which increases the impact of the heart against the chest wall.

There is another group of cases in which left thoracic pain is obviously the result of muscular strain. There were 6 such cases out of a series of 36 patients who complained of severe pain. In these instances pain was the initial symptom, the onset being sudden and dramatic, and occurring when the patient had no thought of heart disease. A good and common example of the kind of effort responsible for these lesions is cranking an engine; another is lifting a heavy weight. Various muscles may be affected, but after testing the effect of vigorous contraction of individual muscles on the pain I believe that the attachments of pectoralis major and minor, of the external oblique, and of the upper slip of the rectus abdominis, to the fifth rib, are especially susceptible. When the pectorals are to blame pain may be referred to the left arm. Some of these patients volunteered that they felt something snap in their chests.

To sum up, left inframammary pain arises in local muscular or fibrous tissue; it may be due to fatigue or strain of respiratory muscles in cases with respiratory neurosis; to strain of certain muscular attachments involved in such actions as cranking a lorry or lifting a heavy weight; to incessant minimum trauma from the overacting heart of cardiac neurosis; it is predisposed to by poor physique in Da Costa's syndrome; it is maintained and exaggerated by the belief that it arises in the heart. Several of these factors may operate together.

(Lectures II and III will appear in our next two issues. The complete list of references will be appended to the third lecture.)

CEREBRAL SYMPTOMS OCCURRING DURING SULPHAPYRIDINE TREAT- MENT OF MENINGOCOCCAL MENINGITIS

BY

D. F. JOHNSTONE, M.R.C.S., L.R.C.P., D.P.H.

Medical Superintendent, City Isolation Hospital, Plymouth

AND

P. FORGACS, M.B., B.S.

Resident Medical Officer, City Isolation Hospital, Plymouth

The value of sulphapyridine in the treatment of meningococcal meningitis is established beyond doubt. According to our own experience as well as the large number of papers published on the subject, rapid improvement of the clinical picture and an uneventful recovery can be confidently forecast provided that the dosage is adequate and the patient not hopelessly overwhelmed by an acute meningococcal septicaemia. Moreover, the drug is generally accepted as having a large margin of safety, and such common toxic manifestations as occur during treatment are usually more unpleasant than dangerous. Of the more serious complications, the possibility of an acute haemolytic anaemia, or anuria following obstruction of the renal tubules by sulphapyridine crystals, should be borne in mind. Fortunately both conditions are very uncommon, and neither has been observed in our own series of cases. Agranulocytosis is a well-recognized sequel of prolonged treatment with sulphapyridine, but as in meningococcal meningitis large doses are usually given over short periods the possibility of this complication need not be considered seriously.

The 5 cases described below are chosen from 70 cases treated at this hospital since the beginning of 1940. Their clinical history suggests that heavy doses of sulphapyridine may give rise to cerebral symptoms closely simulating those of acute meningitis, which may therefore be erroneously ascribed to the infection itself. As this type of toxic reaction may lead to death unless administration of the drug is promptly discontinued, it is unnecessary to stress the importance of recognizing it at the earliest possible moment.

Case I

A boy aged 14 was taken ill suddenly, with headache and vomiting, in the morning of February 12, 1940. By the evening he was in a semicomatose state, and a lumbar puncture performed at home showed purulent cerebrospinal fluid. He was given four injections of 2 c.cm. of sodium sulphapyridine (10 grains) at four-hourly intervals during the night.

He was admitted to hospital in the morning of the 13th in a semicomatose state. He was very irritable, and showed intense head retraction and spasm of the hamstrings. There was a profuse petechial rash on the trunk. The cerebrospinal fluid was under increased pressure, was turbid, and contained numerous pus cells and meningococci. Sodium sulphapyridine 3 c.cm. was given intramuscularly on admission, and was continued every three hours. On the 14th there was a slight improvement, but the cerebrospinal fluid was still turbid and under increased pressure. On the 15th the fluid became clearer, but the boy was still restless and confused. The dosage of sulphapyridine was now reduced to four-hourly injections of 3 c.cm. Although on the 16th the cerebrospinal fluid was clear and under normal pressure, his general condition, restlessness, and confusion became steadily worse, and he died at 9 p.m.

Case II

A male baby aged 20 months was taken ill on March 23, 1940, with abdominal pain and vomiting. He was admitted to a general hospital on April 1, but no signs suggestive of meningitis were found during the first four days. On the 5th photophobia and head retraction were observed and Kernig's sign became positive. A lumbar puncture was performed and some turbid fluid containing meningococci was withdrawn. He was given $7\frac{1}{2}$ grains (one tablet) of sulphapyridine and transferred to this hospital.

