normal blood, a reduction in toxicity invariably takes place. The reduction, however, is only occasionally sufficient to prevent completely the anaphylactic response in subsequent tests with anaphylactic lungs. It is never as complete as in perfusions with anaphylactic blood mixtures.

The detoxicating action of the anaphylactic liver is, therefore due to a functional cooperation between the sensitized fixed hepatic cells and certain circulating normal and anaphylactic blood elements.

Chemical Changes.—Parallel precipitin titrations of perfusion fluids, before and after repeated passage through the anaphylactic liver show that there is no appreciable change in the amount of the foreign protein in the perfusion fluid as a result of the liver perfusions.⁴

The loss of the toxicity of the perfusion fluid is, therefore, not due to a removal or destruction of the foreign protein by the fixed hepatic cells.

On repeated passage through the anaphylactic liver, the perfusion fluid not only loses its power to produce the anaphylactic pulmonary reaction, but acquires a new power, that of causing an unusual relaxation or loss of tone in the pulmonary tissues. The lungs tested with the perfused fluid collapse more promptly and completely than normal. The edges of the lobes curl over, giving a wilted or flabby appearance on expiration. There is also a loss of the occasional power of the perfusion fluid to cause vasoconstriction.

The detoxicating action of the anaphylactic liver is, therefore, accompanied by and may possibly be due to an explosive formation or liberation of vasodilator and bronchodilator substances by the liver.

This finding is in harmony with analyses of the anaphylactic reaction in the dog.⁵ The pronounced fall of blood pressure, which is the essential feature of the acute anaphylactic shock in the dog, is not due to a direct action of the foreign protein on the sensitized blood vessels, but is an indirect phenomenon, due to the explosive formation or liberation of vasodilator substances by the liver.

CONCLUSIONS

The agreement between the foregoing findings would suggest that the explosive formation or liberation of vasodilator and bronchodilator substances by the sensitized liver is an essential feature of the acute anaphylactic reaction in all animals.

The demonstration of a functional cooperation between the sensitized hepatic cells and certain circulating blood elements, in the detoxication of foreign proteins, calls attention to the possibility of similar cooperations being operative in other antitoxic actions.

ABSTRACT OF DISCUSSION

DR. A. A. EGGSTEIN, Nashville, Tenn.: Will the foreign protein anaphylactic blood mixture, after having been perfused through the lung, cause the immobility of lungs of other sensitized guinea-pigs, or is the liver the chief organ in the detoxicating effect on the mixture? Will anaphylatoxin, proteases, and other toxic proteins have an immobilizing effect on the lung of a normal guinea-pig?

4. W. H. Manwaring, Yoshio Kusama and Harold E. Crowe (Jour. Immunol., 1917, 3) give data.

5. Manwaring, W. H.: Ztschr. f. Immunitätsforsch. u. exper. Therap., 1910, 8, 2. The dogs here studied were adult street dogs, sensitized by a single subcutaneous injection with from 5 c.c. to 25 c.c. horse serum; kept in outdoor kennels, at winter temperature (London), and tested at the end of from fifteen to thirty days. It is, of course, possible that additional factors may be operative in more highly sensitized young dogs or puppies.

DR. W. L. MCFARLAND, New York: If my memory is not false I think that something along similar lines was said, so far as the liver is concerned, at a meeting before the Serologic Society several years ago. So far as the action of the liver in anaphylaxis is concerned, I have had no personal experience; but in connection with immunity and the formation of antibodies, at the Institute in Copenhagen six or seven years ago we injected a number of rabbits and goats in branches of the mesenteric vein for the production of agglutinin and found that there was practically no difference in the amount produced or in the rapidity of the production. By that method the liver seemed to have no influence.

DR. W. H. MANWARING, Stanford University, Calif.: There are a number of observations in the literature that point to the liver as having a marked detoxicating function in the acute anaphylactic reaction. Our studies have shown that this antianaphylactic action is not merely an expression of normal hepatic functions, but is largely due to a new, acquired liver function, developed as a result of the process of protein sensitization. To what extent the other tissues of the body share in this antianaphylactic function is a phase of the problem on which we are at present working.

Tests with protein split products give inconclusive results, due to the fact that such a large variety of foreign substances is capable of causing reactions in the isolated guinea-pig lungs.

