GASTRIC HAEMORRHAGE IN ACUTE INTRACRANIAL VASCULAR ACCIDENTS

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GASTRIC HAEMORRHAGE IN ACUTE INTRACRANIAL VASCULAR ACCIDENTS

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With Plates 1 to 3

The occurrence of acute lesions of the gastrointestinal tract in association with intracranial disease has been recognized since the first half of the nineteenth century (Camerer, 1828; Andral, 1831, 1840; Rokitansky, 1842; Siebert, 1842). Although this subject has received much attention in the more recent Continental and American literature, it is one which has been strangely neglected by British clinicians and pathologists. The lesions of the digestive tract may take the form of mucosal haemorrhages, erosions, or acute ulcers. They are found most commonly in the stomach, and especially in the fundal region; the duodenum and lower oesophagus are not infrequent sites of occurrence, while involvement of the remainder of the small intestine or the large intestine has rarely been reported. A further type of lesion described is that of gastromalacia; applied to gross morbid appearances, this term serves to differentiate a large and often poorly demarcated area of dissolution from the small, sharply circumscribed, punched-out ulcer (Schlumberger, 1951). As regards the associated lesions of the central nervous system, examples of nearly all types of intracranial disease have been reported; they have been more frequently acute than chronic, and in the case of new growths the majority of reports give a history of a recent acute episode, either operative interference or spontaneous haemorrhage into the growth.

The acute lesions of the digestive tract may be complicated by haemorrhage or perforation, thus allowing clinical recognition. Thus haematemesis and melena have been reported in the following conditions:

Intracranial neoplasm (von Winiwarter, 1911; Hallé and Lereboullet, 1931; Cushing, 1932; Masten and Bunts, 1934; Bodechtel, 1935; Grant, 1935; Swan and Stephenson, 1935; Davies, 1936; Dott, 1938; Ask-Upmark, 1939; Davidoff, 1944; Fugazzola, 1947; Mossberger, 1947; Nitschke and Suckel, 1947; Bastenie, Desneux, and Kowalewski, 1949; Laruelle and Reumont, 1949; Fisher, Watkins, Gardner, and Klotz, 1951; Globus and Ralston, 1951; Gray, Benson, Reifenstein, and Spiro, 1951; French, Porter, von Amerongen, and Raney, 1952; King and Reganis, 1953; Davis, Wetzel, and Davis, 1955).

Meningitis (Gerdine and Helmholz, 1915; Hart, 1919; Bodechtel, 1935; Opper and Zimmerman, 1938; Letondal, 1940; Benner, 1943; Fuertes, 1943; Picard, Charbonnel, and Giraudet, 1948).

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Head injury (Opper and Zimmerman, 1938; Vanzant and Brown, 1938; Ask-Upmark, 1939; Wyatt and Khoo, 1949; French, Porter, von Amerongen, and Raney, 1952).

Bulbar pachymyelitis (Erskine, Mason, and McDade, 1950; Cook, Hartmann, Sarnoff, and Berenberg, 1951; Lenarsky, Parr, and Señor, 1951; Schilumberger, 1951; Baker, Cornell, and Brown, 1952; Baker, Brown, and Cornell, 1952; Hoxsey, 1953; Schaberg, Hildes, and Alcock, 1954).

Intracranial haemorrhage of the newborn (Spiegelberg, 1869; Genrich, 1877; Pomorski, 1891–2; von Preuschen, 1894; Schweizer, 1896; Gottlieb, Chu, and Sharlin, 1950).

Cerebral infarction (Bodechtel, 1935; Reese and Masten, 1948; French, Porter, von Amerongen, and Raney, 1952; Sarason and Levy, 1954).

Intracranial aneurysm (Cachara, Duval, and Scherrer, 1944).

Encephalitis (Picard, Charbonnel, and Giraudet, 1948).

Chorea-athetosis (Babonneix and Lévy, 1931).

Cerebellar cyst (French, Porter, von Amerongen, and Raney, 1952).

After frontal lobotomy (Sweet, Cotzias, Seed, and Yakovlev, 1948; French, Porter, von Amerongen, and Raney, 1952).

After pneumoencephalography (Masten and Bunts, 1934; Bodechtel, 1935).

We describe seven cases of gastric haemorrhage, each of which occurred in association with a spontaneous intracranial haemorrhage. There was clinical evidence of bleeding in the alimentary tract in six instances, and in the seventh case blood was found in the stomach at autopsy. Previous reports of acute gastroduodenal lesions associated with spontaneous intracranial haemorrhage have been published by Andral (1840), Charcot (1886), Lépine (1895), von Czyhlarz (1912), Hart (1913, 1914, 1919), Masten and Bunts (1934), Daniels (1934), Bodechtel (1935), Opper and Zimmerman (1938), Vonderhehe (1939), Baló (1941), Davidoff (1944), Strassmann (1947), Betz (1949), Staemmler (1949), Wyatt and Khoo (1949), Freisinger, Lapis, and Baló (1950), Globus and Ralston (1951), French, Porter, von Amerongen, and Raney (1952), and Fletcher and Harkins (1954). Haematemesis was noted in only eight of these cases, the total of which exceeds 60 (von Czyhlarz, 1912; Hart, 1913; Daniels, 1934; Bodechtel, 1935; Freisinger, Lapis, and Baló, 1950; Globus and Ralston, 1951; French, Porter, von Amerongen, and Raney, 1952). We also report the results of a special histological study of the stomach, undertaken to elucidate some of the local factors which are involved in the production of erosions and acute ulcers.

