland normally undergoes involution after puberty and is also subject to so-called "accidental" involution in the course of both acute and chronic diseases. It is known that normal involution of the thymus occurs in the chicken, but we know of no evidence to prove that "accidental" involution occurs. To assume the occurrence of accidental involution in any individual case without a knowledge of the age of the animal seems erroneous.

In man, in so far as infantile beriberi is concerned, it is known that accidental involution of the thymus does not always occur, and one of us³ has drawn attention to the occurrence of enlarged thymus in some cases of infantile beriberi associated with status thymico-lymphaticus.

In adult beriberic cases at autopsy our records show that the

¹ Received for publication November 16, 1914.

² *Journ. Physiol.* (1914), 47, 475.

³ Crowell, B. C., *This Journal, Sec. B* (1913), 8, 77.

thymus gland is usually "small," but one case was found with a thymus gland weighing 28 grams in a child 13 years old (2584), and one weighing 12 grams in a case 18 years of age (2645).

In view of the extreme importance of the subject and the unknown factors involved, it was deemed advisable to record some observations made by us in the course of other work, as to the atrophy of the thymus in cases of beriberi.

In addition, it having been reported that the administration of thymus nucleic acid produced marked improvement in birds suffering from polyneuritis,⁴ a further study of thymus tissue seems advisable. Extracts of thymus tissue give the blue color reaction with phosphotungstic acid and alkali⁵ to a marked degree, making the existence of vitamins in the tissue most probable. It seemed possible that the thymus might constitute a store of vitamins in the body to an extent out of proportion to the size of the organ. Some color was lent to this view by the fact that young fowls, in which the thymus is normally large, are slightly more resistant to the onset of acute symptoms of polyneuritis than full-grown ones, and that only a much modified form of beriberi occurs in human infants. On the other hand, any effect the thymus tissue may have upon the onset of polyneuritis may be due to purine and pyrimidine bodies. The results which we have obtained with thymus tissue are preliminary, and more definite decision awaits the isolation of vitamins from the tissue.

AUTOPSY FINDINGS

Three supposedly normal pigeons were procured alive in the market and were killed at once. Their age was unknown. The thymus gland of one was relatively very small; another, small; and another, large. In 4 beriberic pigeons which had been fed on white rice the thymus had completely disappeared in every case, as reported by Funk and Douglas.

However, upon examining 16 chickens in which polyneuritis had developed as a result of a white rice diet, it was found that the thymus had completely disappeared in 7 cases, was considerably atrophied in 5 other cases, and apparently was slightly, if at all, altered in the remaining 4. The disappearance of the thymus, therefore, is not a necessary concomitant of polyneuritis in chickens, although it may occur frequently.

⁴ Funk, *Journ. Phys.* (1912), 45, 491.

⁵ Folin et al., *Journ. Biol. Chem.* (1912), 11, 265; (1912), 13, 363.

That this atrophy is not due simply to the age of the birds is shown by the fact that it took place in half-grown as well as in full-grown fowls.

No relationship could be established between the atrophy of the thymus and the length of the incubation period or the duration, severity, or specific symptoms of the disease. However, our study of the symptoms was not sufficiently minute to exclude the possibility of the existence of such relationship.

The thyroid was also examined in the 16 fowls mentioned, and results similar to those of Funk and Douglas were noted.

Four chickens which had been fed on milk and white rice for varying periods in the course of another experiment were examined after death. These chickens developed evidence of neuritis and were killed. Their sciatic nerves showed microscopic evidences of degeneration in Marchi preparations. The thymus of 1 fed with autoclaved milk and white rice was small. The thymus glands of the other 3 chickens which were fed on whole fresh milk and white rice were large.

The results of all of these examinations are given in Table I.

ADMINISTRATION OF THYMUS TISSUE

Two fowls were fed on white rice with an addition of 10 milligrams of dried sheep's thymus daily. It was estimated that the quantity of thymus tissue ingested during the normal period of incubation would be the same as that normally present in young fowls. This small amount of tissue noticeably retarded, but did not prevent, the onset of the disease.

Two fowls were fed on white rice with a daily dose of the alcoholic extract of 1.5 gram thymus gland. Here again the protection was not complete, although the loss in weight and the onset of the disease were retarded.

