

CXCV. THE VITAMIN B₂ COMPLEX

VIII. FURTHER NOTES ON "MONKEY PELLAGRA" AND ITS CURE WITH NICOTINIC ACID

By LESLIE JULIUS HARRIS

*From the Nutritional Laboratory, University of Cambridge, and
Medical Research Council*

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At present three diseases in experimental animals are known which are analogous with human pellagra. These are canine blacktongue [Goldberger *et al.* 1928], "monkey pellagra" (described in Part VII of this series [Harris, 1937, 1]) and pellagra in pigs [Birch *et al.* 1937]. The discovery by Elvehjem *et al.* [1937; 1938] that nicotinic acid (or amide) cured blacktongue made it desirable that confirmatory experiments should be carried out on the other species. Since tests on "monkey pellagra" were being continued in this laboratory at the time when the preliminary note of Elvehjem and his collaborators appeared, the effect of nicotinic acid was examined without delay. As is now well known, nicotinic acid has in fact been found effective in curing pellagra in pigs [Chick *et al.* 1938], and in human beings [e.g. Fouts *et al.* 1937; Smith *et al.* 1937; Spies *et al.* 1938]. So far as monkeys are concerned only a brief preliminary note about the observations with nicotinic acid has as yet appeared [Harris, 1937, 2]; the fuller experimental details are therefore set out in the present communication.

EXPERIMENTAL

Animals used. The monkeys used (see Fig. 1) varied considerably in size and age, several of them being young animals still rapidly growing, others being nearly full size. Two among the larger ones had been in continuous use since October 1935, first in the experiments reported in the earlier paper and then in later work undertaken in the interim. One of these two, no. 3, had been formerly a positive control receiving yeast (Fig. 1 in Part VII); the other, no. 6, had received in turn numerous curative supplements each followed by a period on the deficient diet (Fig. 4 in Part VII).

Basal diet. This was the same as that described in Part VII and consisted of a modification of Goldberger's blacktongue diet, supplemented with "radio-stoleum" (for vitamins A and D) and orange juice (for vitamin C and possibly other factors needed by monkeys). This basal diet has more recently been given baked in the form of a cake. In the present work extra vitamin B₁ (10 i.u. daily per kg. body weight) and lactoflavin (60 γ daily) were also provided, as an additional safeguard against the possibility of partial deficiencies of these factors.

Doses of nicotinic acid tested. Various graded allowances of nicotinic acid were tested at intervals, including 30 mg., 15 mg., 10 mg., 5 mg. and 2 mg. per day. The corresponding responses are best judged from the weight curves (Fig. 1).

Symptoms of deficiency. As was shown in the previous paper, monkeys kept on such a basal diet thrive provided that a supplement known to contain the P.-P. factor were allowed (e.g. Eli Lilly "343" liver extract powder, or yeast), or if whole wheat were substituted for the maize. Without such supplements the

animals fell ill with the characteristic symptoms of "monkey pellagra"—including loss of appetite, diarrhoea, vomiting, emaciation—and lost weight rapidly and died. No severe skin lesions were noted, but there was often considerable denuding of the fur. The same symptoms were seen again in the present work in those animals receiving no nicotinic acid, or during those periods when it had been withheld for a time. We have also in the later work been specially struck by the anaemic appearance of the animals, the skin becoming very pale in contrast to its normal pink to bluish appearance. Another symptom was the obvious nervousness or "jumpiness" of the deficient animals. Any detailed account of the pathology of the avitaminosis as seen in monkeys is, however, best deferred to a later paper, and for present purposes we may be content to judge the effectiveness of the nicotinic acid by the weight charts. The recovery of good spirits and of normal alertness, as well as the improvement in appearance and loss of symptoms brought about whenever a source of the anti-pellagra factor was given, were always found to be marked by a corresponding gain in the weight curves.

Results with nicotinic acid. Without exception, the administration of nicotinic acid, in doses of between 10 and 30 mg. per day, was followed by a dramatic cure. Even animals which seemed severely ill as a result of the deficiency quickly responded. Appetites were restored and growth was resumed with no apparent lag.