Case 1. Subarachnoid haemorrhage with haematemesis as the presenting feature

A woman aged 76 years suddenly developed severe frontal headache and nausea on April 3, 1954. Half an hour later she vomited 'brown fluid' and felt faint; she was forthwith removed to hospital. After vomiting 'coffee-ground' material in the casualty department, she was referred for admission as a case of haematemesis. There was no previous history of dyspepsia. On examination she was pale, with a clammy skin, and fully conscious. The pulse and respiration rates were 124 and 24 per minute respectively; the temperature was 97.5°F, and the blood-pressure 160/100. There was epigastric tenderness, but no other abnormal findings on abdominal examination. Examination of the central nervous system was negative, and apart from numerous extrasystoles there were no other abnormal findings on physical examination. The following
day the patient became drowsy, and while asleep exhibited Cheyne-Stokes respiration. There was further vomiting, and on this day some unaltered blood was seen among the 'coffee-grounds'. The haemoglobin was 11.7 gm. per 100 ml., white-cell count 13,000 per c.mm., and blood-urea 84 mg. per 100 ml. On the third day the temperature began to rise, and there was an increase in the pulse and respiration rates; crepitations appeared in the lung bases. Systemic penicillin was given. In the course of the next few days the patient slowly lost consciousness, her tendon-reflexes disappeared, and the plantar responses became extensor. There was no evidence of further bleeding from the gastrointestinal tract. She died in coma on the sixth day after admission.

Autopsy was performed eight hours after death. The subarachnoid space contained a large amount of blood-clot, most of which was situated at the base of the brain. The brain on section presented no abnormalities. Examination of the alimentary tract failed to reveal any macroscopic lesion. Both lungs were congested, and the right lower lobe was consolidated. The heart showed slight left ventricular hypertrophy. Microscopically the stomach showed numerous small areas of mucosal damage, in which there was evidence of commencing repair (Plate 2, Fig. 5). The alveoli in the consolidated lobe of the lung were filled with an exudate of polymorph leucocytes. The pituitary and adrenal glands appeared normal.

Case 2. Cerebral haemorrhage. Haematemesis one and a half hours after the onset

A woman aged 41 years was admitted to hospital in coma on November 25, 1953. While at work as a weaver in a cotton mill, approximately one and a half hours prior to admission, the patient complained of the sudden onset of weakness in the right arm, and shortly afterwards lost consciousness. Within an hour of the loss of consciousness she began to vomit bright red blood. A history was obtained of left hemiparesis of rapid onset four months previously; the hemiparesis had cleared spontaneously, and she had been able to resume work three weeks after the onset. On examination she was restless, and breathing stertorously; the face was flushed, and the pulse and respiration rates were 110 and 30 per minute respectively. The temperature was 98.0° F., and the blood-pressure 190/160. She vomited again immediately after admission. On this occasion the vomitus consisted of 'coffee-grounds' streaked with unaltered blood. Neck rigidity and Kernig's sign were both present, and the patient exhibited the features of decerebrate rigidity. The tendon-reflexes were brisk and bilaterally equal, and both plantar responses were extensor. There were no abnormal findings in the other systems. Lumbar puncture yielded blood-stained fluid under a pressure of 210 mm. The patient's condition deteriorated, and Cheyne-Stokes respiration developed; death occurred eight and a half hours after admission.

Autopsy was performed six hours after death. There was a small amount of blood-stained fluid in the stomach. The gastric mucosa showed numerous petechial haemorrhages and ecchymoses; these were mainly confined to the proximal half of the organ, and along the lesser curvature they occupied the crests of the mucosal folds (Plate 1, Fig. 4). The pyloric canal was notably free from haemorrhage. Aggregations of petechiae were present in the mucosa of the first part of the duodenum. The subarachnoid space contained a small amount of semi-fluid blood-clot. Section of the brain revealed a large haemorrhage in the left cerebral hemisphere; this involved the corpus striatum, thalamus and hypothalamus, the lateral and third ventricles, and the cerebral white matter. In the right internal capsule there was a small area of softening. The heart showed a moderate degree of left ventricular hypertrophy. Microscopically
the pituitary showed congestion of the sinusoids; the adrenal glands were normal. The arterioles of the kidneys showed the features of early diffuse hyperplastic sclerosis.

**Case 3. Subarachnoid haemorrhage and transient hyperglycaemia. Haematemesis eight hours after the onset of coma. Recovery**

A housewife aged 57 years was found unconscious at her home on December 21, 1954, and was shortly afterwards admitted to hospital. At the time of admission the duration of coma was estimated to be one hour. The patient had previously been in good health. The pulse-rate was 110 per minute, and there were frequent extrasystoles; the temperature was 96-0°F., and blood-pressure 220/120. There was marked nuchal rigidity, and Kernig's sign was positive. The limbs were flaccid, and all the deep reflexes were absent; both plantar responses were extensor. There were no abnormal signs referable to the cranial nerves. Apart from osteoarthritis of both knees, the remainder of the physical examination was negative. The urine was found to contain both sugar and acetone; there was no albuminuria. The blood-sugar level was 277 mg. per 100 ml., and blood-urea 44 mg. per 100 ml. On lumbar puncture the cerebrospinal fluid was heavily blood-stained, and the pressure was 125 mm. Seven hours after admission the patient began to vomit ‘coffee-ground’ material; this gave a strongly positive benzidine reaction. During the next 36 hours she continued to vomit altered blood at frequent intervals, and slowly regained consciousness. The faeces gave a positive reaction for occult blood on 23.12.54 and 28.12.54, and negative reactions were obtained on 30.12.54 and on four subsequent occasions. The glycosuria, which was initially estimated at 1 to 2 gm. per 100 ml., rapidly decreased in amount after 48 hours, and disappeared in the course of the next fortnight. At the time of her discharge from hospital on 29.1.55 no abnormal physical findings were evident beyond that of hypertension. Radiological examination of the oesophagus, stomach, and duodenum on 24.1.55 failed to reveal any evidence of ulceration. An X-ray of the chest showed a moderate degree of left ventricular enlargement. A glucose-tolerance test on 28.1.55 produced a normal curve. A fractional test meal showed free hydrochloric acid rising to a maximum of 65 mEq. per litre at two hours.

