consacrer aux soins médicaux sans grever au delà de leurs limites les ressources de la société et alors serons-nous forcés de reviser notre éthique sociale et médicale à la lueur des nécessités économiques. Il n'est pas question de renoncer à notre idéal humanitaire et religieux, mais il faut reconnaître que ces problèmes ne pourront pas être résolus par l'application de connaissances acquises dans le passé, L'auteur termine en citant l'épidémiologiste William Farr, qui écrivait jadis: "Les maladies infectieuses se succèdent et quand l'une est extirpée une autre la remplace, ravageant la race humaine de façon indifférente lorsque les conditions propices à la santé font défaut. Elles ont ceci de commun avec les mauvaises herbes et les autres formes de vie que lorsqu'une espèce décline une autre en profite".

# THE UVEO-ENCEPHALITIC SYNDROME OR VOGT-KOYANAGI-HARADA DISEASE

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THIS RELATIVELY RARE DISEASE is characterized by the unusual combination of uveitis, depigmentation of skin and hair, and cerebral manifestations. It has long been recognized by ophthalmologists, and reports of cases have been confined almost exclusively to the ophthalmic literature. But it may present a diagnostic problem to general physicians, neurologists, neurosurgeons, and dermatologists. We propose to review the literature, to report five more cases and to discuss the etiology of the condition. We hope that the publication of this review in a general medical journal may help to spread the knowledge of this disease beyond the ophthalmological domain.

## REVIEW OF THE LITERATURE

Like so many other conditions it was first described by Jonathan Hutchinson[1] in 1892, although Vogt[2] is usually given the credit for being the first to do so in 1906. Other single cases were then reported in the literature, particularly in Japan, where it appears to be more common.

In 1929 Koyanagi[3] wrote the first significant account of the disease. He reviewed the literature and 16 cases, 12 of which were collected from case reports and 4 of his own. He described the clinical picture of headache, fever, bilateral uveitis, dysacousia, vitiligo, poliosis and alopecia. He emphasized that the uveitis was essentially anterior in situation but did mention that exudative retinal detachment occasionally occurred. Following Koyanagi's publication this condition was known as the Vogt-Koyanagi disease.

In 1926 Harada[4] described five cases characterized by bilateral posterior uveitis with inferior exudative retinal detachments.

For nearly two decades it was considered that the Vogt-Koyanagi disease and Harada's disease were two separate entities, the difference being that in the former the uveitis was anterior in situation and no detachment occurred, whilst in the latter condition the uveitis was posterior and was accompanied by retinal detachment. But this distinction is not justified. Koyanagi[3] mentioned that retinal detachment occurred in two of his cases, and in a typical case of Vogt-Koyanagi disease the anterior uveitis is so severe that a retinal detachment is likely to be obscured and missed. Harada[4] mentioned in his article that severe anterior uveitis may occur and recorded that one of his cases had severe alopecia followed by the growth of fine white hair.

Many cases have now been described and it is generally agreed[5] that the Vogt-Koyanagi disease and Harada's disease are identical, but that the severity of the manifestations in different sites may vary from case to case and produce marked differences in the clinical picture. There is now a tendency to drop the eponymous title and to give the condition a name indicating the nature of the disease. Yuge[6] has suggested the title of oculo-oto-cutaneous syndrome, but this fails to indicate the meningitic features. Cowper[7] first suggested the name uveo-encephalitis. We feel that this is perhaps the most explanatory term for this bizarre condition. The integumentary changes tend to occur late and, though significant, diagnostically they are less dramatic than the early cerebral features and the uveitis.

## CLINICAL FEATURES

Great variations in the severity of the clinical picture may occur and incomplete manifestations of the disease are probably common. Walsh[8] pointed out that bilateral uveitis with pleocytosis of the cerebrospinal fluid is not uncommon and that such cases should probably be considered as "formes frustes" of this disease.

Cowper[7] suggested that the clinical course of the disease usually falls into three phases: (1) meningeal phase; (2) ophthalmic phase; (3) convalescent period.

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1. *The meningeal phase* usually begins with an abrupt onset and lasts from two to four weeks, with low fever which may be persistent, and retro-ocular or frontal headache causing insomnia and irritability.

2. *The ophthalmic phase* may follow the meningeal phase but occasionally they occur simultaneously. Both eyes are affected and the patient complains of photophobia, tearing and rapid loss of vision. Inflammatory cells appear in the aqueous and vitreous, so that the media are hazy and funduscopic examination may be difficult or impossible. The anterior part of the uveal coat may be chiefly affected so that the condition presents as iridocyclitis. When the posterior uvea is involved, the optic discs and the retinal veins may be swollen, resembling papillœdema or papillitis. Harada[4] emphasized the appearance of gross œdema of the retina, so that the optic disc seemed to be at the bottom of a funnel. Retinal hæmorrhages may occur.

A gradual sinking of the fluid exudate results in bilateral inferior retinal detachments, which may be slight and peripheral or so gross that the macular area is involved. The medial haze may be so severe that it is impossible to see the retinal detachments with an ophthalmoscope. However, their presence may be indicated by an absence of the sense of light projection in the upper visual field. This occurred in Case 3.

No particular visual field defect is characteristic of this condition. General contraction, enlargement of the blind spots and central scotomata have all been reported.

Headache, vomiting, neck rigidity and a positive Kernig sign may be present. Deafness with or without tinnitus may cause the patient much concern. It is usually bilateral but tends to disappear in several weeks. The cerebrospinal fluid may show marked pleocytosis and increased pressure.

At this stage the clinical picture may resemble that of a rapidly expanding intracranial lesion so closely that several cases have been reported in which exploratory craniotomies were performed. Our third case was so treated.

The ophthalmic phase lasts from three to five months.

