The right cornea remained healthy until investigations into the problems of tear secretion were carried out. After this a keratitis developed which necessitated closure of the lids by tarsorrhaphy. For many months this woman was completely relieved of the pain in the right side of the head, but later began to complain of pains elsewhere in the body and, according to her doctor, was beginning to show distinct mental changes.

On Jan. 24, 1942, Prof. Jefferson wrote to me to say that he had seen the patient again. He told me that my operation had completely relieved the pain on the right side of the head but that obvious migrainous pains were starting on the left side. Moreover, she complained of pains elsewhere in the body.

Discussion

The possible criticism that, in my posterior root section cases, the relief of pain might be due to division of the auriculo-temporal and meningeal arteries is vitiated by the fact that injection of the Gasserian ganglion (Harris, 1936) will give relief, and this does not interfere with the blood vessels concerned. Also, division of the meningeal artery, and presumably also of the auriculo-temporal artery, in some cases of migraine has proved not to give relief (Craig, 1935). Moreover, the auriculo-temporal artery is not necessarily divided in posterior trigeminal root section, and certainly in two of my cases the large trunk of this vessel was not ligatured or diathermized. In any case, the ophthalmic artery is not involved in the lateral approach to the posterior trigeminal root, and it is along this vessel that many migrainous pains presumably arise. Finally, it is unlikely that local interference with a distal mechanism will ease pain of an extensive distribution.

If it is correct that the painful impulses in migraine do, in fact, enter the brain stem along the posterior trigeminal root, then it is still necessary to discuss how they reach the ganglion from the periphery. There are two possibilities—either they enter the ganglion from the autonomic plexus in the region of the foramen lacerum medium or they course along the ophthalmic and maxillary trunks of the trigeminus (first and second divisions). Probably the trigeminal trunks are the anatomical pathways concerned. This opinion is difficult to prove because the critical operation of section of the first and second divisions themselves in a suitable case has never been carried out, for the reason that section of the ophthalmic division (not the ophthalmic fibres in the posterior root) is a very difficult manœuvre, although it can be done (Rowbotham, 1939). In two of my cases, when the pain extended into the face, I sectioned the ophthalmic fibres only in the posterior nerve root, and the second division at the foramen rotundum, with the relief of pain. It must, however, be realized that it is impossible to know precisely how many fibres are being divided when fractional section of the posterior trigeminal root is being performed.

In one case, when a migrainous pain was confined to one side of the forehead, I divided the supra-orbital and supra-trochlear nerves without dividing the supra-orbital vessels, with relief of pain. This is a very simple operation, and is worthy of trial when severe pains are localized to the forehead.

At this point it would be profitable to inquire into the results of thoraco-cervical sympathectomy in the relief of migrainous pains. Unfortunately very few such operations have been carried out for the deliberate relief of headaches, but in cases done chiefly for vasospastic states in the arm, Love and Adson (1936) found that of 16 cases of concomitant headache the headaches were relieved in 12. The efficiency of this method in relieving pain, I find, has been questioned by White (1942) and Telford (personal communication). Whether or not relief is obtained by sympathectomy does not help in settling the route of conduction of the painful impulse, because relief when it is obtained by this operation can easily be explained by destruction of those pathways along which the original disturbance that initiates the painful impulse is conveyed. In other terms, sympathectomy destroys the motor and not the sensory arc of the mechanism of migraine.

My series of cases at least suggest that the painful impulse in migraine passes through the posterior trigeminal root, but they do not prove by any means that this is the main sensory pathway of the autonomic system of the head. Possibly the trigeminal pathway acts purely as a special defence mechanism. The main problem of the sensory pathways of the autonomic system still remains an enigma, and will possibly remain so until better methods of staining autonomic fibres have been discovered.

I have published these cases at this time because they throw light on the state of post-concussional headache, which is one of the main problems in His Majesty's Forces to-day. In many cases of post-concussional headaches no organic cause is demonstrable, either clinically or by encephalography, and many are labelled psychoneurotic or nervous. Possibly in many so-called nervous headaches the pain is not purely one of perception but is due to an unstable mechanism resulting from the injury, leading to atypical migrainous pains. This type of headache in Service cases is, I believe, much more common than the headache due to dural traction the result of adhesions.

REFERENCES

Clark, D., Hough, H., and Wolff, H. G. (1936). *Arch. Neurol. Psychiat.*, Chicago, **35**, 1054.
Craig, W. McK. (1935). *Proc. Mayo Clin.*, **10**, 362.
Harris, W. (1936). *British Medical Journal*, **2**, 112.
Jackson, J. Hughlings (1931). *Selected Writings*, vol. 1, Hodder and Stoughton, London.
Love, J. G., and Adson, A. W. (1936). *Arch. Neurol. Psychiat.*, Chicago, **35**, 1203.
Penfield, W., and McNaughton, F. (1940). Ibid., **45**, 43.
Rowbotham, G. F. (1939). *Brain*, **62**, 364.
White, Jas. C., and Smithwick, R. H. (1942). *Autonomic Nervous System*, 2nd ed., Kimpton, London.
Wilson, S. A. Kinnier (1940). *Neurology*, **2**, 1570, Arnold, London.