On admission the presence of pus cells and meningococci in the cerebrospinal fluid was confirmed. The child was drowsy and showed the characteristic signs of meningitis—well-marked head retraction, positive Kernig's sign, and intense photophobia. There was no rash. Sodium sulphapyridine 2 c.cm. was injected intramuscularly, and 1.4 c.cm. was given every four hours. On the 6th there was no change in his condition. The cerebrospinal fluid, however, was under normal pressure and was much clearer than on the previous day. During the next two days the fluid became clear, but there was no corresponding improvement in the clinical signs. The child was still very drowsy, and head retraction was pronounced. On the 9th the dose of sodium sulphapyridine was increased to 3 c.cm. six-hourly. The cerebrospinal fluid was still clear and under normal pressure, but head retraction and drowsiness remained. On the 13th the dose of sulphapyridine was reduced to 3 c.cm. twelve-hourly. Next morning slight improvement was noticed, but the patient's condition deteriorated later in the day, and he died during the night.

Case III

A girl aged 7 was admitted to hospital on July 14, 1940, twenty-four hours after the onset of her illness. She was drowsy but not unconscious, and resisted examination. Neck rigidity and spasm of the hamstring muscles were well marked, but no petechial haemorrhages were seen. The cerebrospinal fluid was turbid and under increased pressure; microscopic examination showed numerous pus cells and meningococci.

As she was unable to take sulphapyridine by mouth the drug had to be given by intramuscular injection. Sodium sulphapyridine 3 c.cm. was administered immediately, and the injections were repeated three-hourly throughout the next forty-eight hours. Next day she was still confused and restless, and the cerebrospinal fluid was turbid, although no longer under increased pressure. On the 16th the dosage of sulphapyridine was reduced to 2 c.cm. six-hourly. Although

the fluid was only faintly opalescent and was under normal pressure, stupor, confusion, and irritability persisted. At 11 a.m. on the 17th she began taking sulphapyridine by mouth—15 grains (two tablets) six-hourly. As it was suspected that the drug might be responsible for the failure of her mental symptoms to show improvement, corresponding with the almost normal appearance of the cerebrospinal fluid, the dosage was reduced at 11 p.m. to $7\frac{1}{2}$ grains six-hourly, and the drug was omitted altogether twenty-four hours later.

On the morning of the 18th she was beginning to improve and was able to answer simple questions. On the 19th she was more alert and felt much better; neck rigidity was less marked. By the 20th all signs of meningeal irritation had disappeared; she was mentally normal, and spasm of the hamstrings, neck rigidity, and headache were entirely absent. The temperature, however, rose slightly above normal, and one tablet of sulphapyridine was given six-hourly during the next twenty-four hours. On the 21st neck rigidity and a positive Kernig's sign were again noticed, and as she began vomiting the dose was reduced to one tablet eight-hourly, the drug being discontinued on the 22nd. Next day there were no abnormal symptoms or physical signs, and she made a rapid and uninterrupted recovery.

Case IV

This patient, a girl aged 10, was taken ill with headache and vomiting on April 14, 1940. She became delirious on the 16th and was admitted to hospital in the afternoon in an unconscious and extremely restless condition. Rigidity of the neck and a well-marked positive Kernig's sign were found, but no petechiae could be seen. The cerebrospinal fluid was under greatly increased pressure, was turbid to the naked eye, and contained a large number of pus cells and meningococci.

Sodium sulphapyridine 3 c.cm. was given intravenously on admission and intramuscular injections of 3 c.cm. were continued four-hourly during the next sixteen hours. The following morning a lumbar puncture showed the cerebrospinal fluid to be almost clear and under normal pressure. She was much better, and was willing to take tablets by mouth. Two tablets (15 grains) four-hourly were substituted for the injections. On the 18th she again became delirious, with pronounced neck rigidity. As the spinal fluid was quite clear and was under normal pressure the administration of sulphapyridine was discontinued. On the 19th there was a noticeable improvement in her general condition, and by the 20th she had lost all her symptoms and physical signs. Her convalescence was uneventful.

Case V

A girl aged 11 was admitted to hospital on January 24, 1941, twenty-four hours after the onset of the first symptoms—headache and vomiting. She was complaining of intense headache, but answered questions promptly and intelligently, and there was no restlessness. She had a good deal of head retraction, and the lower limbs were held flexed at the hips and knees. No petechial haemorrhages were to be seen. Lumbar puncture showed purulent fluid under increased pressure; from this meningococci were grown.

The girl tolerated sulphapyridine well by mouth, and was given $22\frac{1}{2}$ grains on admission and 15 grains four-hourly for the next forty-eight hours. On the 25th head retraction and spasm of the erector muscles of the spine became more intense; but there was no headache and she remained quiet and rational. During the evening of the 25th she became restless. But next morning she was confused and quite unmanageable; neck rigidity was still well marked. The cerebrospinal fluid was under normal pressure, and was only faintly opalescent. The dose of sulphapyridine was reduced to $7\frac{1}{2}$ grains four-hourly, but, the restlessness not improving, the drug was omitted at 5.30 p.m.