3. *Finally, the convalescent period* follows, and it may last from six to twelve months. The subretinal fluid absorbs slowly and the retina becomes reattached. Scattered white exudates often persist for some time in the previously detached area, but they gradually absorb and disappear. The fundi become depigmented so that the choroid is more obvious than normal. Strands of fibrosis and patches of pigmentation may be grouped about the optic disc. Less than 30% of patients regain useful vision because secondary glaucoma, cataracts, optic atrophy and phthisis bulbi may occur. The ectodermal manifestations of poliosis, vitiligo and alopecia may appear during this period and are usually permanent.

## CASE REPORTS

CASE 1.—Mrs. H.L., aged 34 (one parent was Italian), had a brief attack of iritis in the right eye in December 1952. The inflammation subsided in two or three days following an injection of typhoid vaccine. No investigations were carried out at this time.

She was first seen on April 24, 1953, when she complained that for two weeks she had suffered a severe continuous periorbital ache which was worse at night and was not relieved by aspirin. During this time the vision of the left eye had been blurred. Five days previously a black spot suddenly appeared before the right eye. On examination, with a plus 2.00 D sphere correction before each eye, vision was reduced to Rt. 20/100 and L. 20/200. She had bilateral iridocyclitis and marked macular œdema. A central scotoma was present in each eye (Fig. 1).

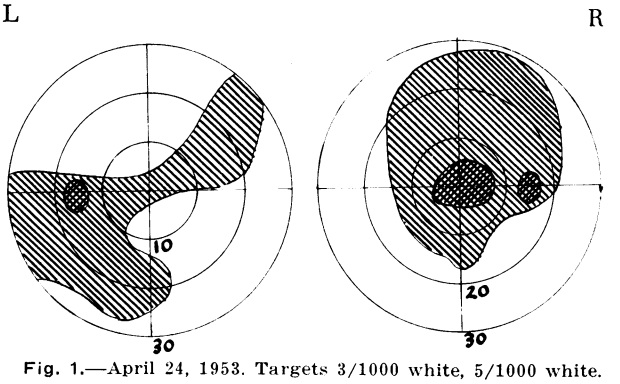


Fig. 1.—April 24, 1953. Targets 3/1000 white, 5/1000 white.

A general medical examination revealed no defect. Radiographs of the teeth, sinuses and chest were normal. Blood examination and urinalysis revealed no abnormality. An audiogram revealed no hearing loss. A Mantoux test was negative.

She was treated with atropine eyedrops and the corrected vision gradually improved to 20/30 and 20/50 by May 19, 1953.

After one month's observation, i.e. six weeks after the onset of the disease, alopecia areata of the scalp and poliosis of the eyelashes first appeared. By this time the ocular inflammation had almost completely subsided. Examination with the binocular microscope revealed no keratic precipitates but slight endothelial bedewing was still present.

After a period of nine weeks, the inflammation had completely subsided, and her vision had improved to 20/30 in each eye despite minimal paramacular scotomata (Fig. 2).

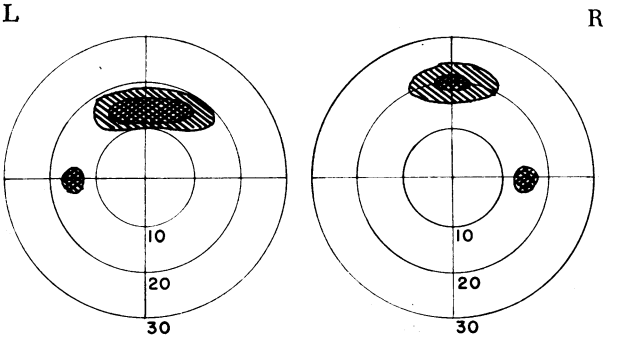


Fig. 2.—May 12, 1953. Targets 3/1000 white, 5/1000 white.

CASE 2.—J.S., a 29-year-old Hungarian immigrant with a previous history of good health, was admitted to the neurological service of the Toronto Western Hospital on January 25, 1956, complaining of headache, fever, sore throat and diarrhœa, of five days' duration. In the two months before admission he had been working with animals in a laboratory, including monkeys used for preparing Salk vaccine. In November and December 1955, he had received 15 c.c. of gamma globulin and had been immunized with three injections of Salk vaccine.

On admission he was drowsy and flushed, with a rectal temperature of 105° F. He had a moderately injected pharynx but no other positive findings except for a questionable left facial weakness. The fundi were reported to be normal and venous pulsation was present at each optic disc.

During the first week in hospital his temperature gradually fell although he received no specific therapy. His mental state fluctuated from lethargy and drowsiness to apprehension. He complained of intermittent headache, and cerebration was slow. There were occasional brief shivering spells. On the fifth day he began excreting about 10,000 c.c. of urine of low specific gravity per day. A diagnosis of diabetes insipidus was made and this condition was controlled by intramuscular injections of Pitressin tannate in oil, 1 c.c. daily.

An electroencephalogram revealed a poorly organized alpha rhythm and many runs of 4-7 cycle per second activity in random fashion from all areas. There were also runs of bilaterally synchronous short bursts of 3 cycle per second of high voltage from all areas. This suggested a diffuse brain disorder which included the deep central structures.

In the second week, though he was now afebrile, his mental state deteriorated. He was alternately drowsy and restless, and occasionally confused and very resistive. Delirium and hallucinations developed. Speech became slurred and his movements incoordinated, especially of his left arm. Left facial weakness and left hemiparesis became evident.

The visual acuity could not be tested because of the confused mental state. The pupils were fixed and dilated. The fundi were pale and, in the mid-periphery, patches of white exudate were seen along the course of the nasal branches of the central retinal arteries. In places the arteries could not be seen and several streaky hæmorrhages were noticed with the exudates. The arteries were extremely spastic. A moderate amount of œdema was present around the right disc, but it was not elevated and venous pulsation could be seen. A clear view of the fundus was not possible because of vitreous haze.