**Case 4. Cerebral haemorrhage. Haematemesis shortly after the onset**

A woman aged 44 years, known to be hypertensive, was admitted to hospital in coma on November 1, 1954. She had been found one hour previously lying on a couch in a semi-comatose state, vomiting bright red blood. Fifteen minutes before she was discovered in this condition the patient had been seen by her son, who had observed nothing untoward. During transit to hospital the patient continued to vomit, and saturated a towel with blood. There was a history of a right hemiparesis 15 months previously, followed by a recurrence two months later. After the latter incident the patient had been admitted to hospital for treatment of her hypertension; hypotensive drugs were administered, but were discontinued several months later because of poor response. On examination blood was trickling from the mouth; the patient was restless, and breathing was stertorous. The pulse and respiration rates were 102 and 24 per minute respectively; the temperature was 96-0°F., and blood-pressure 260/150. There was a left facial paralysis, and marked rigidity of the left upper and lower limbs. All the deep reflexes were absent, and the plantar reflexes were both extensor. Both pupils were dilated and did not react. The fundi showed a grade II hypertensive retinopathy. Apart from lateral displacement of the cardiac apex beat, there were no abnormal findings in the other systems. After a period of extreme
restlessness the patient died, four hours after admission, without regaining consciousness.

Autopsy was performed 12 hours after death. The stomach contained a small quantity of dark red blood. The entire gastric mucosa was congested, and there were numerous punctate haemorrhages and small haemorrhagic erosions in the mucosa of the fundus and cardia. Section of the brain revealed a large haemorrhage involving the right corpus striatum and both lateral ventricles (Plate 1, Fig. 2). Blood was present in the third and fourth ventricles and in the aqueduct. Small cystic areas were found in the left internal capsule and putamen, and in the right putamen. The lungs were congested, and the heart showed a considerable degree of left ventricular hypertrophy. The kidneys were of normal size, and presented a finely granular surface; microscopically they showed the features associated with essential hypertension. There was no histological abnormality of the hypothalamus, pituitary, or adrenals.

Case 5. Pontine haemorrhage. Haematemesis one hour after the onset

A retired labourer aged 68 years was admitted to hospital on November 27, 1954, in coma. Approximately one hour prior to admission he had experienced difficulty with speech, and shortly afterwards had lost consciousness. Five years previously he had had a brief loss of consciousness, which was followed by a period of mental confusion lasting several weeks. Since this episode he had suffered from several transient attacks of loss of consciousness which were succeeded by facial asymmetry and slurring of speech. On examination he was vomiting ‘coffee-ground’ material, which gave a positive reaction on being tested for blood. Breathing was stertorous, and the pulse and respiration rates were 84 and 26 per minute respectively; the temperature was 97·4°F., and blood-pressure 215/140. There was a left internal strabismus, and both pupils were minutely contracted. There was slight spasticity, and an increase in the deep reflexes, in the right upper and lower limbs; an extensor plantar response and ankle clonus were also elicited on the right side. The patient was incontinent of urine. There were no abnormal findings on examination of the other systems. Lumbar puncture yielded slightly blood-stained cerebrospinal fluid with a pressure of 130 mm. During the next few hours the patient vomited 350 ml. of altered blood. Death occurred 19 hours after admission.

Autopsy was performed two and a half hours after death. The internal surface of the stomach was covered with mucus, which contained a mixture of fresh and altered blood; the gastric mucosa was congested and, in the proximal two-thirds of the organ, presented a large number of punctate haemorrhages, which were especially prominent along the ridges of the mucosal folds. Section of the brain revealed a haemorrhage occupying the greater part of the pons (Plate 1, Fig. 3), which had ruptured into the fourth ventricle. This haemorrhage extended into the left basis pedunculi and the left middle cerebellar peduncle. The fourth ventricle was distended with blood-clot; in the right thalamus there was a small area of softening. The heart showed a moderate degree of left ventricular hypertrophy. Microscopic examination of the hypothalamus showed congestion of the capillaries and small veins. The small vessels of the kidneys showed hyaline degeneration, and there was occasional glomerular fibrosis. The pituitary and adrenal glands showed no significant abnormality.

Case 6. Cerebral haemorrhage. Occult blood in faeces 20 hours after the onset

A labourer aged 49 years was admitted to hospital on October 21, 1954, one hour after the sudden onset of loss of consciousness. Eighteen hours previously he had ‘collapsed’ in the street and had to be escorted home. At that time he
A woman aged 65 years, known for 13 years to be diabetic, was admitted to hospital on November 11, 1954 in an unconscious state. She had appeared in good health until three hours prior to admission, when she complained of nausea and vomited a few ounces of bile-stained fluid. The diabetes had always been mild, and she had never required insulin. The patient had recently suffered from a right herpes ophthalmicus. On examination she was breathing stertorously. The pulse and respiration rates were 60 and 30 per minute respectively, temperature 99.0°F., and blood-pressure 180/80. The pupils did not react to light. There was generalized muscular flaccidity, and the deep reflexes were sluggish. Both plantar responses were flexor. The urine contained a trace of sugar, and no acetone. The blood-sugar was 40 mg. per 100 ml., and blood-urea 16 mg. per 100 ml. Lumbar puncture yielded blood-stained cerebrospinal fluid under a pressure of 165 mm. Death occurred 12 hours after admission.

Autopsy was performed six hours after death. The stomach contained 20 ml. of dark red blood; there was extensive involvement of the mucosa with petechial haemorrhages and ecchymoses, the principal distribution of the lesions being in the fundus and lesser curvature. In the left cerebral hemisphere there was a massive haemorrhage involving the temporal lobe, corpus striatum, thalamus, and hypothalamus. The third and fourth ventricles were distended with blood-clot. The heart showed a moderate degree of left ventricular hypertrophy. The other organs appeared healthy.