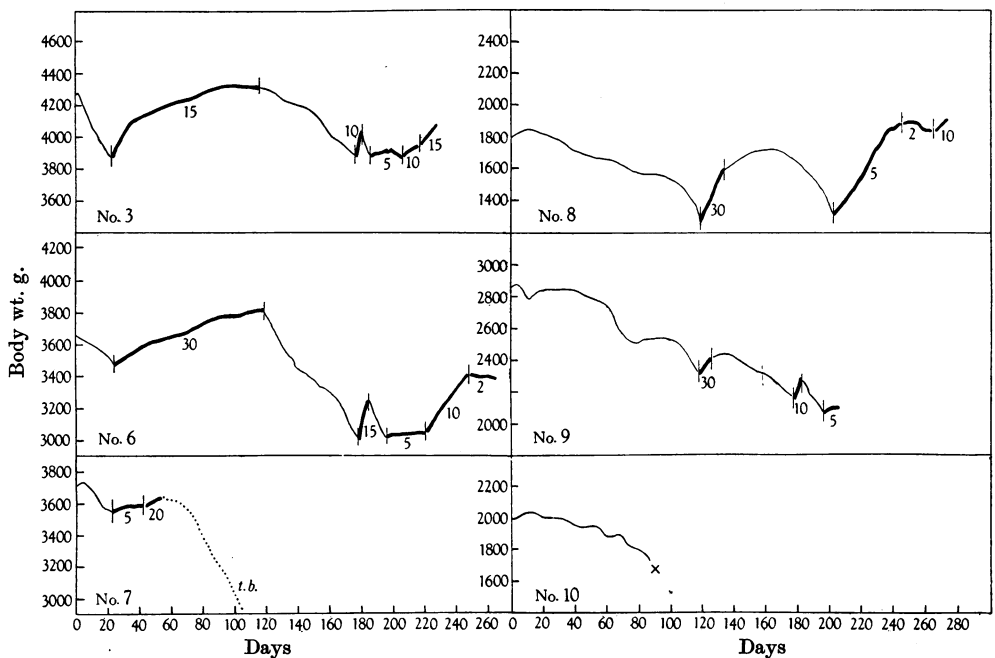


Fig. 1. Growth curves of monkeys. — Pellagra-producing diet alone. — Supplemented with nicotinic acid. The numbers under the curve refer to the dose of nicotinic acid given in mg. per day.

(The dotted line shows the rapid loss in weight of a monkey which on autopsy was found to have been suffering from tuberculosis.)

The effect on the weight curve and on the liveliness of the monkey was generally already clearly marked on the next occasion when it was weighed, sometimes as soon as 2-3 days after the start of the dosing.

Minimum curative dose. Judging from Fig. 1 a daily dose of about 2 mg. of nicotinic acid is not quite sufficient for rapid recovery in an animal weighing about 2 kg., but doses of 5 mg. and upward are adequate (animal no. 8, cf. also no. 9). For larger monkeys weighing about 4 kg., doses of 5 mg. seem barely enough, but doses of 10 mg., 15 mg. or 30 mg. suffice (monkeys nos. 3, 6 and 7).

These doses may be compared with those required by other species. Young pigs weighing on the average 30–50 lb. have been protected with doses of 25–60 mg. per day [Chick *et al.* 1938], and human beings have been cured with doses of between 60 and 1000 mg. per day [references as on p. 1479]. The minimum requirement for a dog is thought to be about 0.5–1.5 mg. per kg. per day [Elvehjem *et al.* 1938].

Experiments with nicotinamide and β -aminopyridine [cf. Subbarow *et al.* 1938] are still in progress.

SUMMARY

In tests which have been continued for a period of over eight months nicotinic acid has been found consistently effective in curing "monkey pellagra". The curative dose is of the order of 5 mg. for a monkey weighing about 2 kg., or 10 mg. for a monkey weighing 4 kg.

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