Between the second and fifth week the patient's mental state improved. His left hemiparesis exhibited peculiar fluctuations in severity with occasional improvement followed by exacerbation of weakness. There was also a variable intensity of true cerebellar ataxia of the left arm. His mental state gradually improved and he became cheerful and talkative with brief episodes of confusion, aggression and automatism. These latter periods seemed to coincide with recurrence of the left-sided weakness and clumsiness. The diabetes insipidus worsened, necessitating larger amounts of Pitressin. By this time the retinal œdema had cleared and the white patchy exudates with the superficial hæmorrhages were more distinctly outlined.

In his sixth week the patient complained of deteriorating vision. Re-examination showed a visual acuity of 20/60, .60 M print in the right eye and 20/80 .75 M print in the left. The vitreous haze had increased and large white precipitates indicative of uveal inflammation were noted on the corneal endothelium, although no flare or cells were seen in the anterior chamber.

By the eighth week, vision in the right eye was reduced to hand movements at three feet (90 cm.) and a large bullous retinal detachment was seen in the lower half of the fundus. Vision in the left eye was 20/70 and no detachment was seen. Frequent examinations failed to reveal a retinal hole. Because the patient stated that his vision was better after a night's sleep, he was kept at complete bed rest with both eyes occluded for a week. This failed to improve his visual field and the fundal appearance did not alter. At this point, two months after admission, no neurological abnormality, apart from the eye signs and the diabetes insipidus, could be elicited.

He was then given oral cortisone, 300 mg. daily. This dosage was reduced gradually over a three-week period. No change occurred in the ocular findings but the diabetes insipidus required more Pitressin for control.

Between the ninth and sixteenth weeks the vitreous haze gradually cleared in both eyes, and extensive thin grey retinal deposits associated with the retinal arteries in the mid-periphery could be seen. The patient's vision in the right eye improved to counting fingers at two feet (60 cm.) but deteriorated to 20/100 in the left eye. He complained of seeing a series of fine black circles surrounding patches of red and green spots on opening his right eye.

Five months after the patient's admission he developed a frankly psychotic mental reaction, depressive and paranoid in type, and was admitted to a provincial mental hospital where he has remained.

One year after the onset of his illness the patient was quiet, withdrawn and delusional, but co-operative. The diabetes insipidus required only intermittent injections of Pitressin for control. The visual acuity of each eye and the appearance of the anterior segments remained unchanged. The vitreous opacities and grey retinal deposits were still present in both eyes, and the detachment in the right eye was complete. In the left eye the retinal arteries were attenuated and the upper nasal branch appeared occluded and sheathed near the optic disc. Areas of choroidoretinal atrophy were seen but pigment cell proliferation was not a noticeable feature. The disease was apparently inactive, and the prognosis for mental and visual improvement seemed poor.

The white cell count and differential were normal on admission but the blood smear showed several large atypical lymphocytes. The erythrocyte sedimentation rate, serum protein, and electrolyte values were normal. Blood and spinal fluid Wassermann tests were repeatedly negative, but the treponema immobilization test was positive on two occasions. It was also of interest that the spinal fluid demonstrated a colloidal gold reaction of 5554331000 three weeks after admission, while one month later this reaction was 0123210000. No history of luetic infection was obtained. Intradermal skin testing was positive with 1/20 mg. of old tuberculin and negative with toxoplasmosis antigen.

The initial spinal fluid cell count was 188 per c.mm., consisting chiefly of lymphocytes, and it gradually fell to normal one month later. Spinal fluid protein was 40 mg. % on admission and rose to 56 mg. % three weeks later before returning to normal. Cultures of the throat, blood, stool, urine and spinal fluid did not reveal significant pathogens. Complement fixation reactions to Listeria antigen were positive but the results indicated a past infection. Extensive virus studies on the spinal fluid in the acute phase, using tissue culture techniques and a variety of experimental animals, failed to reveal any pathogens. The patient's serum was submitted to neutralization tests against 26 different virus strains previously isolated from various cases of encephalitis. In no instance was this informative.

Three months after admission 0.5 c.c. of subretinal fluid was removed from the patient's right eye. A small amount was injected into the aqueous of one eye and into the vitreous of the second eye of a rabbit. Two weeks later the eye which had received the vitreous injection had a moderately severe uveitis with a flare and cells in the anterior chamber. The vitreous and aqueous of this eye were passed into tissue culture and into the eyes of a second rabbit but no further activity developed.

CASE 3.—This Chinese patient was born in Canton in 1897 and emigrated to Canada in 1910.

On February 5, 1954, he was admitted to hospital for investigation. He had had a severe headache for ten days and progressive loss of vision for seven days. The pain was situated just behind the eyes. There was no dizziness, vomiting or any other significant symptom.

General physical examination revealed no abnormality although he had a low-grade fever at this time which reached 100° F. on one occasion. His vision was reduced to perception of light. There was marked conjunctival injection. Early lens opacities and vitreous haze rendered fundus details difficult to see but the optic discs could be seen to be œdematous and there was some congestion of the retinal veins.

At this stage urinalysis, radiographs of skull and sinuses, and blood Kahn reaction were reported negative. Blood examination showed a polymorphonuclear leukocytosis of 17,000 and a sedimentation rate of 26 mm. in one hour. On lumbar puncture the cerebrospinal fluid pressure was found to be 18 cm. water. The cerebrospinal fluid colloidal gold curve and Wassermann and Kahn reactions were negative but lymphocytes were 450 c.mm. and protein value was raised to 59 mg. %. The result of a glucose tolerance test was normal.

A space occupying lesion in the frontal region was suspected and the opinions of a neurosurgeon and an ophthalmologist were obtained. Bilateral central scotomata were present, and both considered the condition to be bilateral optic neuritis. He was treated with 500,000 units penicillin twice daily from February 14 to February 21, and cortisone was given in addition from February 19 to 21, the dose being 50 mg. 4 times a day.

At this time his headaches had reduced in severity but there was no improvement in vision.

He then went to Montreal, and was admitted to the Montreal Neurological Institute on February 22, 1954.*

At the time of this admission he had slight headaches in the evening and morning. His vision was reduced to light perception and hand movements in the inferior part of the field of each eye. In each eye were early lenticular opacities and some congestion of the retinal veins.

