GRADENIGO'S SYNDROME.*

By H. G. ESTCOURT, M.B., B.S. Lond., Late House Surgeon to the Ear, Nose, and Throat Department, Middlesex Hospital.

IN 1904, the late Professor Gradenigo, who was one of the two distinguished foreign members of this Section, first described the syndrome which has ever since borne his name. His paper is founded on the study of five cases of his own, and he describes the general features as follows: The patients are young, and the otitis media which is acute is sometimes, but not always, accompanied by mastoiditis. The drumhead may or may not be perforated. There is severe pain, usually with a temporo-parietal distribution. About a month or so after the onset of the middle ear symptoms diplopia suddenly develops, due to the involvement of the abducens nerve. Optic neuritis is absent. Within about two months from this time, sometimes following surgical interference, and sometimes in its absence, the pain becomes trifling and the diplopia vanishes with it. Occasionally a diffuse meningitis becomes established and the case ends in death. The three characteristic features of this symptom-complex are: an acute inflammation of the middle ear, enduring pain especially in the temporo-parietal region and paralysis of the sixth nerve.

Such cases had been reported previously, scattered sparsely through the literature and Gradenigo quotes a number of these, rejecting, however, the various explanations such as post-influenzal neuritis suggested by the reporters. His own five cases are described in some detail and they may be summarised as follows:—

CASE I. Female, aged 31: The onset was characterised by pain in the right ear with spontaneous perforation of the tympanic membrane on the 9th day; this was enlarged later by operation. On the 25th day a cortical mastoid operation was done, pus being found in the antrum and in a large apical cell. On the 42nd day intense orbital and parieto-occipital pain began and was followed two days later by a palsy of the right external rectus muscle. No other cranial nerves but the fifth and sixth were involved and optic neuritis was absent. By the 64th day the diplopia had vanished and the pain disappeared soon after. The case ended in complete recovery.

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Case II. Male, aged 44: A left-sided acute otitis media arose in the course of a nasal catarrh, but without perforation. Three weeks later pain began in the left side of the head followed, four weeks afterwards, by diplopia due to left abducens palsy. Ten days later Gradenigo first saw the case; he found the drumhead reddened and incised it. An abundant discharge followed with no relief, however, to the pain. A mastoid operation was done on account of the eye symptoms. The bone was found to be healthy, as was also the dura mater covering the upper surface of the petrous bone as far as it could be exposed. In six weeks the ear was dry, the paralysis very much improved, and the patient was discharged from hospital. The pain is not again mentioned.

Case III. Male, aged 22: This case occurred in an out-patient and was very incompletely observed. In the course of a non-perforative left acute otitis media there had been a sudden onset of abducens palsy with pain in the temporo-parietal region. There was no optic neuritis. The tympanic membrane was bulging. Paracentesis was refused by the patient who went home, but afterwards recovered completely without any surgical interference.

Case IV. Female, aged 17: She was seen with a right purulent otitis media of one month's standing. No mastoid tenderness was present but there was much pain in the frontal and temporal regions. The right sixth nerve and the lower right facial muscles were palsied. Bilateral optic neuritis was observed, worse on the right side. Two days later at the Schwartze operation pus was found in the tympanic antrum and neighbouring cells. The pain diminished and the paralysis improved, but the optic neuritis continued, and a month after the first operation a radical mastoid operation was performed. No fistula was found leading into the cranial cavity. When the patient became convalescent and left the hospital, the paralysis and the optic neuritis had much diminished, and three years later inquiry showed that subsequent recovery had been complete.

Case V. Male, aged 31, with ozæna: Left acute otitis media developed without perforation or much pain. After an uneventful course for a month the pain became much worse over the left side of the head, but there were no signs of mastoiditis. On paracentesis only a drop of pus was obtained and the ear was dry in twenty-four hours. As the pain persisted the mastoid was opened in fear of intracranial complications, but it was not found to be extensively involved. The dura mater of the middle fossa was normal. Six days after the operation an abducens palsy appeared, but without optic neuritis. In this case, unlike the preceding one, recovery did not occur but the patient died of meningitis a fortnight later. No post-mortem was made.

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Gradenigo discusses the explanation of the symptom-complex, and favours a circumscribed purulent leptomeningitis due to a lesion of the bone at the petrous tip and spreading to the dura mater, an hypothesis which had previously occurred to Habermann and Brieger. Case V. ending in death from meningitis, he looks upon as strongly confirming this hypothesis. He rejects a coincident sphenoidal sinus suppuration on the grounds of negative rhinoscopic findings, and thinks the duration of the symptoms was too long for it to be a so-called "reflex" effect from the ear.