THE SYNDROME OF HAEMORRHAGIC SUPRARENAL INFARCTION

BY
DORIS V. KEELE
AND
KENNETH D. KEELE, M.D., M.R.C.P.
Major, R.A.M.C.

The syndrome of primary infarction of the suprarenals is very rare, and unilateral infarction has not been described at all. There are only some 14 cases of haemorrhage into the suprarenals in adults recorded in the literature in which any description is made of the clinical picture. None of them were diagnosed in life, even at laparotomy, and all were fatal. The syndrome described in this paper is that produced by thrombosis of the suprarenal vein with resulting haemorrhagic infarction of the suprarenal gland, in an adult. Other causes of haemorrhage into the suprarenal are: (*a*) in the newborn; (*b*) in meningococcal and other acute infections, in which the picture clinically is that of the acute infection: the Friderichsen-Waterhouse syndrome is discussed in differential diagnosis here, and another case added to the 60 already described; (*c*) as a part of a general haemorrhagic state. The thesis put forward is that the suprarenal infarction syndrome is recognizable in life, and possibly treatable.

Case History

The patient (D. V. K.), an intelligent woman aged 32, was 8 months pregnant. The pregnancy had been normal except for occasional morning vomits, in some of which there had been streaks of blood. Two days previous to the illness the urine was albumin-free and the blood pressure 120/80. On March 28, 1941, at 12.30 p.m., she complained of feeling cold, after which she walked half a mile with no further complaint. Half an hour later pain appeared in the right side below the ribs—persistent, "like a stitch"—which made her put her right hand to the side and bend over to the right. This pain was exacerbated by the movement of the car and by walking. The pain below the right costal margin steadily increased in severity. There was no nausea, and the appetite was good. Pallor and sweating now became evident in spite of a strong pulse of 70 a minute.

2 p.m.—Patient restless in bed, in severe pain, which remained the whole time localized to a spot over the fundus of the uterus to the right of the umbilicus about 2 in. below the costal margin in front. There was no pain in the loin. Vomiting began at this time—copious, free, and sudden. This continued repeatedly until the end. Micturition was natural, and urine showed no haematuria. On examination there was some cold-

ness of skin. Pulse 80, temperature 98°, respirations 20. Patient mentally quite clear. Abdominal tenderness was present at the site of the pain, which was located by her accurately with the finger-tips. There was no rigidity. Pressure on the tender region induced nausea and vomiting. The pain did not radiate or shift in any direction. It was very severe, and restlessness was marked, but it was described as "bearable."

5 p.m.—Admitted to the Radcliffe Infirmary and examined by Prof. Chassar Moir and Mr. D. C. Corry. The symptoms and signs remained the same. No abnormal signs were found elsewhere. White cells, 24,000.

10.30 p.m.—Laparotomy performed. A scarred adherent appendix was removed. Patient's condition was quite satisfactory until the skin sutures were being inserted, when mucus flowed into the trachea. This became blood-stained, and was followed by a profuse pulmonary haemorrhage, from which she died in spite of cardiac massage and tracheotomy. Caesarean section was performed, but the infant was dead.

Post-mortem Examination by Dr. Robb-Smith.—No abnormality was found apart from the lungs and the right suprarenal. Lungs showed diffuse haemorrhage filling the bronchioles in the substance of both. No evidence of active tuberculosis was found, though there was the scar of an old healed focus at the right apex. The heart was normal, the right ventricle empty. The right suprarenal was the size and colour of a large plum. The tissues surrounding this were very tense, so that when the organ was cut with a knife there was a sudden spurt of blood-stained fluid under pressure. The left suprarenal gland was normal. On examining the veins a thrombus was found extending along the suprarenal vein from its protrusion into the inferior vena cava. The thrombus in the large vein was older than that in the smaller branches by some 2 to 3 days. Blood culture was negative.

Summary of the Case.—The outstanding points are: (1) the gradual onset with "feeling cold"; (2) the ingravescent nature of the pain, growing in about two hours to great severity, and its accurate location; (3) the severity of vomiting, such that intestinal obstruction was seriously considered; (4) the absence of shock and of purpura; (5) exploratory laparotomy failing to make a diagnosis; (6) the death through pulmonary oedema progressing to profuse haemorrhage. Pathologically the case is unique in that there is none described with infarction of the suprarenal on the right side only, consequent on primary thrombosis of the suprarenal vein.