Examinations of the urine on February 24 and February 26 showed traces of sugar. A lumbar puncture on February 23, 1954, revealed a normal pressure, protein 35 mg. % (Pandy negative), sugar 75 mg. %, chlorides 748 mg. %, Lange 001111000, Wassermann negative, and 650 cells per c.mm., mostly lymphocytes and a number of large mononucleated cells thought to be neoplastic.

On February 23, the blood examination showed hæmoglobin value 96%, erythrocytes 4.8 million, leukocytes 12,200. The differential count was neutrophils 77%, lymphocytes 19%, monocytes 2%, eosinophils 2%; hæmatocrit value 41, sedimentation rate 20; non-protein nitrogen (N.P.N.) 29.4 mg. %. The blood phosphatase and cholesterol were normal.

A radiograph of the skull on February 23, 1954, was reported to show diffuse decalcification of the bone around the left side of the sella turcica. There was no direct invasion of the bone and no evidence of paranasal sinus disease. This was considered to suggest a parasellar expanding lesion on the left side.

The following day a pneumoencephalogram was done. It was reported that the superior surface of the diaphragm of the sella turcica had not been visualized. This was taken to indicate that the diaphragm was either tilted, elevated or covered with some abnormal soft tissue mass.

On February 25, 1954, a left frontal craniotomy was performed and the chiasmatic cistern was explored. No evidence of neoplasm was found, but adhesions were present around the chiasm tending to bind the subcallosal region to the optic nerves. When the left optic sheath was incised there was no bulging of its contents.

The patient recovered from his operation without complications. Postoperatively he was given intensive penicillin therapy, of one million units a day for ten days, with no benefit. He was then given 150 mg. cortisone daily for nine days, later reduced to 75 mg. a day.

The glucose tolerance test results on March 3, 1954, were: fasting—112 mg. %, 1 hour—260 mg. %, 2 hours—224 mg. %, 3 hours—108 mg. %, 4 hours—92 mg. %, 5 hours—66 mg. %.

On March 15, 1954, another examination of the cerebrospinal fluid revealed no significant change except that the cells were reduced to 170 in number. Numerous cultures of the cerebrospinal fluid for bacteria and fungi were negative.

At the time of discharge, re-examination showed that the medial opacities had cleared surprisingly and that the retina was detached in the lower half of the left eye and probably in the right eye as well.

At his discharge from the Montreal Neurological Institute the diagnosis was considered to be bilateral lens opacities, optic neuritis of unknown etiology and inferior retinal detachment.

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*Dr. Wilder Penfield kindly supplied the report of the findings at the Montreal Neurological Institute, and the patient's medical history in Regina was provided by Dr. J. M. Ferries, Dr. Douglas T. Martin, Dr. P. B. Ryan and Dr. W. L. Kurtze.

He returned to Regina and was in hospital from March 28 to June 17, 1954. During this time he was treated with cortisone 25 mg. 4 times a day and ascorbic acid 50 mg. 3 times a day, and was given some injections of vitamin $B_{12}$ and sterile milk. At this time he could distinguish between light and dark.

On July 16, 1954, he was examined again and much scattered pigment could be seen in the lower half of each fundus resembling an old choroiditis.

On October 17, 1954, he was again admitted to hospital with bilateral acute glaucoma secondary to iris bombé. Bilateral iridectomy was performed, followed by treatment with atropine and cortisone. He was discharged on November 12, 1954. Iridocyclitis recurred on November 24, 1954, and it was treated with atropine, cortisone and injections of sterile milk.

The condition then remained quiescent. He was blind but had no return of acute symptoms.

He was referred to the Eye Department of the Winnipeg Clinic on January 23, 1956. On examination he was found to have a mature cataract in each eye with the iris adherent to its anterior surface. The iridectomy on each side was partially filled by organized exudate but there was no evidence of active inflammation. Light perception was present in each eye but the sense of light projection was inaccurate.

Patches of vitiligo were present on his back and both hands. He stated that these developed at the time of the onset of the disease in February 1954.

It was explained to him that whilst there was little hope of great recovery in vision, cataract extraction offered the only hope of any improvement. A left intracapsular extraction was performed on January 26, 1956, and a right intracapsular extraction on February 15, 1956. At each operation a piece of iris was removed for histological examination. He made a good recovery and was discharged on February 29, 1956.

Dr. D. W. Penner, pathologist to the Winnipeg General Hospital, reported on the histological appearance as follows:

"The iris is œdematous and shows migration of pigment. Scattered throughout is a rather dense infiltration of numerous plasma cells, almost an equal number of lymphocytes with an occasional large mononuclear cell and only very infrequent eosinophils. In one area there is a prominent proliferation of fibroblasts. These are young fibroblasts and in areas form a 'tubercle-like' grouping. No true epithelial or giant cells are seen. The picture is that of a non-specific chronic inflammatory reaction."

He was last seen on April 30, 1956. His vision was then perception of light with each eye, but the sense of light projection was not accurate in all quadrants of the field. The vitreous of each eye was still hazy, preventing a clear view of the fundus. Each optic disc was pale and the retinal arteries were narrow. No abnormal pigmentation or scarring of the fundi could be seen.

CASE 4.—Mrs. N.C., aged 29. This patient, who was part Indian, was first admitted to the University of Alberta Hospital to the service of Dr. R. W. Robertson in September 1953. Two months previously she had pain in the left eye with progressive impairment of vision. One week later, the right eye became similarly affected. The vision in the two eyes fluctuated with the pain in the eyes, the vision being worse when the pain was severe. Examination of the eyes showed bilateral choroidoretinitis with haziness of the media. The visual acuity was right—20/20; left—hand movements at 2 feet.

*Laboratory findings.*—Kahn test negative; Hb. 10.5 g. %; R.B.C. 3.78 million; W.B.C. 12,700; neutrophils 82%; lymphocytes 17%; monocytes 1%; hæmatocrit 34%; sedimentation rate (corrected) 22 mm. in one hour; chest x-ray examination negative.

