

RECURRENT RETINAL HEMORRHAGES.

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This paper states the characteristics of this symptom complex, gives the writer's own experience of it, four cases, and discusses the different views held with regard to its etiology and pathology, diagnosis and treatment, and advances the view that disturbance of function of the endocrin organs is an etiologic factor. Read by invitation before the New England Ophthalmological Society, April 20th, 1920.

The disease originally described by v. Graefe, to which Eales gave the name "Recurrent Retinal Hemorrhages," is one of unusual interest, one might say fascination, because of its distressing features; affecting as it usually does, young men who have previously been in fair health, the attack coming on with alarming suddenness and running a long course with alternating periods of hopefulness and depression, both to the patient and physician, and terminating only too frequently in partial or total blindness. It has seemed worth while to reread the original papers by Eales that we may have a clear conception of the clinical features of the cases which he recognized as a clinical entity.

Too often latter-day descriptions have been shorn of important and sometimes, essential features, as each succeeding systematic writer has used as his source of information an abstract quoted by some previous compiler. An excellent illustration of how far afield writers of books may thus be lead from the original descriptions and in the perpetuation of an error is the recent exposure that there is not one American text book and only one or two in any language, but have an entirely erroneous description of Gunn's dots. In consulting the literature of the disease under consideration it has seemed to me that cases have been described under this head that differ in many of the striking particulars of Eales disease; and the conclusion is forced upon one that, tho they may be allied conditions, some underlying factor is either different or wanting. The cases which I have to report conform in their essential details to the cases upon which Eales built up the symptom complex with which his name is linked.

The features of the disease as described by Eales are taken from a study of seven cases. All the patients were males ranging in age from 14 to 20 years. They were dyspeptic, low spirited, wanting in energy and complained of frontal headache, expistaxis and constipation. The pulse rate was habitually under 60, altho in the interval of ocular and nasal hemorrhage it might rise to 72. The number and proportion of blood cells was normal. The exciting causes of the intraocular bleeding were recumbent posture, stooping, coughing and laughing. In three of the cases the fathers had epistaxis. In all of this group the left eye was primarily and chiefly affected. When first seen the vitreous was opaque from hemorrhage and the fundus was either invisible or visible thruout a small portion of the upper part of the periphery, and here extravasated blood was found in the retina. There was often a rapid diminution of the opacity of the vitreous followed by a sudden recurrence of the opacity from fresh hemorrhage after a few weeks or months. Many such recurrences took place. In each case vision seemed to suffer only in proportion to the opacity of the vitreous. Between the attacks it sometimes recovered its normal acuity altho vitreous shreds were discoverable. The vessels in each eye were large and tortuous, especially the veins which were also remarkably dark colored. The hemorrhages were confined almost entirely to the extreme periphery of the retina. The extravasations were almost always large and round, and bleeding could often be seen to proceed from venous radicles. In one case glaucoma supervened. He also notes the tendency for the formation of vascular membranes in the vitreous.

Many cases have been reported in literature since the appearance of this admirable contribution, and so far as the ocular findings and clinical course are concerned, little has been taken from or added to it. The female sex has been found not to be immune and probably too much stress was laid on the dominant participation of the left eye; altho in my experience that eye has suffered the more.

CASES.

CASE 1. A. B. First seen Feb., 1917. Male age 18 years. History of sudden impairment of vision in L. E., 10 months ago. Cleared up in a month's time. For ten years previous to this he had noticed a streak in front of this eye. Present trouble about 6 weeks, in L. E. and a few days in R. E. No serious illness. Measles and scarlet fever. Does not use tobacco or alcohol. Parents living and well. Two sisters well. Feels well. No epistaxis. Physical examination by Dr. M. H. Fussell. Large fat individual. Pulse 82. B. P. 140—75. No enlargement of thyroid. Blood—hemoglobin 78% R. B. C. 4,020,000; W. B. C. 9000; Polys. 67%, Lymphs 28%; Large 5%. Blood nitrogen .016 per litre. Tuberculin, v. Pirquet positive. Wassermann negative. Coagulation from normal, to slow. Phys. Exam. Other respects normal. While in hospital pulse ranged from 68 to 89. T. 99—101°. When first seen Feb., 1917, V. R. E. 5/7.5; L. E. Hand movements at 1/3 M. Vitreous so opaque no fundus reflex. R. E. Vitreous filled with fine opacities. In the region of the ora serrata there was a zone of hemorrhages in the retina. The inferior retinal vein was greatly distended.