Gradenigo's article seems to have attracted a considerable amount of attention and several cases were reported in Italy, France, and the United States; but no record has been found of any cases in the English otological literature of this period. In 1908, Baldenweck in France published an important article on the alterations of the Gasserian ganglion and of the sixth nerve in the course of inflammation of the ear, and part of this article deals exclusively with Gradenigo's syndrome. This was followed two years later by an admirable paper by Perkins published in the American Annals of Otology. He reported three cases and gave a very comprehensive account of the symptoms and pathology of this syndrome. One of his cases is of special interest in that all the symptoms ceased immediately after an operation had been performed on the mastoid, and this, despite the fact that the mastoid did not appear to be diseased. We shall see that this is not an uncommon occurrence in these cases.

Wheeler of New York seems to have been the first ophthalmic surgeon to notice cases of Gradenigo's syndrome, and in 1918 he wrote an article dealing mainly with the ophthalmic side of the question. He describes two interesting cases. The first was a child, aged 11, who two years previously had an operation for acute mastoiditis on the left side. When first seen she complained of a discharge from the right ear of six weeks' duration, quite recently complicated by double vision and by severe pain in the right side of the head, most marked over the right eye. Examination revealed a complete paralysis of the right external rectus muscle. The mastoid cells were opened. The process was discovered to be of the pneumatic type, but nothing unusual was found in spite of a careful search in the direction of the sixth cranial nerve. The day after operation there was great improvement

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in the diplopia which entirely disappeared together with the pains three days later. There was no recurrence of the trouble.

Wheeler's second case occurred in a girl aged 5. For two weeks she had complained of severe earache in the right ear, and this was associated with unusually severe pain in the right half of the face and in the right eye. The right side of the mouth was so sore that the child refused to eat solid food. The mother had noticed for some days that the right eye turned in. On examination there was found to be complete paralysis of the right external rectus muscle. Vision was normal as was the visual field. The right drumhead was slightly red and appeared to be bulging a little. There was no perforation. As the pain in the ear itself was slight, it was thought that the aural condition was on the way to recovery, and paracentesis was not performed. Two weeks later the pains had nearly ceased and the child was much better. The drumhead was almost normal but the ocular paralysis was unchanged. A week after this, signs of action of the external rectus muscle began to appear, and six weeks later the mobility was normal. Convalescence was interrupted by a brief but severe attack of headache and earache.

Coming to more recent times, Mr Just described an interesting case at a Meeting of the Section of Otology, in March 1924. The patient gave a history of a slight discharge from the right ear seven weeks previously. The discharge ceased after a few days and there had been none since. Examination revealed complete paralysis of the right external rectus muscle with hyperæsthesia on the same side of the head. There were no signs of active ear disease, no mastoid swelling or tenderness. In spite of this, and because of the external rectus paralysis, Mr Just decided to operate. The whole mastoid process was found to be infected and behind the external semicircular canal an infected gallery of cells was found running in towards the tip of the petrous bone. These cells were curetted and packed and the wound was left open. Three days later the sixth nerve paralysis had completely disappeared. At the operation the dura mater of the middle cranial fossa was explored but it was found to be normal. Lumbar puncture revealed clear fluid under increased pressure.

In 1921, Mr W. M. Mollison described two cases of paralysis of eye muscles occurring in connection with mastoiditis. They were not true cases of Gradenigo's syndrome, but one of them

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bears a considerable resemblance to the type of case that we are now considering. This was a boy, aged 10, who had an eight weeks' history of earache and intermittent discharge from the right ear following chicken-pox. For ten days there had been vomiting of the cerebral type. The temperature had been as high as 103° F. Examination revealed the following points: The patient complained of pain above the right eye; the temperature was 99° F.; there was ptosis of the right upper eyelid and paresis of the right external rectus muscle; no optic neuritis was present and nothing abnormal could be found in connection with the central nervous system; there was a little pus in the right meatus and granulations were seen on the tympanic membrane; there was no tenderness or œdema over the mastoid process. A diagnosis of acute mastoiditis was made with the alternative possibility of a cerebral abscess or tuberculous meningitis. Operation on the mastoid showed extensive suppuration; the dura mater of the middle and posterior cranial fossæ was exposed and found normal. Lumbar puncture revealed cerebro-spinal fluid of normal appearance and under normal pressure. Some improvement followed the operation, but a week later the symptoms were again marked. The wound was opened up; no further suppuration was found; the dura mater was exposed as far towards the tip of the petrous bone as was possible but nothing abnormal was found. The temporo-sphenoidal lobe was explored, but no pus discovered. After this operation the boy quickly improved and the paralysis of the eye muscles had disappeared at the end of six weeks.