She was treated with 25 mg. ACTH in 1000 c.c. normal saline given intravenously daily for twelve days. Cortisone 0.5% eyedrops were instilled locally. Throughout the admission she ran an irregular low-grade fever up to 99.8° F. On discharge her vision had improved. She was then seen frequently as an outpatient by Dr. Robertson for recurrent pain and "redness" of the eyes. On March 15, 1955, she was readmitted to the University of Alberta Hospital with severe pain in the right eye developing three days after a severe cold. On admission she had multiple "cold sores" around her mouth and some on her tongue. Examination of the eyes showed irregular fixed pupils. Neither fundus could be seen because of haziness of the media.

Her temperature was 102.2° F. and gradually fell to normal. At discharge on April 8, 1955, her vision was R.—light perception only, and L.—hand movements.

The laboratory findings were similar to those of the previous admission.

She was treated with cortisone orally starting with 100 mg. a day and tailing off to 25 mg. in three weeks and hydrocortone 2.5% drops to the eyes 4 hourly. Nine intravenous injections of Piromen were given.

On April 19, 1955, she was readmitted with pain in the left eye. It was so severe that she was crying and vomiting. Examination revealed secondary glaucoma and uveitis. She was treated and her symptoms gradually subsided.

She was readmitted in January 1956, two months pregnant. Her previous four pregnancies had been associated with a flare-up of her eye condition with precipitation of secondary glaucoma. In view of this, a therapeutic abortion was carried out and followed by hysterectomy.

After hysterectomy, she began to complain of headache. The left occipital region was chiefly involved and the pain tended to spread to involve the left side of the head. Towards the end of 1957, she had repeated vomiting attacks with headaches and fever. This was accompanied by increasing weakness of the right arm and leg so that she required a cane to assist her walking. She had no further pain in the eyes.

She was readmitted to hospital in Feburary 1958 for neurological investigation. At this time she was looking much older than her years. She had moderate greying of the hair and marked facial vitiligo. There was no oral ulceration. Between bouts of distress with headache, she was rather euphoric.

On examination there was some stiffness of the neck. Apart from the eye changes the cranial nerves were normal. She had a right hemiparesis with about a 50% reduction in power. The tendon reflexes on the right side were increased, and the right plantar reflex showed an extensor response.

During this admission a low-grade fever up to 100° F. occurred.

*Investigations.*—The laboratory findings again resembled those of the first admission.

The E.E.G. showed a very low amplitude record with excess generalized slow wave activity.

*Cerebrospinal fluid.*—Cells 280; lymphocytes 90%; protein 70.4 mg. %; chlorides 734 mg. %; glucose 40 mg. %; colloidal gold 011000000; Pandy negative; Kahn negative.

This patient was most anxious to go to her children and was allowed out on the understanding she would return in ten days.

She was readmitted March 1958 and given Meticorten 40 mg. daily. After two weeks of therapy, her hemiparesis improved considerably. Her headache subsided and she was able to walk about without a cane.

CASE 5.—Mrs. G.B., aged 22, who is partially of Indian extraction, was first seen on December 13, 1957, complaining of transient double vision and pain and blurring of vision in the right eye. Ophthalmological examination at that time did not reveal any abnormality. Her visual acuity was 20/20 in each eye.

The following day she returned complaining of more pain and reduced vision in the right eye. On examination at this time the visual acuity was 20/50 in the right eye, and she had a central scotoma extending to 10°.

Her sight became progressively worse and by December 19 had deteriorated to R. 20/200, L. 20/100. She was admitted to hospital for investigation with a tentative diagnosis of bilateral retrobulbar neuritis. Pertinent findings at this time were: blood count: W.B.C. 7500, 67% neutrophils, 26% lymphocytes, 7% monocytes, Hb. 14.2 g. %, sedimentation rate 15 mm. in one hr. Cerebrospinal fluid cell count: 20 lymphocytes, 40 erythrocytes; glucose 70 mg. %.

The patient was given Meticorten 20 mg. twice a day and, although her visual acuity did not improve, she discharged herself on December 24, 1957.

The patient was readmitted to hospital on December 27, 1957. At this time her visual acuity was R. 18/200, L. 14/200. She complained of severe headache and severe pain in each eye. The optic disc margins of each eye were blurred. There was diffuse œdema throughout the entire retina of each eye, more concentrated in the macular region. This œdema gave the retina a striated clock dial appearance.

At this time the superficial and deep reflexes were found to be markedly diminished. Meticorten was again administered, and ACTH was given in addition.

December 28, 1957: A retinal detachment was present in the superior temporal and inferior temporal quadrants of the right eye. In the left eye there was an inferotemporal retinal detachment. The cerebrospinal fluid on this date contained 500 lymphocytes, glucose 50 mg. %, chlorides 742 mg. %, and protein 104 mg. %.

Acetazolamide (Diamox) 1000 mg. was given daily from December 28 to January 3, 1958.

December 29, 1957: In each eye the retinal detachment had increased and there was a corresponding decrease in the œdema at the posterior pole.

January 3, 1958: The cerebrospinal fluid cell count was 226 lymphocytes and sugar was 83 mg. %.

January 5, 1958: The retinal detachments had improved and were present in the temporal regions of each eye only. The remainder of the fundus revealed a peculiar fine pigmentation with scattered round circumscribed whitish-yellow dots.

The retinal detachments gradually subsided and on January 17, the patient was discharged from hospital. The visual acuity had improved to R. 20/20 and L. 20/60. On slit lamp examination there was no flare in the anterior chamber of each eye. Early lenticular opacities were noted in each eye following the embryonal nuclear suture line. The posterior lenticular space and anterior vitreous was filled with fine pigment particles. On ophthalmoscopic examination the entire fundus of each eye had heavy pigment deposits, more concentrated in each macular region, and dispersed amidst these pigment deposits were peculiar round yellowish-white spots. The intraocular tension of each eye was normal.