FAMILIAL HEAD NYSTAGMUS IN FOUR GENERATIONS ASSOCIATED WITH OCULAR NYSTAGMUS*

N. S. YAWGER, M.D.

PHILADELPHIA

Combined nystagmus of the head and eyes, persisting during life and reappearing in consecutive generations, must be exceedingly rare, since we seldom find mention of this disorder.

The family reported in this article is of Russian Jewish nationality, and at least four generations of the family have shown the affliction, members of three of which I have examined. The features of these cases are the persistence of the associated nystagmus in the stock and throughout the lives of the individual members, together with certain other nervous manifestations, notably, stammering. Both sexes had the combined nystagmus and both transmitted it to their children.

FIRST GENERATION

From the fact that two brothers exhibited the condition, it is possible that other instances of nystagmus preceded them. Concerning one brother, we have no additional information. The other died at 86 years, and notwithstanding his disease is said to have had good vision. His descendants I have traced.

SECOND GENERATION

There were eight children, three sons and five daughters. Most of them died in early life, and I have been unable to gather any clinical data respecting them. One daughter who had nystagmus lived to be 80 years old. Another daughter did not have the disorder, although she transmitted it to her two sons, and it is interesting to note that these children were by different husbands. This Russian peasant woman came to America when she was 60 years old. She is still

* From the Department of Neurology, University of Pennsylvania, School of Medicine.

* Read before the Section on Nervous and Mental Diseases at the Sixty-Eighth Annual Session of the American Medical Association, New York, June, 1917.

active although now 78, and has given me the details regarding the family history.

THIRD GENERATION

It is in this period that the afflicted persons became available for study. Of three children, the daughter is normal and has no family, while the two sons, who are half brothers, exhibit the combined nystagmus. The elder patient, aged 48, is distinctly neuropathic; as a child he stammered badly, and eight years ago he had an attack of facial paralysis. He has been nystagmic from infancy, but during adult life the manifestations have been less apparent. The patient is not conscious of the head shaking, although the phenomenon often recurs several times a day. Suddenly, and usually during moments of abstraction, the head undergoes a series of horizontal, coordinated movements, consisting of five or six oscillations, of considerable amplitude and with an approximate frequency of twenty per minute.

No opportunity has been afforded to observe the eyes at the time of the head movements. The irises are brown. The ocular tremor has seldom been spontaneous since childhood, but it may be brought out by any extreme movement of the eyes. The oscillations are horizontal, the range is greatest when looking toward the left, and the speed, though irregular, is about 160 per minute. He has eight children who shall be referred to later.

The younger brother, aged 40, has exhibited nystagmus of the eyes from birth and of the head for the past five years. He is a tailor, enjoys excellent health, and has good personal habits except for incessant smoking. He is slightly dwarfish, his neck and thorax being disproportionately short. Though not subjectively aware of his head movements, he has been told that they occur many times a day. When looking in a mirror and with his attention directed toward the phenomenon, it is never manifested. The oscillations, which appear in series, are usually made up of ten or twelve individual movements; they are always horizontal, and impress the observer as a repeated sign of negation. While of less amplitude, the individual movements are more rapid, and the series recurs with greater frequency than do those of his half-brother. The speed is about 120 per minute.

Although he labors long hours at exacting work, he has not yet worn glasses. The irises are brown. An almost constant unsteadiness of the eyes is seen, and this is intensified by all extreme ocular movements; but the direction is invariably horizontal. The rate of movement is about 200 per minute.

His head nystagmus, though embarrassing, is not without its humorous side, and in childhood afforded much amusement to the schoolchildren. A customer entered his tailor shop to order clothes, and just then the dissent spasm occurred. The customer in surprise asked, "You do not wish to sell me again?" On another occasion, a collector called and, observing the persisting sign of negation, exclaimed, "You say no! You won't pay?"

FOURTH GENERATION

In the family of the younger brother there are two sons and one daughter. The older son, aged 16, shows no stigmata and has the mental alertness not uncommon to the Jewish race. The other children, who are twins, are undersized, rather delicate, and the boy is of slightly lowered mentality. The sister, aged 10, alone shows nystagmus of the head and eyes; the manifesta-

tations in the eyes date from birth, and those of the head began a few months later. The head movements are not so uniformly horizontal as are those of her father and half-uncle. Her eye movements, which are horizontal, are irregular both in time and in amplitude; this ocular nystagmus is usually present, and has a speed at times of as much as 200 per minute.