Before passing to a general discussion of Gradenigo's syndrome, there is one more case that I should like to describe.

A male, aged 21, was admitted to the Middlesex Hospital in the summer of last year. On 7th July while in hospital having treatment for a skin condition, he developed left acute otitis media with copious discharge. This improved under treatment, although when the patient left the hospital the ear was still discharging a considerable amount of pus. He was not seen again until 20th August, when he was admitted under Mr Cleminson, with the following history.

The left ear had been discharging continuously since 7th July, but the patient had no pain in the ear itself. On 6th August he had an acute attack of pain over the left side of the face and scalp, and similar attacks had occurred frequently ever since. On 11th August he developed double vision. On examination it was found that the patient exhibited a typical Gradenigo's syndrome. He complained of severe pain over the left side of the face, forehead and scalp, with cutaneous

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hyperæsthesia over this area. The pain was absolutely confined to the left side and it was most severe above the left eye. Paralysis of the left external rectus muscle was complete. The optic discs were normal; there was no nystagmus nor any signs of involvement of the other cranial nerves. A profuse discharge came from the left ear but mastoid tenderness and swelling were absent and the temperature and pulse were normal. Unfortunately a lumbar puncture was not performed.

On 24th August the ordinary Schwartze operation was done by Mr Cleminson. Some pus was found in the tympanic antrum along with a little softened and unhealthy bone surrounding the antrum. Most of the mastoid cells appeared to be perfectly healthy and no unhealthy cells could be found running in the direction of the apex of the petrous bone. The dura mater was not exposed. The patient improved after the operation, but the pain still persisted though it was not so severe as before. On 31st August (*i.e.*, a week after the operation) the external rectus muscle began to act, very feebly at first, but six weeks later it was acting normally. The pain persisted for a fortnight after operation and then after a particularly severe attack, which was evidently a kind of swan-song, it completely disappeared and has never returned.

Symptoms and Signs.—The cases described really show all the symptoms and signs associated with Gradenigo's syndrome, and on this side of the question there is very little more that need be mentioned.

It is rare for the pains and the external rectus paralysis to commence simultaneously; the pain usually precedes the paralysis. In Mr Cleminson's case the attacks of pain appeared five days before the paralysis. Moreover, both these symptoms usually appear some considerable time after the onset of the otitis media.

Hyperæsthesia or even anæsthesia of the skin may be present over the area in which the pain occurs and the latter may be associated with an attack of herpes. In one case severe toothache was a prominent symptom. As one would expect, owing to the close proximity of the motor with the sensory part of the fifth nerve, it is not very uncommon for the former to be involved giving rise to spasm or paralysis of the muscles of mastication.

The ocular palsy is always seated in the external rectus of the side corresponding to the otitis media, and I have found one case in the literature in which there was a double otitis media associated with the paralysis of both external recti muscles. One of Wheeler's cases developed an acute mastoiditis on one side with paralysis of both external recti. It is difficult to know how to account for this.

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Lumbar puncture has been performed in many of these cases. The cerebro-spinal fluid is usually found to be under increased pressure, but very rarely, if ever, is any other abnormality present. Very few references to the condition of the optic discs are to be discovered, but both Gradenigo and Baldenweck state that in typical cases there is never any optic neuritis. This was so in Mr Cleminson's case, and I think it is what one would expect. If the inflammation were extensive enough to cause optic neuritis, other cranial nerves besides the fifth and sixth would be involved and the case would not be likely to show a typical Gradenigo's syndrome. However, Gradenigo's fifth case developed bilateral optic neuritis. It is worth noting that it is the only case I can find in the literature that definitely exhibited this sign.

Apparently the mastoid process may or may not be infected. From the point of view of treatment this is a very important question to decide and unfortunately often a very difficult one. But the many cases that have shown a perfectly healthy mastoid at operation clearly prove that Gradenigo was quite correct in stating that this syndrome could arise after a simple uncomplicated otitis media. One case is reported by Wheeler in which there was no evidence even of an otitis media. This patient developed a paralysis of the external rectus muscle five days after some boils in the external auditory meatus had been opened. The Wassermann reaction was negative. Wheeler suggested that the cause of the condition was a transient œdema dependent on the boils and involving the periosteum at the apex of the petrous bone, in which position the sixth nerve might be affected. This leads us to consider the pathology of Gradenigo's syndrome.