Field of V. R. E. Two rather deep reëntering angles above. L. E. Entire upper field gone.

By Sept., 1917, V. in L. E. nearly normal; R. E. 5/50. Beginning formation of new tissue over temporal border of disc. In July, 1918, V. L. E. 5/5; R. E. unchanged. By Oct. V. L. E. 6/6; R. E. 5/9. The proliferating tissue has greatly increased. Vision continued to improve in L. E. and when last tested March, 1919=5/4; R.

E. 5/20. (Patient reported April 17, 1920.) V. R. E. counts fingers. L. E. 6/6. Mass of proliferation tissue and probable detached retina. Has had one attack of nose bleed. Present weight nearly 200 lbs.

CASE 2. E. B., female, married, age 33 years. (Patient of Dr. W. T. Shoemaker.) First seen April, 1917. Father and mother living and well. Five brothers and sisters. No history of tuberculosis. Has been married 5 years. One child living and well. One miscarriage. She had had the usual diseases of childhood.

Phys. Exam. Well nourished. Wassermann negative. X-ray of sinuses chest and teeth, negative. Urinalysis negative. No record of tuberculin test.

Blood Exam. Hem. 74%, R. B. C. 3,740,000. W. B. C. 50600; Polys, 50%, Lymphs. 42%. Coag. time 12 min. B. P. 115—65.

Eye trouble dates from Aug., 1914, when the left eye was hit by a tennis ball. Some time after this vision of left eye was lost but was later recovered. This again occurred but recovery was not so complete. Recently again lost it. Thinks R. E. now failing.

When first seen by Dr. Z. May, 1917, V. R. E. 20/50; L. E. 1/100. In R. E. marked proliferating retinitis. L. E. Vitreous filled with blood. While under treatment vision of R. E. fluctuated greatly, but there was practically no change in that of L. E. up to the time of using fibrolysin in Jan., 1918, at which date it was reduced to 1. p. After one month's use of fibrolysin it again=1/100. Indirectly it is learned that at the present time the patient has had relapses in R. E. which have reduced the vision.

CASE 3. A. S., male, age 23 years. Seen in consultation with Dr. P. H. Kleinhans, of Bethlehem, Pa., April, 1918. Vision failing in R. E. since Feb., in L. E. for few days. Has had no serious illness. Tuberculosis on his mother's side. Parents living and well. Four sisters and 2 brothers living and well. One sister died of spinal meningitis, at 20 months and one of "throat consumption" at 5 months. No epistaxis. Constipated. Is gaining weight (140 lbs.).

v. Pirquet and Wassermann negative. The blood was normal except for a slight simple anemia. Coag. time of blood 5 minutes. Physical examination negative.

V. R. E.=1/60, L. E. 15/30. In R. E. central and lower part of vitreous is so dense that no fundus details are possible, elsewhere a red reflex is obtained; and to the nasal side a proliferating mass is visible. L. E. Several retinal hemorrhages in peripapillary region. In July, 1918, V. each eye about normal. Sept., 1919, V. R. E. 20/70; L. E. 1/200 eccentric. R. E. showed large sheets of hyperplastic tissue. L. E. Vitreous almost filled with blood.

At this time a subcutaneous tuberculin test was made and proved negative. April, 1920, Dr. Kleinhans reports that the patient now weighs 165 lbs. (height about 5 ft. 9 in). Since above date has had many vicissitudes and at present V.=5/21 each eye. In R. E. the retina is detached up and out. L. E. Vitreous very hazy, no fundus lesions made out.