She was next seen on April 25, 1958. By this time poliosis of the hair of the head had developed.

Intraocular and intraperitoneal injection of the patient's cerebrospinal fluid into rabbits was unsuccessful in reproducing this disease.

## DISCUSSION

These five cases show the great variations in severity and clinical picture which may be encountered.

The first patient exhibited mild manifestations of the disease. Apart from the marked macular œdema, there were no posterior ocular manifestations of inflammation and iridocyclitis was not severe. The alopecia and poliosis developed six weeks after the onset of the disease. It is possible that a low-grade uveitis was present during the interval of four months after the first attack of iritis.

Case 2 developed the retinal detachment in one eye only and the detachment persisted. The case was unusual in that he developed a severe encephalitis which resulted in diabetes insipidus and a permanent psychosis. It might be argued that the psychosis was due not to the encephalitis but to the psychic trauma of the prolonged illness. The pigmentary changes in skin and hair did not occur in this patient.

The third patient had a condition typical of the picture described by Harada with bilateral retinal detachments. He had some features of the Vogt-Koyanagi pattern, however, because he later developed severe iridocyclitis with secondary glaucoma and cataracts. He became blind. This patient was thought to have a rapidly increasing intracranial space-occupying lesion, and an exploratory craniotomy was performed.

The fourth patient illustrates an unusual mode of onset because recurrent uveitis preceded the neurological signs. It is interesting that whereas the ocular manifestations failed to respond to corticosteroids, the neurological lesions rapidly responded to a dose of Meticorten which was more than double the previous dose. It might be argued that recurrent attacks of uveitis and secondary glaucoma, with on one occasion ulcers of tongue and mouth, are more in favour of a diagnosis of Behçet's syndrome. But there were no genital ulcers, no lesions were present on the legs, and the oral ulcers never recurred. Moreover, marked

vitiligo appeared on the face, and vitiligo is not a feature of Behçet's syndrome.

Case 5 presented as a bilateral retrobulbar neuritis and then developed into an apparently typical Harada pattern with good recovery.

## ETIOLOGY

Two theories concerning the cause of this disease have been advanced, namely, that it is (a) a virus infection and (b) an allergy to uveal pigment.

The histological appearance of the uveal tract is that of a non-specific chronic granulomatous inflammation, and it does not especially favour either a virus or an allergy as the cause of this condition. At the present time the weight of evidence suggests a virus as being the cause, but it is by no means proven.

### A. *The Evidence Concerning the Viral Theory*

The subretinal fluid of a case with detachment of both retinæ was inoculated into the vitreous of a rabbit by Tagami.[9] This resulted in a disease closely resembling the human condition. Takahashi[10] also injected vitreous from affected eyes in to the basal cisterns of rabbits and produced a descending optic neuritis and uveitis. He then injected some of the brain tissue from an infected rabbit into the basal cistern of another and caused the same disease. Similarly optic neuritis and uveitis resulted when Malbran and Muhlmann injected vitreous from an eye with Harada's disease into the subarachnoid space of rabbits. Sugiura, Fukuda and Eda[12] inoculated mouse brain with material from eight eyes affected with uveo-encephalitis and two with sympathetic ophthalmia. Only from the eighth case of uveo-encephalitis, which happened to be an early one, was a virus grown. This was found to be neutralized by the blood serum of one of the other patients in a dilution of 1 in 100.

These findings suggest a viral origin, but Bruno and McPherson[13] injected the subretinal fluid of their cases into the brains of mice and were unable to confirm the results of the Japanese workers. Repeated egg embryo and mouse brain inoculations of aqueous, subretinal fluid and spinal fluid from affected patients at the Wilmer Institute [14] have also been negative. In our series subretinal fluid from Case 2 and cerebrospinal fluid from Case 5 were inoculated into rabbits' eyes but no virus was grown in either case. Moreover, as Walsh[8] has pointed out, the virus D disease is widespread in rabbits and it is possible that it may remain latent and be provoked into activity by an intracranial injection.

The results of the search for a virus are thus equivocal. But it must be remembered that the diagnosis is seldom made in the early stages. The negative reports in the literature may be due to the fact that by the time the diagnosis is made the virus has disappeared. It may well be that a positive virus culture may be obtained if the aqueous, subretinal fluid or vitreous is inoculated at an early stage before the virus has disappeared from the ocular fluids.

The integumentary changes are difficult to explain. They develop about the third month in the course of the disease in at least 80% of cases. No satisfactory explanation of the alopecia, vitiligo, and poliosis in this condition has yet been advanced. It is still more difficult to relate these ectodermal manifestations to the uveo-encephalitis.

In his exhaustive study of this condition, Hague[15] reviewed the embryology and anatomy of the hypothalmic region and suggested that a lesion in this area might be responsible for the complaints of chilliness, the deafness, and the depigmentation. He quoted a patient of Vonderahe and Abrams[16] who had an ependymoma of the third ventricle and depigmentation of skin, alopecia, greying of the hair and polyuria. It is interesting that our second patient had diabetes insipidus but no depigmentation. Our third patient had some abnormalities of glucose metabolism and operation revealed adhesions in the hypothalamic area. Hague[15] pointed out that these observations might also be related to some of the unusual features of the Laurence-Moon-Biedl syndrome. It seems reasonable, therefore, to postulate that this condition might be due to a virus infection involving the hypothalamic area of the brain and the uveal tract of the eyes.