Pathology of the Stomach Lesions

The mucosal haemorrhages, erosions, and acute ulcers of the stomach found in association with intracranial disease do not differ in their gross or microscopic appearances from those found in patients without disease of the central nervous system, or from those produced in animals by various experimental means. The initial lesion observed in the mucosa is either a small area of haemorrhage or an area of ischaemic necrosis, the former being the more common type of lesion.
The haemorrhages are usually situated superficially in the mucosa, and when well formed are wedge- or cone-shaped, the base being on the free surface of the mucosa; less commonly the areas of haemorrhage occur in the deeper aspects of the mucosa, and in this situation they are usually irregular in shape. Not infrequently both superficial and deep mucosal haemorrhages are found in the same specimen. Ivy, Grossman, and Bachrach (1950) have called these two types of haemorrhage ‘primary interstitial haemorrhage followed by necrosis’, and they are distinguished from a third type of mucosal haemorrhage, occurring as a secondary feature in an area of anaemic necrosis—‘primary necrosis followed by interstitial haemorrhage’. Sloughing or digestion of the necrotic or damaged mucosa produced by the early lesions results in the formation of an erosion or, if the muscularis mucosae is penetrated, an acute ulcer. The formation of an erosion or an acute ulcer from a mucosal haemorrhage has been observed under direct vision in experimental animals (Roth and Ivy, 1945) and gastroscopically in the human subject (Jones, 1947). Early histological studies, with detailed descriptions of the process in dogs and rabbits, were made by Schiff (1887). Histological observations in human material have been recorded by Hagemann (1909), Nicolaysen (1920), Robertson (1939), Merkel (1944), Staeammier (1949), and others. It will be appreciated from the foregoing observations that a study of the formation of a mucosal haemorrhage is of fundamental importance in the pathogenesis of erosions and acute ulcers. Since a knowledge of the vascular anatomy of the gastric mucosa is necessary for the further consideration of this subject, we offer a brief description of the mucosal blood-supply. We have summarized the arrangement of the arteries and capillaries from the results of the studies with injection and microradiography made by Barlow, Bentley, and Walder (1951), while the micro-anatomy of the veins is based on the descriptions of Hagemann (1909) and supplemented by our own observations.

The mucosal arteries in the anterior and posterior walls of the stomach arise from an arterial plexus situated in the submucosa; in the region of the lesser curve, however, the mucosal arteries do not arise from such a plexus, but have their origin outside the stomach directly from the right and left gastric arterial chain. As each mucosal artery approaches the muscularis mucosae it divides into two to three smaller branches, which pierce the muscular layer (Fig. 1). In the region immediately below the muscularis mucosae there is a free anastomosis between adjacent mucosal arteries and their branches. Having pierced the muscularis mucosae, the mucosal branches form an anastomotic channel on its mucosal aspect, and then split up into leashes of capillaries which run vertically towards the surface. From the vertical vessels smaller capillaries arise, which ramify among the glands and join with adjacent capillaries, while at the surface they form capillary loops round the openings of the glands. Blood from the mucosal capillaries drains into venules, which take origin immediately beneath the surface epithelium (Fig. 1). Several of these venules join to form a single vertical mucosal vein, which terminates by entering one of the basal mucosal veins lying along the glandular surface of the muscularis mucosae. The basal mucosal veins form mutual anastomoses in varying degree, and each is
joined by several vertical mucosal veins. Blood finally passes from the basal mucosal veins into the veins of the submucosa, through communicating veins which pierce the muscularis mucosae. Occasionally a vertical mucosal vein passes through the muscularis mucosae without communicating with a basal mucosal vein.

Roth and Ivy (1945) have followed, by direct vision and histological sections, the processes leading to mucosal haemorrhage and the formation of erosions; their observations were made in the stomach of the cat after the parenteral administration of caffeine and histamine. The first change observed was hyperaemia of the mucosa; this was followed by cyanosis, and during the transition stage the mucosa became swollen and succulent and the veins of the mucosa and submucosa were seen to be engorged. Scattered collections of red blood-cells and transudate were then found in the interstitial tissues, and when viewed from above they appeared as petechial or ecchymotic haemorrhages in the mucosa. In three to five hours, in the presence of highly acid gastric juice, these haemorrhagic areas were digested, leaving punched-out or ragged erosions. Wolf and Wolff (1947), from direct observation of the gastric mucosa of a human subject with a gastric fistula, found that certain emotionally charged situations were accompanied by severe and prolonged engorgement, with excessive secretion and motility of the stomach. In such a phase mucosal haemorrhages and erosions could be readily induced by even the slightest trauma, and minute mucosal haemorrhages often spontaneously succeeded vigorous contractions of the stomach wall. From a histological study of punctate haemorrhages of the gastric mucosa in human and in animal material, Hagemann (1909) concluded that the irregular-shaped haemorrhages occurring in the deeper layers of the

![Diagram of the vascular arrangement in the mucosa of the stomach](image-url)
mucosa are caused by damage of the mucosal arteries and capillaries, whereas the more superficial cone-shaped haemorrhages result from damage to the mucosal veins and venules. Hagemann pointed out that the superficial haemorrhage begins immediately beneath the surface epithelium, at the site of origin of the venules, and when fully formed assumes the shape of a cone corresponding exactly to the region occupied by the tributaries and stem of a vertical mucosal vein. In five of the cases described above, in which death occurred within 24 hours of the onset of the acute illness, we were provided with an opportunity to reinvestigate the early vascular changes which occur in the gastric mucosa.

Methods. Our study is based on post-mortem material from Cases 2, 4, 5, 6, and 7. After fixation of the stomach in 10 per cent. formalin, frozen sections were cut at a thickness of 200 to 300 µ and stained by a modified Lepehne-Pickworth method (Campbell, Alexander, and Putnam, 1938). Although this staining method was described for the demonstration of the vascular pattern of the central nervous system, we have found that it also gives very satisfactory results when applied to the stomach. The principle of the method is that the red blood-corpuscles contained in the vessels are selectively stained by the application of the benzidine test for haemoglobin, while its advantage over the usual histological techniques lies in the fact that the thick sections permit the vascular tree and the areas of vascular disturbance to be seen as a morphological entity. In addition to the frozen sections, horizontal strips of mucosa were stained by the same method; these were obtained by separating the mucosa from the submucosa by means of a sharp blade and forceps. We were thus able to visualize the vascular disturbances in the mucosa in vertical and horizontal planes. Paraffin sections were also prepared, and these were stained with haematoxylin and eosin.