CASE 4. J. M., male. April, 1918, a cloud came before R. E. First seen by Dr. Gemmell of Monessen, Pa., who reported that V. at that time was; R. E. 6/40; L. E. 6/6. One month later it had fallen in L. E. to 6/40 due to an extensive hemorrhage. He was later under the care of Dr. Burke and also Dr. Greene, of Washington, D. C. When seen by me Oct. 14, 1919. R. E. 5/35; L. E. hand movements at 3/4 M. He was the youngest of a family of 2 males and 2 females. All living and well. His mother died in a few minutes of hemorrhage from nose and mouth. Father living and healthy.

Physical examination: 5 ft. 3 in. Weight 132 lbs. Bones of lower part of face heavy. v. Pirquet positive. Wassermann negative. Skiagraph of skull nothing abnormal. Urinalysis normal. Blood—Slight anemia. Coag. time slightly increased to normal. Pulse ranged from 72—120. Temperature from 97.4° to 99.4°. L. E. Divergent. R. E. Numerous hemorrhagic opacities in vitreous. Periphery of fundus visible and shows some organized tissues. L. E. No red glare from

pupil. At end of one week V.=R. E. 5/12; L. E. Fingers at 1/3 M. End of 2 weeks R. E. 6/6 pt. L. E. Unchanged. At this date tuberculin injections were begun, and 10 days later V. in R. E. had fallen to 1/60. Subsequently it temporarily rose to 5/4 and when last tested, 5 days later, was 5/9. Two months later the patient sailed for Italy and wrote that vision seemed about the same.

In all of these four cases the Wassermann was negative. In 2 the tuberculin test was positive, in one negative and in one not recorded. Blood pressure was normal in all. Coagulation time of blood was normal in 2 and slow in 2. The blood count showed no marked alteration. Hemoglobin was below normal in all.

In all four cases the treatment was much the same as will be spoken of later. The effect of treatment was uncertain, as fluctuations in vision dependent upon hemorrhages occurred and one eye would improve and the other grow worse despite the nature of the treatment. In the second case, because of the failure of the left eye to improve while the right continued to fail, it was decided to try fibrolysin. As the patient lived at a distance and intended shortly to return home it was deemed expedient to use every other method which offered any hope at the same time. Twelve doses of 2.3 cc. of fibrolysin were given in the course of a month. At the same time subconjunctival injections of salt and of dionin were used. At the end of this time V. R. E. remained unchanged, that of L. E. had improved from 1. p. to 1/100.

ETIOLOGY. The predisposing causes which stand out in this disease are age and sex. The age limits at which it occurs in males fall within the period of adolescence. In the vast majority of cases the male sex is afflicted. The nature of the underlying cause of the bleeding is not so definitely determined. The views held by the earlier observers as to the fundamental causes are probably due to the limitations of research of the period. Eales originally attributed the condition to auto-intoxication resulting from constipa-

tion; but in his second paper was more speculative and viewed the condition as a neurosis affecting both the circulatory and digestive systems—a vasomotor contraction of the vessels of the alimentary canal resulting in a compensatory dilatation of the systemic capillaries. Nettleship's idea that gout was the cause is hardly tenable at this day.

The researches of Stock and Axenfeld, which have thrown so much light on the tuberculous nature of certain types of endophlebitis have led to the acceptance of tuberculosis as the cause of the type of intraocular hemorrhage with which we are dealing. According to Knapp the tuberculous nature of recurrent vitreous and retinal hemorrhages was developed entirely from clinical factors, positive tuberculin reaction, presence of tuberculous lesions in other parts of the eye and in the rest of the body. The tuberculous origin is often supported by the family history and the previous history of the patient. Axenfeld suggests that where vitreous hemorrhages occur without previous appearance of tuberculosis of the eye, they may be due to tuberculous involvement of the retinal vessels either directly or indirectly by the toxins of the bacilli.