In the family of the elder brother there are eight children, three of whom stammer the same as their father; but one appears to have acquired the habit through imitation. Another child, a daughter, also stammered during the period of a nervous breakdown of several weeks' duration. None of the children show spontaneous nystagmus of the head or eyes, but in one daughter extreme excursion of the eyes in any direction causes a horizontal nystagmus.

THE NATURE OF NYSTAGMUS

The term "nystagmus" is here extended beyond its usual application. Literally, it means to nod; and we observe in ophthalmology that the "nod" may be in different directions, giving us the various forms of nystagmus.

Nystagmus may be said to be involuntary, coordinated and rhythmical movements, of frequent occurrence and resulting from alternate contractions in opposing muscles. The term appears equally applicable to certain head movements, and occasionally it has been so used.

In describing nystagmus, Gowers¹ cites an interesting case; he writes:

Very rarely there is a slight movement of the head, corresponding to that of the eyes in direction, or in the opposite direction of that of the eyes. In a case lately under my care, with symptoms of cerebellar tumor and cerebellar nystagmus, the pharynx and the larynx were the seat of similar movement; that of the pharynx as horizontal, toward the median line; in the larynx there was a similar lateral movement of the arytenoid cartilages. The rate of movement was the same as in the ocular muscles, 180 per minute.

Nystagmus extending beyond the eyeballs was described by Popper,² and still later by Pick, who designated the condition accompanying the eye nystagmus as lid nystagmus. The latter was obtained with both the lateral and vertical movements of the eyeballs. It exceeded the ocular nystagmus when the patient looked to the right or to the left. Even head nystagmus was observed by Popper in a case of multiple sclerosis. The phenomenon of lid nystagmus as explained by Pick was that of diffusion of the disturbance causing ocular nystagmus, to the nucleus of the levator palpebrae superioris.

Conjugate deviation of the eyes is reported by Sklodowski³ as a new sign occurring with apoplexy. These peculiar movements lasted for more than forty-eight hours preceding death in a hemiplegic patient. The movements were lateral, continuous, slow and rhythmical, and at the rate of about sixteen per minute.

After death an area of softening was found in the right lower parietal lobe, the posterior portion of the second temporal convolution and in the adjacent part of the occipital lobe. The explanation offered by Sklodowski is that irritation of the subcortical region beneath the lesion may have caused movements of the eyeballs to the opposite side. After the active period subsided, exhaustion as a result of irritation occurred,

1. Gowers: *Diseases of the Nervous System*, Philadelphia, P. Blakiston's Son & Co., 1898, 2, 208.

2. Popper: *Monatschr. f. Psychiat. u. Neurol.*, 39, 188.

3. Sklodowski: *Ztschr. d. g. Neurol. u. Psychiat.*, 31, 163.

and then the center of the opposite side provoked a movement.

In a patient studied by Rosenfeld,⁴ there was observed head nystagmus and also facial nystagmus; the latter occurred as rhythmic twitchings in one of the branches of the facial nerve, and appeared synchronously with ocular nystagmus. Rosenfeld assumes that there was a bilateral softening particularly in the central ganglions of the cerebrum. He states that vestibular nystagmus is characteristic of a supranuclear lesion.

During infancy, there are sometimes observed imperative movements of the head or nystagmus of the eyes, and occasionally these manifestations are associated; even a family form has been mentioned. However, the condition passes away in infancy or in childhood. Furthermore, the phenomenon probably represents a different disease. Thompson⁵ in an article "On the Etiology of Head-Shaking with Nystagmus (Spasmus Nutans) in Infants," writes:

The condition presented in the following article is a functional, coordinated neurosis of a harmless nature, which affects young infants and has a short, well defined clinical course.

He adds:

Dr. Alexander Bruce tells me that the nucleus of Deiters (one of the nuclei of the vestibular nerve lying in the lateral angle of the fourth ventricle) is in all probability the seat of the disturbance. He implies this from its connection with the oculomotor nuclei and with the anterior cornua of the cord.