Pathology, Anatomical Considerations.—As already stated Gradenigo, in his original article, suggested that the cause of this syndrome was a purulent leptomeningitis localised in the region of the apex of the petrous portion of the temporal bone. This theory seems to have been overlooked by the writers who followed him and for some years a "reflex" theory held the field. But what reflex arc was concerned I have been unable to ascertain, and apparently others have felt this difficulty too, for, when the whole matter was seriously considered by Baldenweck and Perkins, the "reflex" theory was abandoned as being altogether too fanciful and obscure, and Gradenigo's original suggestion again came into favour. The latter based his theory of a purulent exudate at the petrous tip on the fact that one of

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his cases died from meningitis. But we now know that nearly all these cases ultimately run a benign course, and this seems to suggest that it is more likely to be a serous than a purulent exudate that involves the fifth and sixth nerves; in confirmation of this we see that in those cases in which a lumbar puncture has been performed there is no alteration in the cerebro-spinal fluid, except that it may sometimes be under increased pressure.

In order to understand why it is that the fifth and sixth nerves may be the only nerves affected by the inflammation, we must consider the anatomy of the region at and about the apex of the petrous portion of the temporal bone.

The sixth cranial nerve emerges from the brain at the lower border of the pons and, as a very thin cord, passes forward and upwards beneath that part of the dura mater which is lying on the basilar surface of the sphenoid bone. The length of this part of its course is about one centimetre. The nerve then enters the cavernous sinus through a small perforation below the posterior clinoid process and a little below the level of the tip of the petrous portion of the temporal bone, and passes forwards through the whole length of the sinus. In following the course of the sixth nerve, after dissecting away the dura mater where the nerve penetrates it, one sees a layer of connective tissue. The nerve pierces this layer diagonally as it passes upwards and forwards. Just in front of this point the nerve trunk is found in contact with the periosteum at or near the apex of the petrous portion of the temporal bone, and then it immediately enters the cavernous sinus usually just external to the junction of the superior petrosal and cavernous sinuses. Here the nerve may lie in contact with the external wall of the inferior petrosal sinus or it may pierce the external wall and reach its position in the cavernous sinus, after having first entered the lumen of the inferior petrosal sinus. But from our point of view the important fact is that for a few millimetres the nerve actually lies in contact with the apex of the petrous portion of the temporal bone. Its position here is marked by a little groove in the bone. Stretching over this groove from the uppermost part of the apex of the posterior clinoid process is the petro-clinoid ligament, and to this ligament is attached the dura mater and the connective tissue layer which has already been mentioned. This ligament is always very firm and often undergoes partial or complete ossification. The sixth nerve passes under it and in this position is therefore completely surrounded by unyielding structures. It is easy to see that

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even a small inflammatory exudate or œdema at this point would be likely to interfere with the function of the nerve.

In a hollow near the apex on the antero-superior surface of the petrous pyramid lies the Gasserian ganglion of the fifth nerve, and it is obvious that a process which would affect the sixth nerve at the tip would also be likely to involve this ganglion. No other nerves are so intimately related to the apex of the petrous portion of the temporal bone. The third and fourth nerves which are the nearest are, all through their course, at an appreciable distance from this bone and enter the cavernous sinus much further forward than the sixth nerve. This is probably the reason why the fifth and sixth nerves are often the only nerves involved in an inflammatory process at the apex of the petrous bone.

We have now to consider how the infection reaches the petrous tip. Perkins in his excellent article mentions the following routes of invasion :—

1. The infection may follow the sublabyrinthine route extending from the tympanum below the labyrinth and the internal auditory meatus to the tip of the petrous bone. This is illustrated by a case published by Lombard in 1906. One of his patients developed a fatal meningitis following an acute otitis media. At autopsy pus was found in the cells at the apex of the petrous bone and the bone itself was of a very pneumatic type. The autopsy also showed that the infection had spread by the sublabyrinthine route. On the healthy side large cells were found at the apex of the petrous bone, and mercury poured into them worked its way beneath the labyrinth into the middle ear. Mr Just's case is another example of infection travelling by this route, except that the infection spread from the tympanic antrum to the petrous tip and not from the tympanum.

2. Infection may follow the course of the small veins that run from the tympanum beneath the dome of the superior semicircular canal to pass through the subarcuate fossa and enter the superior petrosal sinus. Infection spreading in this direction may reach a layer of cells sometimes lying above the internal auditory meatus and in this way arrive at the tip of the petrous bone.