The clinical histories in many of the reported cases are not definite enough upon the question of the manifestations of tuberculosis from which to draw conclusions. Among 25 case reports, in less than 20 per cent there was either no statement as to the clinical or laboratory evidences of tuberculosis or it was noted as absent. Perhaps no better summary of the evidence favoring tuberculosis as the cause, could be had than that of Jackson, who concludes "that in the well recognized association of intraocular hemorrhage and subsequent connective tissue formation, constituting retinitis proliferans, we have the same association of pathologic processes as in tuberculous lesions in general. The few cases that have been studied anatomically, the responsiveness of a large number of cases to the specific tuberculin test, and the relative

recoveries that are now recorded to the credit of the recognized treatment of tuberculosis, give sufficient basis for the view that tuberculosis, chiefly of the retinal vessels, is the essential nature of the clinical condition, represented by cases of recurrent retinal hemorrhages in young persons, followed by retinitis proliferans."

The view that seems to meet with most favor is that the disease is an autotoxic one, the source of the toxemia being in most cases the intestines. As the result of this toxemia, inequalities of the circulation occur either too high or too low blood pressure. Many clinicians of authority seem not to be strongly impressed by the tuberculous view. Thus Fuchs and also Römer consider the nature of the affection unknown. Collins believes that the coagulability of the blood is raised, and that this leads to the formation of thrombi in the venules which rupture as the result of the vis a tergo.

Nieden believes the cause to be slow development of the sexual apparatus, in these cases unrelieved, as in females by menstruation. This view is also held by Koenigin; and Panas believes that the nature of the disease is the same as epistaxis. The latter even suggesting the name "epistaxis interoculaire." Both Nieden and Panas evidently agree with Hutchinson and Eales in considering the blood pressure an important factor as they state that by studying the sphygmographic tracings of the pulse we can not only determine the cause of the difficulty, but tell the prognosis very accurately.

There is some difference of opinion as to the source of the bleeding. Mostly it appears to come from the retinal venules. Nieden, however, believes that it comes from the choroidal vessels, and an anatomic study by Brewster confirmed this view. In other cases it seems to come from the vessels of the ciliary body. Eales attributes the more frequent involvement of the left eye to the origin of the left common carotid direct from the arch of the aorta, and the more circuitous route of the innominate vein, both favoring a higher vascular tension. Both Eales

and Nieden believe that the menstrual function acting as a safeguard accounts for the rarity of the condition in females. Schweigger denies the correctness of both of these clinical points, as to the preponderance of male sex and of the left eye, but recorded cases bear out Eales.

PATHOLOGY. Very recently Fuchs has recorded the anatomic changes which he observed in a large number of vitreous hemorrhages of spontaneous origin. The hemorrhage occurred on the outer surface of the vitreous, in the posterior lenticular and orbicular spaces and into the vitreous itself. In rare cases they were confined to the outer limiting layer, the blood corpuscles being within the lamellar structure of this layer, or they were spread immediately under it, coming usually from the ciliary region, or they penetrated into the interior of the vitreous. The change in the hemorrhages most frequently noted was hemolysis, i. e., exit of hemoglobin and lipoid from the corpuscles. This process takes place within a month of the time the hemorrhage appears in the vitreous, but does not occur uniformly.

There is no reaction in the vitreous as the result of the presence of the hemorrhage or its derivatives. The absorption of the blood is in part effected by phagocytosis, but in case of large hemorrhages absorption is due more to hemolysis and the formation and the removal of the granules, or where the hemorrhage is traversed by connective tissue the gradual disappearance of the corpuscles enclosed in its meshes. The formation of connective tissue begins from the ciliary body or the retina and is more likely to occur when beside the hemorrhage there is some inflammatory reaction. It was first seen fourteen days after the occurrence of the hemorrhage in the form of fibroblasts going in towards the blood, then in between the corpuscles to form long narrow threads or membranes. In other cases the connective tissue is developed on the surface of the hemorrhage, making a membrane around it. This formation of tissue may go on with or without phagocytosis.

Schreiber found that the greater part of blood injected into the vitreous disintegrated at once at the site of the injection and was taken up by migratory cells from the ciliary processes and the perivascular lymph spaces of the central vessels, while the anterior chamber took no part. In the greater number of cases in the course of one or two weeks there could be demonstrated connective tissue formation presenting the microscopic picture of retinitis proliferans. Some reaction of the neuroglia is seen at the points where groups of hemosiderin containing migratory cells accumulate in the retina; this usually occurs in the lower part. Here also is seen glial proliferation of Müller's fibres. The connective tissue formation of the papilla plays the most important part in the development of retinitis proliferans. Parsons holds the same opinion as to the part played by the mesoblastic tissue of the papilla in the reparative reaction.