Histological findings. The predominant lesion in all our cases was the superficial mucosal haemorrhage. Haemorrhages into the deeper aspects of the mucosa also occurred, but were much less frequent; no areas of anaemic necrosis were observed. The earliest stage in the formation of a superficial haemorrhage was an aggregate of small perivascular collections of red blood-cells immediately beneath the surface epithelium. These small perivascular, and presumably diapedetic, haemorrhages increased in size, and eventually coalesced to form a typical wedge-shaped superficial haemorrhage; the surface epithelium overlying this lesion was always lost by the time the lesion was fully formed. By the Lepehne-Pickworth method it was clearly demonstrated that the superficial mucosal haemorrhage was of venous origin. Each group of small haemorrhages, which ultimately compose the fully developed lesion, was seen to occur in relation to the most superficial tributaries of a vertical mucosal vein (Plates 2 and 3, Figs. 6, 7, 8, and 10). The venules forming the source of these haemorrhages were often much dilated (Plate 3, Fig. 8). The veins of the mucosa and submucosa always showed some degree of congestion, and in the later stages, when the small haemorrhages had fused to form single lesions, the vertical and basal mucosal veins were especially engorged (Plate 3, Fig. 10). A greatly distended vertical mucosal vein thus formed the apex of each
superficial mucosal haemorrhage, the conical shape of the haemorrhage corresponding to the region occupied by the tributaries of the vein (Plate 3, Fig. 10). The haemorrhages in the deeper aspects of the mucosa were ill defined, and much smaller than those at the surface; they occurred in relation to the mucosal capillaries, close to their arterial origin. The capillaries themselves appeared normal. On a few occasions a small extravasation of erythrocytes was seen adjacent to one of the small venous channels passing obliquely through the circular muscle coat. The mucosal haemorrhages were unaccompanied by any cellular reaction.

In the later stages laking of the red cells and local destruction of the mucosa transformed the areas of mucosal haemorrhage into amorphous necrotic masses. The formation of erosions through digestion or sloughing of these necrotic masses was observed in cases in which their removal or separation was incomplete. Such lesions are termed haemorrhagic because of the necrotic, haemorrhagic debris which has remained adherent to their walls. Numerous non-haemorrhagic erosions were also observed, presumably having been formed by the clean separation or removal of haemorrhagic and necrotic areas. There is little doubt that the cause of the majority of the erosions was superficial mucosal haemorrhage and not the less frequent deep mucosal haemorrhage; the haemorrhages in the latter case were much smaller, and few had advanced to the stage of causing destruction of the mucosa. In most instances the erosions were funnel-shaped, and on a few occasions a vertical mucosal vein in the base of the lesion was closed by a thrombus. The fact that no venous thrombi were seen unless an erosion was present is strong presumptive evidence that the thrombosis is not primary but probably secondary to the exposure of the vessel to the gastric juice. No arterial thrombi were discovered in the numerous paraffin sections examined. In Case 6 several of the mucosal defects penetrated the muscularis mucosae, but none of these acute ulcers extended deeper than the submucosa. There was a scanty inflammatory-cell infiltration in the tissues immediately adjacent to the erosions and acute ulcers. In Cases 2 and 7, although bleeding had occurred into the lumen of the stomach, there was no microscopic evidence of any of the mucosal haemorrhages having reached the stage of erosion. In Case 5, in which the only macroscopic lesions were mucosal haemorrhages, a few haemorrhagic and non-haemorrhagic erosions were found on microscopic examination.

Discussion

Although erosions and acute ulcers of the upper digestive tract are always included in the differential diagnosis of haematemesis and melaena, the possibility of their association with intracranial disease is seldom considered in clinical practice. Gastrointestinal haemorrhage, occurring in organic brain disease and following neurosurgical operations, has been the subject of papers by Bodechtel (1935), Picard, Charbonnel, and Giraudet (1948), French, Porter, von Amerongen, and Raney (1952), Hoxsey (1953), and Davis, Wetzel, and Davis (1955). We consider that the occurrence of haematemesis or melaena in
cases of spontaneous intracranial haemorrhage is by no means rare, since seven cases of haemorrhage in the alimentary tract were observed by us within 13 months. Case 1 is of particular interest, because haematemesis was the presenting feature in a patient who was only subsequently found to have an intracranial lesion. A similar case was reported by Bodechtel (1935) of a man aged 35 years who was admitted to hospital because of haematemesis. He had complained of headache during the previous eight days, and was later found to have an intracranial lesion, a glioma of the right temporal lobe. The fact that haematemesis may be one of the presenting features in intracranial disease is illustrated further by the case reported by Laruelle and Reumont (1949) of a man aged 23 years, who developed sudden haematemesis and melaena, and died in coma a few days later. The intracranial disorder was a haemorrhagic tumour in the right frontal lobe, which proved to be a metastatic deposit from a testicular chorion-epithelioma. An analysis of the histories of these three cases shows that headache occurred either before or shortly after the haemorrhage. We suggest, therefore, that the presence of headache in these circumstances should direct attention to a possible neurogenic basis for the haematemesis.