3. It is possible that the thin floor of the tympanic cavity might be sufficiently eroded for infection to reach the carotid canal, pass along it, and finally reach the apex of the petrous bone. But if this were the usual route one would expect the nerves of the jugular foramen to be frequently involved.

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4. The last route described by Perkins is by way of a layer of cells extending along the wall of the Eustachian tube and thus passing from the tympanum to the petrous tip. In connection with this Mr Cleminson has suggested to me that a possible and even easy route would be for the infection to pass directly along the canal for the tensor tympani muscle, and then spread through the suture between the sphenoid and the petrous bone. In a young person this suture would offer no resistance to the passage of infection. This route would also explain why the fifth nerve is usually involved before the sixth. The anterior extremity of the canal for the tensor tympani muscle is only 5 millimetres from the Gasserian ganglion, whereas it is more than twice that distance from the sixth nerve. All these routes are in direct communication with the middle ear and would therefore explain those cases in which there is no accompanying mastoiditis.

Prognosis and Treatment.—We have seen that nearly all the cases exhibiting this symptom-complex make a complete recovery, though it may be weeks or even months before this occurs. However, Gradenigo had one case that died from a streptococcal meningitis, and, from the condition found at operation, one can but assume that Mr Just's case might easily have proved fatal if it had been left alone.

On the other hand, I have described cases, and there are many others in the literature, which have recovered, some without any operation at all, and others after paracentesis has alone been performed. In those cases that have been operated upon and show little or nothing wrong with the mastoid cells it is difficult to see what good the operation can have done. It seems hardly possible that it has facilitated the drainage of the apex of the petrous bone, and yet in Wheeler's first case and in one of Perkin's cases the operation was followed by an almost miraculously speedy recovery. Moreover, excepting two of Gradenigo's original cases in which all the symptoms appeared after an operation had been performed, I have been unable to trace a single case in which the symptoms have persisted unabated for more than a week or two after operation. In Mr Cleminson's case the pain was relieved from the first and had completely disappeared a fortnight after the mastoid was opened up. Yet we know that in an untreated case the symptoms may persist for months. Is it possible that the operation in these cases acts as a strong counter-irritant and by stimulating the blood supply enables the part to overcome

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the infection? Whatever the cause may be the operation has not been performed in vain if the excruciating agony of the pain associated with this condition (it is often quite untouched by large doses of morphia) has been relieved.

A consideration of Mr Just's case raises another point. His patient did not exhibit any of the classical signs suggesting that the mastoid was involved and yet extensive disease was found at operation. This seems to suggest that there is a certain danger in leaving these cases alone. Though no doubt some of them would come to no harm, a certain proportion might prove fatal when they could have been cured by operation.

A consideration of the above facts suggests to me that provided there are no signs of mastoid disease, and the patient can be carefully watched, palliative treatment may be safely undertaken for a week or ten days. Lumbar puncture should be performed. The fluid will probably be clear but come out under pressure. The ordinary treatment for otitis media should be instituted and possibly counter-irritants (*e.g.* leeches) be applied round the ear. The patient should be kept in bed and the temperature and pulse watched. Pain will have to be relieved by morphia. Paracentesis may be necessary. If under this treatment the symptoms begin to abate then one can safely assume that the patient will recover without operation. However, if after a week or ten days of this treatment no relief has been obtained it is not wise to postpone operation any longer. The ordinary Schwartze operation should be performed and a careful search made for any infected gallery of cells likely to be leading to the apex of the petrous portion of the temporal bone. If the mastoid is discovered to be infected there is no question that the correct treatment has been adopted. On the other hand, even if the mastoid cells are found to be healthy the operation will almost certainly be found to give relief, and one can confidently expect the symptoms gradually to abate in severity and finally clear up altogether.

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REFERENCES.—Baldenweck, *L'Ann. d'Ocul.*, 1908, p. 246; Gradenigo, *Archives ital. di Otologia*, 1904, vol. xv.; Just, *Journal of Laryngology and Otology*, March 1924, vol. xxxix.; Lombard, *Ann. d. Mal. de l'Oreille*, 1906, vol. xxxii., p. 321; Mollison, *Proc. Roy. Soc. Med.*, 1921, vol. xiv., p. 31; Perkins, *Ann. Otology*, 1910, vol. xix., p. 692; Wheeler, *Journ. Amer. Med. Assoc.*, 1918, vol. ii., p. 1718.

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