On the morning of the 27th the patient was quite rational, and rigidity of the neck and spasm of the erector spinae were much less noticeable. She continued to improve rapidly, and had lost all her abnormal signs by the morning of the 29th. She made an uninterrupted recovery.

Discussion

The most striking feature of the five cases reported above is the persistence of their cerebral symptoms in spite of intensive sulphapyridine treatment. Although this type of clinical history was not at all unusual before sulpha-

pyridine therapy of meningococcal meningitis was introduced, the average patient responds to the drug so rapidly and so well that some explanation must be found to account for those cases which are exceptions to this rule.

The first and most obvious answer would be to call these cases drug-resistant and to suggest that their symptoms were due to persistence of the infection. A closer study of the case histories shows that this view is untenable. The appearance of the cerebrospinal fluid, which in this disease is a very reliable guide in assessing the response to treatment, showed gradual return to normal in every case. The patients' symptoms, however, either became progressively more severe (Cases I and II) or returned after a transient improvement (Case IV). The contrast is even more marked in Case V, whose first symptoms of cerebral irritation appeared on the third day of treatment, although the cerebrospinal fluid was by then under normal pressure and was almost clear. The strongest point against the infective origin of the cerebral symptoms is the marked improvement which occurs so rapidly after withdrawal of the drug.

These facts not only contradict the theory of a drug-resistant infection but seem to indicate that the persistence and increasing severity of the mental symptoms were due to the toxic effect of sulphapyridine. If this view is accepted it is easy to see why improvement follows so quickly when the drug is omitted; also, the reason for the discrepancy between the clinical picture and the appearance of the spinal fluid becomes obvious. It now remains to be seen how this type of toxic reaction can be recognized.

It is often extremely difficult to decide whether cerebral symptoms persisting after the second or third day of treatment are due to the disease or to the drug. All the mental symptoms which our cases have shown—irritability, restlessness, confusion, and stupor—are part of the clinical picture in acute meningitis, and by themselves may easily be ascribed to the infection. The differential diagnosis is least difficult in patients who are mentally normal when first seen, and whose cerebral symptoms appear on the second or third day of treatment (Case V). The origin of the symptoms in such cases is obvious. Others show a clearly marked period of remission, after which the mental symptoms return in spite of continued intensive treatment. In some patients, again, the transition between the two sets of symptoms is imperceptible, and the diagnosis cannot be made on purely clinical grounds.

The temperature chart affords no assistance, being a most unreliable guide even in uncomplicated meningitis. The degree and type of pyrexia vary from case to case. Some of our patients have been afebrile throughout their stay in hospital. Similarly, cerebral symptoms may occur in association with a raised as well as a normal temperature. Clinical signs, such as head retraction and spasm of the hamstrings, are also misleading. These sometimes persist for days into convalescence, and their presence in association with cerebral symptoms must not be taken as a certain indication that the infection is still active.

If it is suspected that the persistence of the symptoms is due to the toxic effect of the drug a lumbar puncture should be made without delay. If the fluid is clear and under normal pressure, administration of the drug must be discontinued immediately. Where this is done in time the prognosis is favourable and no additional therapeutic measures are required. On the other hand, if administration of sulphapyridine is continued in these circumstances the outcome of the condition is likely to be fatal. The assistance afforded by lumbar puncture in the diagnosis of these toxic reactions raises the question whether this procedure should be carried out daily in all cases. We believe that this is unnecessary as a therapeutic measure

in patients who respond well to drug treatment and in the absence of symptoms of increased intracranial tension. On the other hand, a sample of the cerebrospinal fluid should be obtained from every patient whose cerebral symptoms fail to clear up within two or three days after the beginning of treatment and in all cases in which these symptoms set in during the course of treatment or recur after a transient improvement.

It is unlikely that any constant relation exists between the concentration of sulphapyridine in the blood or cerebrospinal fluid and the appearance of this type of toxic reaction. Although the amount of sulphapyridine given in the first four cases is much higher than the dose which would be used to-day, a number of patients have taken similar large doses without ill effect. On the other hand, the dosage in Case V would not seem to be excessively high, and yet the patient developed toxic manifestations. It is probable that individual sensitivity to the drug plays an important part in the causation of these toxic symptoms.

Conclusion

The number of cases treated at this hospital during the past fifteen months is too small to allow us to draw any definite conclusions as to the incidence of cerebral symptoms attributable to sulphapyridine treatment. It seems, however, that they are not at all uncommon. It is safe to say that the incidence of this type of toxic reaction is greater among children than among adults, and those receiving the drug by the parenteral route are more liable to it than are those taking it by mouth.