All degrees of gastrointestinal haemorrhage have been reported in association with intracranial disorders. Davis, Wetzel, and Davis (1955) recorded 12 deaths from massive gastrointestinal haemorrhage following neurosurgical operations. Cases of fatal (Fisher, Watkins, Gardner, and Klotz, 1951) and nearly fatal (Globus and Ralston, 1951) gastroduodenal haemorrhage have occurred in children within a few days of successful intracranial operations. In a child with meningococcal meningitis, who suddenly collapsed and died 12 days after the onset of the illness, the cause of death was found to be haemorrhage from an acute duodenal ulcer (Hartung and Warkany, 1938). An example has been described of severe gastrointestinal haemorrhage, requiring blood transfusion, three days after a head injury (Ask-Upmark, 1939). Severe bleeding from the digestive tract developed in a woman 15 days after cerebral infarction; operation revealed four acute gastric ulcers high up in the lesser curvature (Sarason and Levy, 1954). Finally, Baker, Brown, and Cornwell (1952) recorded seven cases of severe gastric haemorrhage complicating bulbar poliomyelitis. In four of these cases, in which the patients had appeared to be progressing satisfactorily, the first indication of the bleeding was the sudden appearance of shock; two of these patients died within a few hours, and the correct cause of the sudden deterioration was apparent only at autopsy; in the other two patients vomiting of blood indicated the correct diagnosis, and measures to combat the loss of blood were instituted. The authors emphasized the importance of early recognition and treatment of gastrointestinal haemorrhage in bulbar poliomyelitis, pointing out that it may constitute a medical emergency which should be watched for in all cases. We suggest that this dictum be extended to include all forms of acute intracranial disturbance, since the examples we have quoted above indicate that severe gastrointestinal haemorrhage may complicate a wide variety of such disorders.

Rapid healing is the natural course of erosions and acute ulcers of the stomach,
and there is no evidence that such lesions do not follow a similar course when associated with intracranial disease. In Case 1, in which the stomach was examined on the sixth day after the haematemesis, the widespread focal damage to the mucosa was only discovered on microscopic examination, and in Case 3 radiological examination of the stomach and duodenum one month after the onset of the haematemesis revealed no evidence of ulceration.

Although chronic peptic ulcer and intracranial disease are occasionally found to coexist, most authors consider that there is no aetiological relationship between the two conditions. From an analysis of 2,437 autopsies performed in Zurich in 1947 and 1948, Betz (1949) found the combination of intracranial lesions and chronic peptic ulcer to be no greater than the calculated chance association. Sack (1946) made a clinical and radiological study of the upper digestive tract in 100 patients who had sustained brain damage as a result of head injuries; these patients were examined six to 24 months after the injury, and in only one instance was there evidence of chronic peptic ulceration. A similar series of cases was reported by Kalk (1946-7): 342 patients were examined radiologically and gastroscopically 17 to 40 months after brain injury, and chronic peptic ulceration was found in only five cases. The ulcer was known to have been present before the injury in three of these five cases. In a series of 512 cases of pituitary tumour, Wilson, Olson, and Rivers (1946) discovered only five (one per cent.) associated with peptic ulcer. Ivy, Grossman, and Bachrach (1950), after a review of the literature dealing with experimental production of ulcers, reached the conclusion that no acceptable evidence had yet been presented to show that chronic peptic ulcer results from a lesion of the brain.

The generally accepted theory that the acute gastrointestinal lesions associated with intracranial disease are due primarily to vascular disturbances in the mucosa is strongly supported by the histological findings of our cases. The cause of the local vascular disturbance has been disputed. Schiff (1846, 1867) considered the primary disorder to be dilatation and stasis of the blood-vessels arising as a consequence of vasomotor paralysis. Others (Beneke, 1908; Hart, 1919) have regarded prolonged vasoconstriction as the essential underlying factor, while a third hypothesis (Nicolaysen, 1920; Cushing, 1932) attributes the vascular disturbance to compression of arteries and veins by spasmodic contractions of the gastric musculature. The recent demonstration in the human stomach of arteriovenous anastomoses in the submucosa, capable of short-circuiting the mucosal arteries directly into the veins (Barlow, Bentley, and Walder, 1951), introduces yet another possible mechanism. Venous dilatation and perivascular haemorrhages were observed in all our histological material. This picture, well shown by the Lepehne-Pickworth method, appears to be characteristic of partial or complete stasis (Campbell, Alexander, and Putnam, 1938). It is not possible to determine whether the stasis resulted from vasomotor paralysis, venous compression, or transient ischaemia of the mucosa due to one of the mechanisms already mentioned. Whatever the precipitating factor, there can be no doubt that the associated venous dilatation and perivascular haemorrhages are of great importance in the train of events leading to erosion.
and the formation of acute ulcers. We have confirmed Hagemann's observations that the small perivascular mucosal haemorrhages, situated immediately beneath the surface epithelium, occur in relation to the tributaries of a vertical mucosal vein, and that these minor haemorrhages eventually coalesce to form a typical wedge-shaped superficial mucosal haemorrhage. The superficial mucosal haemorrhage, which was the predominant lesion in our cases, is followed by necrosis, and sloughing or digestion of the necrotic area leads to the formation of the mucosal defects.

