The day-to-day constancy of the increase in polymorphonuclear leucocytes and the decrease in lymphocytes in animals injected daily with adrenotropic hormore and the lack of any leucocyte changes in prolactin treated animals emphasize the significance of the adrenal cortex in the phenomena which are being reported.

The changes which have been observed in the leucocyte picture following adrenotropic hormone injection are essentially those which have been described for a variety of circumstances, some of which may now be directly attributed to adrenal cortical stimulation. For example, inanition stimulates adrenal cortical activity and produces a similar leucocyte picture.[7] It is not unlikely that other agents and experimental procedures which affect the adrenal cortex, and lymphoid tissue, are accompanied by these leucocyte changes. These possibilities are being subjected to experimental study.

The experiments summarized here will be published in detail elsewhere.

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THE NATURAL OCCURRENCE OF RIBOFLAVIN DEFICIENCY IN THE EYES OF DOGS[1]

OBSERVATION of malnourished persons for thirteen years has convinced me that the natural development of dietary deficiency diseases is slow; the onset insidious and difficult to recognize. Long before the nutritive failure can be diagnosed as pellagra, beriberi, scurvy, riboflavin deficiency or some one clear-cut syndrome, the afflicted persons have had months or years of ill health. Often they are unbelievably weak, listless and able to do little if any work. In the carefully selected case, the rapid improvement following intensive and persistent nutritive therapy leaves no doubt that the tissues function at a higher level soon after the missing substances are provided in sufficient amounts. Although the whole matter is very complex, comprehensive study over a period of several years has given us some valuable information. Since members of a family living together tend to eat a similar diet, we have adopted the policy of studying the entire family. That is to say, whenever a diagnosis of deficiency disease is made, we extend our studies to include the family. All members of the family are asked to report to the clinic for observation. Dietary surveys on the patient and on each member of his family are made by frequently visiting the homes. During such visits, we have observed that the family pets often appear emaciated and weak. Realizing that these animals usually subsist on scraps from the family table, it was natural for us to think that they, too, might have nutritional deficiencies. Examination of the dogs showed that black-tongue was not uncommon. (This spontaneous canine black-tongue responds as quickly to nicotinic acid as does pellagra in human beings.) Still more recently we have observed eye symptoms in dogs which appear similar to the ocular lesions of riboflavin deficiency in persons. These lesions respond as dramatically to riboflavin therapy as do those in human beings.

This communication is concerned primarily with such lesions in the eyes of four dogs belonging to families on which we were making laboratory and clinical studies. As these findings give an idea of the far-reaching effect of inadequate nutrition they seem worthy of separate publication at this time.

The dogs were emaciated, weak, sluggish, apathetic and held their heads much lower than the rest of their bodies. They refused food and all efforts to coax them to eat were without avail. Each dog had diarrhea characterized by frequently watery, foul-smelling stools. Saliva drooled continuously from their mouths. Examination of the mouth revealed the oral mucous membrane lesions characteristic of black-tongue.[2] While examining these animals lacrimation was observed. Even the light from a small flashlight in their eyes enlisted photophobia. In general the eyes appeared similar to those of persons with riboflavin deficiency which I have described,[3,4] and this suggested to me that these dogs had not only black-tongue, but riboflavin deficiency as well. A careful examination of their eyes showed pronounced injection of the sclerae and conjunctiva of both eyes. The vessels were unusually dilated and tortuous. There was a suggestion of rotary nystagmus. The animals did not keep their eyes still enough to carry out satisfactory slit lamp examinations. However, clinically the process appears similar to that in human beings, although in each of these dogs it was more extensive than I usually have seen in persons.

[7] C. F. Shukers and P. L. Day, *Jour. Nutrition*, 25: 511, 1943.

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[2] Garfield G. Duncan, "Diseases of Metabolism," 489 pp. Philadelphia: W. B. Saunders Company. 1942.

[3] Tom D. Spies, William B. Bean and William F. Ashe, *Annals of Int. Med.*, 12: 1830–1844, May, 1939.

[4] H. D. Kruse, V. P. Sydenstricker, W. H. Sebrell and H. M. Cleckley, *Public Health Reports*, 55: 157–169, January 26, 1940.

The photophobia was so severe and it was so difficult to keep the eyes still that satisfactory colored photographs were obtained only after numerous trials and errors.