Sugamuma concludes that the newly formed tissue in proliferating retinitis results from a proliferation of the retinal glial fibres as well as connective tissue subsequent to hemorrhages.

PROGNOSIS. The prognosis of the disease is grave. As stated by Roemer it is very remarkable how rapidly the resorption of such hemorrhages takes place, while that of an ordinary hemorrhage is wretchedly slow and incomplete. (I think that this is sometimes due to the slow coagulability of the blood in this affection.) But unfortunately there is the marked tendency to the formation of connective tissue membranes, which not only cover portions of the retina but may cause its detachment.

TREATMENT. The treatment resolves itself into an attempt to prevent the recurrence of the hemorrhages and to bring about the absorption of the extravasated blood. There is considerable testimony as to the curative value of tuberculin in the cases in which tuberculosis was the cause or an associated condition. Alterative drugs such as iodid of potassium, Donovan's solution, syrup of the iodid of iron and syrup of hydriodic acid in large doses,

seem all to be of some value. Darier advises the use of vasoconstrictors.

Ormond, Ollendorff, Thilliez, Westphal, Lamb and others have had sufficient success with fibrolysin to recommend its use. In one case in which I used it the effect was negligible. Bennett, in a typical case with retinitis proliferans where practical blindness had resulted and all of the usual drugs, including fibrolysin, were of no avail, secured a permanent improvement to 6/6 and 6/18 after 3 weeks use of thyroid.

I have thought that the use of thyroid extract was of real value. The use of radium is of doubtful utility, because the greater resistance of connective tissue cells than epithelial cells to its influence possesses an element of danger.

In view of the variability of many of the factors that have been considered as of possible etiologic importance; the very definite picture of tuberculosis of the retina not usually found in these cases; the fairly constant age incident, that is, adolescence, in the cases occurring in males; the physical condition of the patients as described by Eales and present in some of my cases—lassitude, low spirits, variations in local temperature, cold hands and feet, in other words, asthenia, the tendency to over size in 3 of my cases, and the beneficial effect of thyroid in the treatment of the disease, the thought has long been in my mind that disturbed secretion of some of the ductless glands may be an important etiologic factor. As the activities of the endocrin organs are interlocking it would be impossible probably to indicate definitely the one at fault, altho the symptoms

point to the adrenals as the primary one.

In connection with another hemorrhagic affection, Moret speaks of the cause as being probably an interference with the angiotonic functioning of the ductless glands, probably the adrenals. In discussing this idea with Sajous he stated that the adrenal secretion acts directly on the arterioles and sustains their tone, and further that this function when deficient, owing to relaxation of these precapillary vessels may represent in "Recurrent Vitreous Hemorrhages of Adolescence" an indirect cause of the hemorrhages. He further pointed out that the sympathetic system is studded with adrenal medullary substance, supplied probably by the medullary portion of the adrenals, and says that "If this is true the sympathetic ocular supply must also suffer—another cause of vasodilatation, probably of the choroidal vessels."

I do not wish it to be understood that I wholly reject the tuberculous cause of this disease, but I do think that some other factor must be found to explain the striking characteristics of this group of cases and that this may be found in the adrenals, whether acting independently or in conjunction with tuberculosis. I merely put it out as a suggestion that should be borne in mind in the further study of this affection, tho it is well also to remember that, to paraphrase a recent sentence of MacRobert,—the endocrin organs possess a strange proclivity to evoke suspicion towards themselves as being the source of incomprehensible ailments.

RECURRENT RETINAL HEMORRHAGE OF ADOLESCENCE.

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This report of a case and comparison of it with a case previously reported by the same author was read before the American Ophthalmological Society, June 16, 1920.

In 1912 I reported before this society the case of a young man (F E. B., aged 22), where there were not only repeated and extensive hemorrhages into

the vitreous, but a most pronounced perivasculitis especially affecting the veins, followed in each eye by proliferating retinitis, vascular veils, partial