The recognized efferent pathways through which the central nervous system acts on the stomach are the connexions of the autonomic nervous system and the pituitary-adrenal axis; controlling centres of both these systems are situated in the hypothalamus. In Cases 2, 6, and 7 there was damage to the hypothalamus, while in Case 4 the intracranial haemorrhage was in a position to interfere with its centripetal connexions with the frontal lobe, and in Case 5 with its centrifugal fibres in the brain-stem. In Case 1 the localization of the large amount of blood-clot at the base of the brain may have resulted in hypothalamic disturbance, and in Case 3 it is possible that the transient hyperglycaemia was a manifestation of hypothalamic upset. We should like to point out that intracranial lesions which involve the hypothalamus are not always associated with lesions of the digestive tract, which occur only in a minority of cases. Furthermore, mucosal erosions and acute ulcers may be associated with intracranial lesions which do not involve the hypothalamus or its known fibre connexions (Globus and Ralston, 1951; French, Porter, von Amerongen, and Raney, 1952; Davis, Wetzel, and Davis, 1955). Activity of the autonomic nervous system has been shown by Wall and Davis (1951) to be influenced by three separate cerebral cortical systems; only one of these, which arises in the frontal lobe, passes through the hypothalamus; the others arise from the sensorimotor cortex and the temporal lobe respectively, and do not traverse the hypothalamus. The existence of these latter two systems implies that absence of hypothalamic involvement does not exclude involvement of the autonomic nervous system. In spite of considerable experimental work, the role of the autonomic nervous system in the production of the acute gastrointestinal lesions is still not clear. Cushing (1932) considered the primary disturbance to be one of parasympathetic overactivity. He suggested that intracranial lesions might stimulate the parasympathetic centre in the hypothalamus, or the fibres therefrom as they descend in the brain-stem. Alternatively the lesion might paralyse the antagonistic sympathetic fibres, causing a functional release of the vagal system. On the other hand Watts and Fulton (1935) suggested that the gastrointestinal lesions, which they produced in monkeys by means of hypothalamic lesions, were due to a release or irritation of the sympathetic nervous system. Each of these hypotheses, attributing the lesions of the alimentary tract to the overactivity of one or other component of the autonomic system, has received support from other investigators; the experimental evidence on which the support is based has been the subject of reviews by Sheehan (1940) and Ivy, Grossman, and Bachrach (1950).
There was severe brain damage in five of the seven cases reported in the present paper. It has been observed, in experimental lesions of the interbrain (Sheehan, 1940), that the severity of the intracranial lesion appears to influence the frequency of production of gastroduodenal lesions, the large destructive injuries being those most likely to provoke gastrointestinal haemorrhages and erosions. In man, also, there appears to be little doubt that the severity of the intracranial lesions is a factor in the production of acute lesions of the alimentary tract, although its precise importance is difficult to assess. Since, in the great majority of reported cases, the diagnosis of the lesions in the digestive tract has been made at autopsy, the severe and fatal forms of intracranial lesion naturally predominate. In patients with less severe, non-fatal intracranial lesions, there is the possibility of acute gastrointestinal lesions which remain clinically silent and so pass unrecognized. Knowledge of the incidence of acute lesions of the digestive tract in non-fatal forms of intracranial disease would be of practical value in assessing the risks of anticoagulant therapy, which is at present undergoing trial in certain forms of cerebral vascular disease (Wright and McDevitt, 1954).

It has long been known that mucosal erosions, acute ulcers, and perforations of the gastrointestinal tract may occur in association with a wide variety of acute pathological processes other than those of the central nervous system, and also in the terminal stages of many chronic diseases. In 1825 Desbarreaux-Bernard described several examples of spontaneous perforation of the stomach in patients who died after surgical operations, burns, and compound fractures. Acute peptic ulceration following burns was originally reported by Swan (1823), and Curling (1842) was the first to emphasize the frequency with which the two conditions are related. It is of interest that changes in the brain, consisting of oedema, degeneration of ganglion-cells, and demyelination, have been described in cases of death after extensive burns (Globus and Bender, 1936; Walker and Shenkin, 1945; Madow and Alpers, 1954). As far back as 1867 Billroth described a case of acute duodenal ulceration following a surgical operation, and in 1899 von Eiselsberg reported a series of eight cases of gastric and duodenal haemorrhage after operation. Mucosal erosions and acute ulcers of the gastrointestinal tract have been described in association with many other conditions, including acute inflammatory disease (Perry and Shaw, 1894; Hurst and Stewart, 1929), acute myocardial infarction (Globus and Ralston, 1951; Mears, 1953; Fletcher and Harkins, 1954), and fractures (Wangensteen, 1945; Mears, 1953). Several hypotheses have been advanced to provide a common aetiological basis for the gastrointestinal lesions found with these diverse conditions. Desbarreaux-Bernard (1825) considered that the severe pain resulting from surgical operations or burns was the causal factor in his cases of spontaneous perforation of the stomach, but did not speculate on the mechanism involved. In animal experiments Ebstein (1874) found that stimulation of a peripheral nerve containing pain-fibres readily produced haemorrhages and erosions in the gastric mucosa. He was able to produce similar lesions by asphyxiating processes, injections of strychnine, lesions of the central nervous system, and damage to the internal
ear, and attributed the mucosal haemorrhages to the rise in blood-pressure which accompanied these procedures. Penner and Bernheim (1939) pointed out that shock, characterized by a decrease in the circulating blood-volume, is of frequent occurrence in the wide variety of pathological conditions described above. They attributed the mucosal damage to the increased capillary permeability resulting from stasis, the latter being a consequence of arteriolar constriction arising in response to shock. Selye (1946) has shown that gastrointestinal ulceration occurs in animals during the shock phase of the alarm reaction. Among other authors, Aschoff (1924) held the view that vomiting was a factor of importance in the aetiology of haemorrhagic erosions; he considered that venous stasis and mucosal haemorrhages result from compression of arteries and veins produced by the strong contractions of the gastric musculature which occur during the act of vomiting.