### *Relation to Sympathetic Ophthalmia*

Harada[4] drew attention to the many ways in which the disease he described resembled sympathetic ophthalmia. The important difference between the two diseases is that sympathetic ophthalmia follows a penetrating wound of the eye whilst uveo-encephalitis does not. Both give rise to severe generalized uveitis with depigmentary changes in skin and hair. In sympathetic ophthalmia, however, these ectodermal changes occur much less commonly than in the Vogt-Koyanagi-Harada disease. But several cases of sympathetic ophthalmia have been reported with the full clinical picture of the Vogt-Koyanagi[17-19] disease. Occasionally sympathetic ophthalmia may give rise to optic neuritis or inferior retinal detachements as in Harada's disease, but the retina can seldom be seen because of the severe anterior uveitis. It may also cause deafness, fever and signs suggesting meningeal involvement (Duke-Elder).[20] The histological findings in the eye in sympathetic ophthalmia and the Vogt-Koyanagi-Harada diseases are very similar. Harada considered the two conditions to be closely related. Cowper,[7] Swartz[18] and Hager [21] believe them to be identical.

There is, however, one important feature in which the two conditions differ. Typically, sympathetic ophthalmia results from an injury of the eye in which uveal tissue is involved in the wound.

This history is never obtained in Vogt-Koyanagi-Harada disease. However, if both conditions are believed to be due to a virus it is possible that the two conditions may be identical, the only differing feature being the way in which the virus reaches the eyes, i.e. via the blood stream or optic nerves in uveo-encephalitis, and a penetrating wound of the eye in sympathetic ophthalmia. It appears to the authors that sympathetic ophthalmia is but a variant of uveo-encephalitis.

### B. *The Allergy Theory*

Woods[22] suggested that sympathetic ophthalmia is an allergic reaction to uveal pigment but the evidence is by no means conclusive. In an attempt to determine whether the Vogt-Koyanagi disease has an allergic basis, Rones[23] performed sensitivity tests upon three cases. One test was positive and two were negative. Bruno and McPherson[13] also performed skin tests for allergy to uveal pigment on four patients but their results were negative. Fine and Gilligan[19] obtained a positive reaction to uveal pigment in one case. But the presence of a positive skin test does not necessarily indicate that the disease is caused by allergy to uveal pigment. Since his original suggestion, Woods[24] has pointed out that a similar hypersensitivity reaction to uveal pigment may occur after penetrating ocular injuries.

It may be of some significance that the uveo-meningo-encephalitic syndrome appears to affect the pigmented races such as Negroes and orientals more frequently than the white-skinned races. Four of our cases were in patients who were of more darkly pigmented racial origin. One was partly Italian, two had Indian blood and one was Chinese.

## TREATMENT

There is no known effective treatment for this condition but there are several reports in the literature which suggest that corticosteroids might be of value. Our second, third and fifth cases were not benefited at all, but the hemiplegia of the fourth patient appeared to show some response when more than double the usual dose was administered. Crawford[25] found cortisone to be of value in one case. Bronstein[11] reported a case in which 20 mg. of prednisone daily produced rapid improvement. A relapse occurred when the prednisone was reduced to 10 mg. daily and there was a rapid response when the dosage was raised to 30 mg. daily. The results in this case and our fourth patient suggest that prolonged and maximal dosage with cortiscosteroids is required if a satisfactory response is to be obtained. It must not be forgotten, however, that there is a great difference in severity in different cases, the course may fluctuate, and this apparent response may have been due to a natural resolution.

## SUMMARY

The literature of the Vogt-Koyanagi-Harada disease is briefly reviewed.

The essential features of the disease are described. Five cases are recorded.

The etiology and treatment of the condition and its relationship to sympathetic ophthalmia are discussed.

Severe cases may resemble a rapidly expanding intracranial space-occupying lesion. This condition therefore deserves wider recognition to prevent unnecessary exploratory craniotomies.

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## REFERENCES

1. HUTCHINSON, J.: *Arch. Surg., London,* **4**: 357, 1892-3.
2. VOGT, A.: *Klin. Monatsbl. f. Augenh.,* **44**: 228, 1906.
3. KOYANAGI, Y.: *Ibid.,* **82**: 194, 1929.
4. HARADA, E.: *Acta Soc. Ophth., Japan,* **39**: 356, 1926.
5. CORDES, F. C.: *Am. J. Ophth.,* **39**: 499, 1955.
6. YUGE, T.: *Ibid.,* **43**: 735, 1957.
7. COWPER, A. R.: *A.M.A. Arch. Ophth.,* **45**: 367, 1951.
8. WALSH, F. B.: Clinical neuro-ophthalmology, 2nd ed., Williams & Wilkins Company, Baltimore, 1957, p. 466.
9. TAGAMI, K.: *Acta Soc. Ophth., Japan,* **35**: 1289, 1931.
10. TAKAHASHI, M.: *Acta Soc. Ophth., Japan,* **34**: 506, 1930.
11. BRONSTEIN, M.: *A.M.A. Arch. Ophth.,* **57**: 503, 1957.
12. SUGIURA, S., FUKUDA, M. AND EDA, K.: *Acta Soc. Ophth., Japan,* **57**: 117, 1953. (Abstract Ophth. Lit., 7: 42, No. 86, 1953).
13. BRUNO, M. G. AND MCPHERSON, S. D., JR.: *Am. J. Ophth.,* **32**: 513, 1949.
14. WOODS, A. C.: Endogenous uveitis, Williams & Wilkins Company, Baltimore, 1956, p. 11.
15. HAGUE, E. B.: *Arch. Ophth.,* **31**: 520, 1944.
16. VONDERAHE, A. R. AND ABRAMS, N. R.: *Ibid.,* **12**: 693, 1934.
17. CRAMER, E.: *Klin. Monatsbl. f. Augenh.,* **51**: 205, 1913.
18. SWARTZ, E. A.: *Am. J. Ophth.,* **39**: 488, 1955.
19. FINE, B. S. AND GILLIGAN, J. H.: *Ibid.,* **43**: 433, 1957.
20. DUKE-ELDER, W. S.: Textbook of ophthalmology, Vol. 3, Henry Kimpton, London, 1940, p. 2338.
21. HAGER, G.: *Klin. Monatsbl. f. Augenh.,* **131**: 89, 1957.
22. WOODS, A. C.: *Am. J. Ophth.,* **19**: 9, 100, 1936.
23. RONES, B.: *Arch. Ophth.,* **7**: 847, 1932.
24. WOODS, A. C.: Endogenous uveitis, Williams & Wilkins Company, Baltimore, 1956, p. 19.
25. CRAWFORD, H. E.: *Hawaii M. J.,* **13**: 26, 1953.