Thompson further remarks:

It may, however, be said in passing, that head nodding and nystagmus (separate or combined) lasting during life is obviously an essentially different condition from the transitory neurosis with which we are at present dealing.

Nettleship believes that in spasmus nutans ocular nystagmus is never present at birth, and also that patients recover from the condition.

INFLUENCE OF HEREDITY

In 1911 Nettleship⁶ exhibited cases of hereditary nystagmus, some of which manifested head movements. His patients showed that transmission was more frequently through the mother, though not so invariably as in nystagmus without head movements.

To explain this phenomenon, Nettleship says:

If the object of the head movements were to cancel, neutralize or compensate for the eye movements, i. e., to steady the retinal images, we should expect, I think, that the two movements, although in the same plane and probably equal in rapidity, would have opposite directions.

As to my cases, the head movements and eye movements were in the same plane, but they varied greatly in speed.

Under certain conditions, rhythmical head movements are observed in animals. A well known instance is the weaving of the horse, which consists of lateral oscillatory movements of the head and neck. The habit is observed in some restless horses that are confined too closely to the stable, and therefore has its origin in idleness. Almost every one has observed the weaving of the bear in captivity, and a somewhat

similar swaying is seen in the elephant. However, such movements are probably entirely under the control of these animals.

ETIOLOGIC FACTORS

Ocular nystagmus in man may arise from many nervous diseases or disorders, and the site of origin often varies greatly. Sometimes it is observed in the lower animals. The horse shows nystagmus in epilepsy, meningitis and always in the stage of excitement of chloroform anesthesia. Nystagmus has been observed in dogs born blind and also in those with a congenital underdevelopment of the eyeballs. In certain toxic states the symptom is present in swine, as after drinking brine; in this type the nystagmus is due to the ingestion of a large quantity of sodium chlorid.

The importance of the color of the iris in ocular nystagmus has been commented on. In albinism the irises are without color and persons showing this condition are remarkably nystagmic. Nettleship⁷ observed a family in which a number of males had nystagmus and all of these were blue-eyed. In the cases I have studied, dark irises predominated. However, one would hardly expect the color of the iris to have much bearing on nystagmus of central origin, which is the probable seat of the disorder in this family.

As to transmission: in some diseases, such as hemophilia, night-blindness and the myopathies, the transmission is noticeably through the mothers, who are themselves often unaffected. This tendency was observed in the cases I have reported. In both instances in which the fathers transmitted the nystagmic tendency, they were themselves affected, while the mother who handed down the disorder was not nystagmic, but transmitted the affection to her two sons, who were children by different husbands.

Ophthalmologic studies and Bárány tests were not possible since these patients did not wish to submit to an investigation. I am unable to explain the remarkable cephalic and ocular movements exhibited by certain members of this family. Possibly the disorder belongs to the realm of physiologic pathology and is caused by some obscure instability of the centers governing these movements.

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ABSTRACT OF DISCUSSION

DR. I. ABRAHAMSON, New York: Dr. Yawger indicates that the head-nodding and the stammering speech were connected. If this were the case then there would be a quivering of the voice. I think the fact that the stammering speech occurred must be accounted for on other grounds, and not on the ground that there was nystagmus of the vocal cords.

7. Nettleship: Royal Ophth. Hosp. Rep., 1886-1887, **11**, 366.

The Automobile as an Instrument of Death.—An upward trend in the mortality from automobile accidents is, possibly, to be expected in view of the steadily increasing use of these vehicles. Nevertheless, the continuously climbing death rate is deserving of more than passing notice. In the registration area in 1915, 3,978 persons were killed by automobiles. In 1914, only 2,826 suffered death in this manner. The death rate rose from 4.3 per hundred thousand population to 5.9, an increase of 37 per cent. Had there been seventy-five more deaths from automobile accidents in the registration area, more people would have died in this manner than through surface cars, subway trains, elevated trains, bicycles and all horse drawn vehicles combined.

4. Rosenfeld: Ueber Vestibulären Kopfnystagmus und facialis Nystagmus bei Pseudobulbärparalyse, Arch. f. Psychiat., 1914, **53**, 1130.

5. Thompson, in Festschrift in honor of Abraham Jacobi, New York, Knickerbocker Press, 1900, p. 65.

6. Nettleship: Tr. Ophth. Soc., U. Kingdom, 1911, **31**, 159.