Considerable attention has recently been directed to the possibility of an increased secretion of corticotrophin as the basis of gastric erosions and acute ulcers found in association with so many different disorders (McDonnell and McCloskey, 1953; Fletcher and Harkins, 1954). After the administration of corticotrophin or cortisone there is an increase in the gastric secretion of acid and pepsin, unaltered by vagotomy or ganglion-blocking agents, and a similar increase in acid and pepsin secretion follows surgical operations (Gray, Ramsey, Reifenstein, and Benson, 1955). Surgical operations are found to raise the plasma levels of 17-hydroxycorticosteroids (Franksson, Gemzell, and von Euler, 1954) and increase the urinary excretion of corticosteroids (Thorn, Jenkins, and Laidlaw, 1953). Similar increases in plasma steroid levels are commonly observed in painful conditions, and also at the time of death (Bayliss, 1955). Moreover, in many medical diseases there is an increased output of urinary corticosteroids (Cope, Boysen, and McCrae, 1951). Hume (1949) has demonstrated in dogs that lesions placed in certain areas of the anterior hypothalamus abolish the usual eosinopenic response to such stress-provoking stimuli as trauma, chemical irritants, and injections of adrenaline and insulin. Porter (1953) has brought together three lines of evidence which support participation of the hypothalamus in the pituitary-adrenal response. Using the cat as the experimental animal, he observed that the administration of various stress-producing agents increased the electrical activity of the posterior hypothalamus; after destruction of the posterior hypothalamus stress stimuli failed to induce an eosinopenia, whereas in normal animals electrical stimulation of the posterior hypothalamus produced an eosinopenia. In animals subjected to the stress of trauma it has further been shown (Hume, 1953) that nerve impulses from the injured area are essential for the initiation of the hypothalamic-pituitary-adrenal response. If the area of trauma has been denervated there is no evidence of increased corticotrophin secretion. The hypothesis that increased adrenocortical activity is of aetiological significance in peptic ulceration is supported clinically by several reports of the occurrence of acute ulcers, and the exacerbation of chronic ulcers, in patients receiving corticotrophin or cortisone (Gray, Benson, Reifenstein, and Spiro, 1951; Davis and Zeller, 1952; Forbes,
It has been demonstrated in animals (Selye, 1946) that stimulation of the pituitary-adrenal mechanism is not essential for the production of acute gastrointestinal ulceration; the lesions of the digestive tract which occur during the alarm reaction are not prevented by hypophysectomy or adrenalectomy; indeed, they tend to be more severe in the absence of either or both of these glands. Selye (1951) presumed that these acute ulcers are largely due to the intense autonomic discharge which occurs during exposure to stress and elicits marked peristaltic, vasomotor, and secretory reactions in the gastrointestinal tract. The effect of cortisone on the blood-vessels of the stomach is at present unknown, and no satisfactory evidence has yet been presented to show that cortisone is capable of producing the early vascular lesions in the mucosa which we have described above. Whatever the causal factors in the production of these early vascular disturbances may be, it appears highly probable that the resulting mucosal damage will be further aggravated by any increase in the output of a substance, such as cortisone, which is known to increase the secretion of acid and pepsin.

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Summary

Seven cases are described of gastrointestinal haemorrhage occurring in association with a cerebro-vascular accident. In five instances the intracranial lesion was a cerebral haemorrhage, and in two it was a subarachnoid haemorrhage. Haematemesis occurred in five cases, and melena in one; in the seventh case no clinical evidence of bleeding was obtained, but blood was found in the stomach at autopsy.

In the five cases of cerebral haemorrhage death occurred within 24 hours of the onset. At autopsy the outstanding feature in the digestive tract in each of these cases was the presence of numerous punctate haemorrhages and ecchymoses in the mucosa of the stomach. There were also erosions in two cases, and erosions and small acute ulcers in one.

A histological study was made of the early lesions in the gastric mucosa. With the benzidine stain (Lepehne-Pickworth method), described for the demonstration of the vascular pattern of the central nervous system, areas of vascular disturbance in the stomach were clearly outlined. The predominant lesion was found to be a wedge-shaped haemorrhage situated superficially in the gastric mucosa. The observation of Hagemann (1909) that this superficial mucosal haemorrhage is of venous origin, and owes its characteristic shape to the anatomical arrangement of the mucosal venules, has been confirmed. The superficial haemorrhage is followed by local necrosis of the mucosa, and digestion or sloughing of the necrotic area leads to the formation of an erosion or, if the muscularis mucosae is penetrated, an acute ulcer.
Haematemesis was the presenting feature in one of the two cases of subarachnoid haemorrhage. This patient died six days after the onset of the illness; at necropsy the stomach appeared normal, but microscopic examination revealed evidence of widespread focal mucosal damage. The other patient with subarachnoid haemorrhage survived, and radiological examination of the upper gastrointestinal tract one month after the onset of the haematemesis gave a negative result.

The pathogenesis of acute gastrointestinal lesions associated with intracranial disease is discussed.

REFERENCES

Czyhlarz, E. von (1912) *Arch. VerdaKr.* 18, 85.
Eiselsberg, F. von (1899) *Arch. klin. Chir.* 59, 887.


Genrich (1877) Quoted by von Preuschen (1894).


— and Ralston, B. L. (1951) *J. Mt. Sinai Hosp.* 17, 817.


Hurst, A. F., and Stewart, M. J. (1929) *Gastric and Duodenal Ulcer*, London.


GASTRIC HAEMORRHAGE

— (1867) Leçons sur la physiologie de la digestion, Florence, 2, 416.
Schlumberger, H. G. (1951) Arch. Path. (Chicago) 52, 43.
Winiwarter, J. von (1911) Arch. klin. Chir. 95, 181.
Fig. 2. Case 4. Brain, coronal section showing haemorrhage involving right corpus striatum and lateral ventricles.

Fig. 3. Case 5. Brain, coronal section showing pontine haemorrhage with extension into the midbrain.

Fig. 4. Case 2. Stomach and first part of duodenum showing distribution of the mucosal haemorrhages.
Fig. 5. Case 1. Stomach, showing early repair of an area of mucosal damage. MM = muscularis mucosae (haematoxylin and eosin, ×250)

Fig. 6. Case 2. Stomach. Early stage in the formation of superficial mucosal haemorrhages, with small extravasations occurring in relation to the surface venules (benzidine stain, ×50)

Fig. 7. Case 2. Gastric mucosa showing the appearance of lesions, similar to those in Fig. 6, in horizontal plane (benzidine stain, ×40)
Fig. 8. Case 3. Gastric mucosa showing perivascular haemorrhages in relation to dilated venules (benzidine stain, ×60)

Fig. 9. Case 4. Gastric mucosa, showing dilated vertical mucosal vein and superficial haemorrhage (haematoxylin and eosin, ×70)

Fig. 10. Case 4. Stomach. Fully developed wedge-shaped superficial mucosal haemorrhages and marked engorgement of the vertical and basal mucosal veins (benzidine stain, ×55)