## RÉSUMÉ

Le syndrome uvéo-encéphalique que l'on a vu jusqu'à présent surtout dans le domaine des ophtalmologistes, se compose d'uvéite, d'achromie de la peau et des cheveux, et de manifestations cérébrales. Les auteurs donnent un rappel historique commençant par Jonathan Hutchinson qui en a fait la description princeps en 1892 bien que son nom ne fasse pas partie de l'appellation éponymique du syndrome. Il est possible que les uvéites bilatérales avec pléocytose du liquide céphalo-rachidien représentent des formes frustes de cette affection. Dans son plein épanouissement l'évolution clinique se répartit en trois phases. La première est la phase méningée caractérisée par des céphalées frontales ou rétro-orbitraires à début brusque et d'une durée de deux à quatre semaines, accompagnées de fièvre. La période ophtalmique suit ou peut aussi se manifester concurremment à la première. On y trouve de la photophobie, du larmoiement, une cécité rapidement progressive et de l'irido-cyclite quelquefois. Le malade

présente des milieux troubles, un œdème rétinien ainsi que des hémorragies et des détachements bilatéraux inférieurs. Une surdité souvent bilatérale mais transitoire avec ou sans bourdonnement peut inquiéter le malade. Le tableau clinique ressemble alors à celui d'une lésion intracranienne progressive. La convalescence s'amorce à la troisième période pendant laquelle la majorité des lésions disparaissent lentement au cours des mois. Moins de 30% des malades, cependant, recouvrent une vision satisfaisante à cause des complications oculaires (glaucome, cataracte, atrophie optique, contraction du globe oculaire etc.). C'est pendant cette période que l'on voit s'installer la poliose, le vitiligo et l'alopécie. Les faits cliniques de cinq cas sont donnés en guise d'illustration.

Les auteurs s'engagent dans une discussion des deux théories sur l'étiologie de cette affection, à savoir: une infection à virus ou une allergie aux pigments uvéaux. Le gros des preuves semble indiquer une infection virale. Certaines humeurs injectées au lapin reproduisent la maladie d'assez près; on peut également transmettre d'un animal à l'autre l'affection qui en résulte. On aurait même isolé un virus d'un cas à ses débuts. Il faut se rappeller cependant que les résultats n'ont pas toujours pu être reproduits et sont donc équivoques. Cette théorie d'ailleurs est impuissante à expliquer les manifestations ectodermiques de la troisième période. Le syndrome uvéo-encéphalique a plus d'un trait en commun avec l'ophtalmie sympathique si bien que certains auteurs refusent de voir deux entités nosologiques différentes et prétendent que la seule différence réside dans le mode de pénétration du virus (par blessure dans l'ophtalmie sympathique).

Les bases de la théorie allergique sont très mal établies. La maladie semble s'attaquer plus fréquemment aux individus de races pigmentées qu'aux blancs. Il n'existe aucun traitement spécifique bien que les cortico-stéroïdes aient donné des résultats appréciables.

# THE HAZARDS AND PRINCIPLES OF ANÆSTHESIA FOR TONSILLECTOMY AND ADENOIDECTOMY IN CHILDREN*

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TONSILS IN OR OUT? This is a problem that has troubled the medical profession for many years, and it seems that the question is still unanswered. In England in 1938 a Medical Research Council report regarded the operation as "a prophylactic ritual carried out for no particular reason with no particular result".[7] The truth, of course, is that some benefit does accrue from the removal of some tonsils and adenoids. The possibility that some tonsils and adenoids might just as well be left where they are is purposely stressed not because anæsthetists are often asked to decide this point but, if no great harm is likely to befall a child who retains these items, it is a major catastrophe if some harm does befall him in the process of losing them.

## HISTORY

Hindu surgeons were attacking the tonsils as long ago as 1000 B.C.[1] and Celsus, in A.D. 30, would tear them out with a fingernail.[2] However, the real benefactor of the modern otolaryngologists was a certain Dr. Bosworth, who around 1884 expounded the view that all faucial tonsils were abnormal.[3] Since this time some form of guillotine operation held the field almost until the present day, though Waugh described his technique of blunt dissection in 1909,[4] but taking three minutes to complete, this took at least six times as long as the guillotine operation.

For a long time the operation was performed without anæsthesia and this surprisingly enough was being advocated as recently as 1935.[5] However, though Warren remarked on the use of ether in 1848,[6] general anæsthesia was probably not much in vogue until the 1890s.[2] Two of the favourite techniques were the single-dose method with ethyl chloride or nitrous oxide for the guillotine procedure and ether insufflation of the oropharynx for dissections. Both methods are still widely used.

## PRESENT POSITION

Today the operation still retains much of its popularity, and though the guillotine method is still employed it is gradually giving way to more careful methods of dissection; this paper is therefore concerned mainly with anæsthesia for the latter operation.

In 1954, at a cost to Great Britain of eight and a half million dollars, close upon a quarter of a million children underwent tonsillectomy and/or adenoidectomy,[7] and in Ontario in 1951, 8% of all hospital discharges – medical and surgical – were labelled "hypertrophy of tonsils and adenoids".[8] In the United States the operation is reported as comprising one in four of all surgical operations,[9] and at the Montreal Children's Hospital it comprises around 28% of all operations on children.[10]

With this long history and high incidence, it is surprising that Collins and Granatelli were able to write in 1956, "The most neglected of anæsthetic procedures is that for tonsillectomy",[11] and in spite of the number of articles which have recently appeared on this subject, their remarks still contain more than a grain of truth.

## HAZARDS

In 1955 in Canada, 27 children under 15 years of age died, and tonsillectomy and adenoidectomy appeared on the death certificate.[12] In a review from a town in the United States of 20,000

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