Two fowls were fed in the same manner, but with a daily dose of the extract of 3 grams of thymus with less protective results.

For comparison 2 fowls were fed on white rice and 2 milligrams of uracil daily. One contracted chicken cholera as shown by a blood smear. The other was apparently partially protected by the uracil.

Five fowls suffering from polyneuritis were treated with hydrolyzed extract of thymus gland in doses of from 5 to 50 grams of the gland. No cures were obtained.

Two human cases of beriberi were treated with small quantities of thymus, and a slight improvement was shown in each case. This improvement did not continue after the first few

TABLE I.—Autopsy findings in pigeons and chickens fed on milk and white rice.

Animal.	Neuritis.		Cause of death.	Diet and treatment.	Thymus, with microscopic control.
	Developed within— Days.	Duration. Days.			
Normal pigeon					
Do			Killed		Very small.
Do			do		Large.
Do			do	White rice only	Small and of involuting type.
Chicken	23	3	Polynearitis	do	None.
Do	27	2	do	do	Do.
Do	29	3	Choline poisoning	do	Do.
Do	33	36	Polynearitis	do	Do.
Do	33	36	do	do	Do.
Do	(?)	10	do	do	Normal (?) amount.
Do		40	do	do	Small.
Do		21	do	do	Fairly large.
Do	15	3	do	do	Very small.
Do	17	1	do	do	None.
Do	13	3	do	do	Very small.
Do	16	5	do	do	None.
Young chicken		30	Muscarine poisoning	White rice plus 2 doses nicotine acid	Moderate.
Do		21	do	do	Fairly large.
Chicken		9	Polynearitis	White rice plus 2 mg. nicotine acid daily	None.
Do	27	8	do	do	Do.
Do	30	3	do	do	Small.
Do	31	3	do	White rice plus 10 mg. thymus daily	Moderate.
Do	31	5	do	do	None.
Do	16	12	do	White rice plus 2 doses extract of thymus.	Do.
Do	28	9	do	White rice plus 5 mg. allantoin daily	Do.
Do	37	5	do	White rice plus 5 mg. uracil daily	Do.
Do	30	3	Killed	Autoclaved milk plus white rice.	Small.
Do	30	5	do	100 cc. fresh milk plus 40 grms. white rice.	Large.
Do	64	1	do	do	Do.
Do	90	1	do	do	Do.

days of treatment, and the patients at the close of the treatment still showed the characteristic symptoms of the disease, although in a less distressing form. Inasmuch as it was not practicable to place these cases in a hospital for accurate observation during treatment, the results are of more or less doubtful value, but are given here for what they may be worth. The dose used was 0.3 gram of dried sheep's thymus six times daily. No change was made in the diet of the patients.

CONCLUSIONS

The experimental evidence indicates that (1) there is no apparent fundamental connection between beriberi and the atrophy of the thymus; (2) when the latter occurs in birds fed on polished rice, as it frequently does, it is due to some other cause; (3) the thymus gland contains no extraordinary amount of vitamines, and the protective effect of administering the tissue is probably largely due to purine and pyrimidine derivatives; (4) the presence of a comparatively large amount of thymus gland in young animals does not appear to be responsible for their modified susceptibility to beriberi.

We feel that the experimental evidence presented by Funk and Douglas is far too meager to warrant any positive conclusions, much less forming any useful theory regarding the rôle of the vitamines in the body.

TABLE II.—*Thymus-feeding experiments.*

Fowl No.	Addition to daily diet of 50 grams of white rice.	Time re-quired to de-velop neu-ritis.	Length of life.	Loss in weight.	
				Total.	Daily.
		Days.	Days.	Per ct.	Per ct.
5	+ 10 mg. thymus	34	37	28.5	0.77
6	do	32	37	33.7	0.91
20	+ 1.5 gm. thymus gland	46	46	20.8	0.57
21	do	52	53	20	0.66
36	3 gm. thymus gland	25	29	31.9	1.57
38	do	31	35	27.5	1.25
8	2 mg. uracil	38	43	36.6	0.85
Average of 6 controls		17.5	21	26.9	1.41