Summary

Five cases of meningococcal meningitis showing persistent cerebral symptoms are reported.

It is suggested that these symptoms were due to the toxic effect of sulphapyridine.

We have to thank Dr. T. Peirson, medical officer of health to the city of Plymouth, for permission to publish the case notes.

LOSS OF VISION FOLLOWING HAEMORRHAGE

BY

H. L. TIDY, M.D., F.R.C.P.

Physician to St. Thomas's Hospital; Colonel, Consulting Physician to the Army at Home

Loss of vision following haemorrhage attracted considerable attention in the earlier decades of the nineteenth century, when blood-letting provided a cause which fortunately no longer operates. It is a rare complication, and surprisingly so after haemorrhage due to accident or trauma, such as occurs in warfare.

The mode of development of the disturbance of vision falls into two groups. In the first group the disturbance closely or immediately follows the haemorrhage. Thus on recovering from syncope due to loss of blood the individual finds that the vision is entirely lost or is impaired in varying degrees. With the more severe grades, especially complete blindness, there is often considerable emotional disturbance, and for this reason the condition has been held to be functional. But more probably it is due to sudden anaemia of the cortical visual centres or of the retina, analogous, as Rolleston points out, to the impairment of hearing which may occur. There are no changes in the fundus. The disturbance is transient, recovery beginning immediately and being as a rule complete and permanent. This group is not further referred to.

The second group is more important, but is undoubtedly rare. In this type there is usually an interval after the

haemorrhage before vision is affected. The impairment may then advance for several days before recovery begins, and some degree is often permanent. Oedema of the disk is nearly always recognizable, though the swelling may be only slight, and oedema of the retina has been described in recent cases. Optic atrophy develops in permanent cases.

The Literature

Harbridge (1924) could find only 18 cases recorded in the literature between 1912 and 1924, a period which included the last war. There has been much discussion as to what is the cause or lesion; it is generally agreed that a combination of several factors is necessary, and possibly these are not identical in all cases. It is probable that blindness never follows haemorrhage in an individual who is in normal health. Haemorrhage alone is not a sufficient factor, since permanent or prolonged disturbance of vision does not follow a single haemorrhage, however profuse, and there is no recorded instance of permanent loss of vision in the bleeding of haemophilia.

Anaemia likewise is not a sufficient cause by itself. In the Victorian and pre-war era two great anaemic diseases were prevalent—pernicious anaemia and chlorosis. For the purposes of a discussion on the ophthalmological complications of diseases of the blood, Panton (1935) investigated a series of 117 consecutive cases of pernicious anaemia admitted to the London Hospital between 1911 and 1920. In this series there were only two cases in which there was disturbance of vision. In one case the patient complained of dimness of vision, and the ophthalmic surgeon's note reads, "Oedema of both disks and retinæ: about 2D of swelling in right disk, less in left disk. Many linear haemorrhages in fundi." In the other case the patient complained of rapid loss of vision, ending in almost complete blindness associated with complete optic atrophy. She had, in addition, fairly advanced cord changes. This is the only case recorded in the literature of severe loss of vision occurring in pernicious anaemia. In chlorosis it may be accepted that papilloedema is occasionally found, and there are many discussions in the older literature as to its significance. Nevertheless it is clearly not of a high degree, and is usually recorded as blurring or haziness of the edge of the disk. It is noteworthy that Clifford Allbutt (Allbutt and Rolleston, 1909), who must have had an enormous experience, stated that he had never seen a case of permanent blindness developing in chlorosis. Before the days of modern treatment the oozing from haemorrhoids sometimes reduced the subject to a state of extreme anaemia, and a profuse haemorrhage might then occur. Nevertheless there is no instance in the literature of disturbance of vision in this condition.

There is little evidence on which to assess the influence of oedema. Certainly gross oedema, apart from a nephritic origin, has no part in producing permanent loss of vision, but most of the recent ophthalmological examinations, when made shortly after the onset, record oedema of the retina and some swelling of the disk, though the latter may be slight. Such localized oedema might well occur after a severe haemorrhage or after a more moderate haemorrhage in an otherwise debilitated subject. It is not impossible that shock may be an important factor.

Site and Circumstances of Haemorrhage

The site of the haemorrhage is of interest. Fries (quoted by Barr, 1934) gives the statistics of 106 cases recorded up to 1876 as follows: Gastric ulcer, 36%; uterus, 25%; epistaxis, 7%; blood-letting, 25%; accidental wounds, 5%. In those days the condition especially attracted attention as a sequel of blood-letting, and Gowers refers to this at some length in his *Medical Ophthalmology*. He states that loss of vision occurred only after repeated bleedings