A brief case report follows:

It is common knowledge that dogs with severe black-tongue are likely to die suddenly and since we have been able to relieve animals with spontaneous black-tongue,[2] we injected 150 mgs of nicotinic amide as soon as the dog had been carefully examined and illustrations made. Twenty hours later the dog showed remarkable improvement. He was obviously much stronger and ate the food offered. The fiery redness of the oral mucous membranes had faded considerably. Salivation had decreased and the diarrhea had stopped. The appearance of the eyes, however, remained unchanged. Next, 50 mgs riboflavin[5] were injected intravenously. Twenty-four hours later there was less lacrimation and photophobia. The injection had receded and there were fewer dilated and tortuous vessels in the conjunctiva and sclerae. Nystagmus was not present. Seventy-two hours later there was no detectable lacrimation or photophobia, and the redness and general increase in vascularity had subsided. Indeed, only very careful examination revealed "ghost vessels"—vessels which had been engorged but were now only faintly discernible.

SUMMARY

In four dogs, the diarrhea, increased salivation and mucous membrane lesions characteristic of black-tongue were relieved within 24 hours following the administration of 150 mgs nicotinic amide, whereas the lacrimation, photophobia and extreme injection of the eye vessels did not diminish. These severe eye lesions regressed greatly 24 hours after the injection of 50 mgs of riboflavin, and in 72 hours had disappeared.

The simultaneous occurrence of nicotinic acid and riboflavin deficiency in four dogs is evidence that such deficiencies occur as mixed diseases rather than as single entities.

These findings are further evidence of the universality of nutritional deficiencies, since they suggest that deficiency diseases among the pets of families with deficiency diseases are not uncommon. In at least one instance the finding of nutritional deficiencies in a dog eating scraps from the family table led to a better understanding of the ill health of the family, none of whom had diagnostic lesions of deficiency disease at the time, although they all complained of weakness, nervousness, irritability and loss of appetite—the vague and ill-defined symptoms characteristic of deficiency diseases in the early stages.

TOM D. SPIES

SCIENTIFIC APPARATUS AND LABORATORY METHODS

IDENTITY OF A LETHAL AGENT IN BROTH FILTRATES OF HEMOLYTIC STREPTOCOCCI WITH ERYTHROGENIC TOXIN[1]

THE similarity of a recently described lethal agent produced in broth cultures by hemolytic streptococci (Lancefield Group A)[2] to erythrogenic toxin raises the question of their differentiation.

Marked differences in heat stability indicate the existence of at least two kinds of hemolytic streptococcus toxin: the heat stabile erythrogenic and the heat labile hemolytic toxins. The resistance of eyrthrogenic toxin to comparatively high temperatures for considerable periods of time is well established.[3, 4] Since the lethal agent described, which was resistant to temperatures which do not completely inactivate erythrogenic toxin, and was lethal for mice, the effect of intravenous injection of heated and unheated erythrogenic toxin in mice was studied.

The toxins used were unpurified filtrates. Skin test doses per milliliter were determined by toxin-antitoxin flocculation. Table 1 summarizes the results obtained in mice by the intravenous injection of unheated

TABLE 1

DETERMINATION OF M. L. D. OF EROTHROGENIC TOXIN: INTRAVENOUS INJECTION IN MICE

Toxin	Dose (ml)	Skin test doses ×100	Result
Streptococcus NY 5 (Type 10)	1.0	300	+
	0.5	150	+
	0.25	75	−
Streptococcus BFO (Type 2)	1.0	300	+
	0.5	150	+
	0.25	75	−

(+) = death within 10 min.
(−) = no reaction.
Undiluted toxin contained approximately 2,000,000 skin test doses per ml. Toxins diluted 1:66 contain approximately 30,000 skin test doses per ml.
Mice 20–25 g in weight used.

toxins. Table 2 summarizes the results obtained with heated toxins and toxin-antitoxin mixtures. Toxin-antitoxin neutralization with heated and unheated toxins was checked by the intracutaneous rabbit test described by Fraser and Plummer.[5]

[5] A special concentrated product sent to me for experimental trial by Hoffmann-La Roche, Inc.

[1] From the Department of Preventive Medicine, Harvard Medical School and House of the Good Samaritan, Boston, Mass.

[2] T. N. Harris, *Jour. Bact.*, 43: 739, 1942.

[3] H. J. Parish and C. C. Okell, *Jour. Path. and Bact.*, 33: 527, 1930.

[4] G. A. H. Buttle and A. S. R. Lowdon, *Jour. Path. and Bact.*, 41: 107, 1935.

[5] F. H. Fraser and H. Plummer, *Brit. Jour. Exp. Path.*, 11: 291, 1930.