Diagnostic Criteria

The salient question is that of diagnosis. Is there a picture on which diagnosis of infarction of the suprarenal can be based? On retrospect it is my belief that in this case, and in some others collected from the literature, diagnosis is possible—that there is a clear-cut syndrome here which is not yet generally recognized. This rests mainly on: (1) the characteristics of the pain; (2) the severity of vomiting; (3) the surprising absence of "shock."

1. *Characteristics of the Pain.*—Both authors of this paper had been interested in the subject of pain over a period of some years. For this reason the description given by D. V. K. at the time of her illness was deliberately shaped to comply with Ryle's ten points (Ryle, 1936), which form the standard clinical description of pain. In the production of pain as a symptom, sensitivity is obviously a factor to be taken into consideration. For some years sensitivity to pressure pain has been used as a clinical guide to this factor, which it is believed is of definite significance (unpublished work). In the case of D. V. K. many tests had been made at various intervals of time, including four during the 8-months period of pregnancy designed to ascertain whether there was any detectable alteration in sensitivity during that period. Sensitivity to pain measured thus was near the average of 100 normal people in the case of D. V. K. For this reason, and because of her knowledge of the relevant features of pain, her evidence is of singular value from the diagnostic point of view. The pain in this case had the following characteristics:

Onset was gradual, not sudden, accompanied by a feeling of coldness. *Site:* From the first and during the whole 12 hours of the illness it was localized to a point to the right of the umbilicus about 2 in. below the costal margin. Location was accurate to an area about the size of a half-crown. There was no *shift* or *radiation*. *Severity:* At first mild in degree, it steadily increased until it was of great severity; but at its worst it was described as "bearable" by D. V. K. *Character:* First described as a "stitch"; later the word "cramp" was used. *Duration:* At all times it was persistent. And from its commencement until she was anaesthetized the pain never left her, except at the end of two hours for a brief period of about 2 minutes, when she surprisedly exclaimed that it had vanished. Then it returned with increased intensity. *Relief:* Nothing relieved completely. At first bending to the right appeared to be a more comfortable position. Veganin gr. 10 failed. Heroin gr. 1/12 gave some relief. *Aggravation:* Pain was made worse by any movement such as walking or the movement of the car. Pressure on the fundus of the uterus produced acute pain and nausea with vomiting. *Accompanying symptoms:* A feeling of cold preceded the pain. Vomiting occurred after about 3 hours, becoming persistent and repeated until operation. It had no marked effect on the pain. Micturition was free. There was no dysuria. The temperature remained between 98° and 99° F. throughout, the pulse about 80. *Tenderness* was located with the finger-tips to the area previously described, to the right of the umbilicus. There was hyperalgesia of the skin in this region. No rigidity was detected at any time. No pain or tenderness was present in the loin or in the region of the posterior renal angle.

2. *Vomiting.*—This was a symptom which obscured diagnosis. Starting about 3 hours from the onset, it was copious without retching, almost projectile in character, and repeated; there appeared to be little nausea between, when fluids were well taken. And in spite of it dehydration was not marked. Its character and persistence suggested intestinal obstruction.

3. *Absence of "Shock."*—This is so surprising as to merit a prominent part in the clinical picture: it is a finding so completely opposed to expectations in a patient with suprarenal disease, and with vomiting of the severity mentioned. Blood pressure was unfortunately not recorded during the few available hours, but three observers remarked on the full normality of the pulse at the wrist. Two days previously blood pressure was 120/80, and there was little detectable difference on palpating the pulse then and during the illness. The pulse rate never exceeded 88 in the half-hourly records taken over the last 6 hours. A white cell count showed a leucocytosis of 24,000.

The Clinical Picture in Other Recorded Cases

The above clinical picture is confirmed when analysis is made of the few available clinical records of similar cases, though it will be seen from the Table that many points are unfortunately omitted in these descriptions. Only one case, Arnaud's (1900), has been found which is comparable (Case 2)—that of a girl of 17 who developed symptoms 11 days after a severe burn. Here the pain is described as "epigastric." One feels that the word covers a wide area of abdominal wall which might well include the site described in the present case. Apart from this possible discrepancy there is similarity in the picture, so far as it is described, in the severity of the pain, the vomiting, and the duration of some hours.

In Case 3, described in detail by Pearl and Brunn (1928), there was haemorrhage into the right suprarenal, followed 7 days later by haemorrhage into the left. For its first phase this case, therefore, is similar: there was sudden onset of severe pain, which was first in "the right kidney region" and on the second day "under the ribs," with tenderness "in the region of gall-bladder." The advent of the left-sided haemorrhage was indicated by pain in "the left flank and under the ribs." Other points of similarity about this case are the absence of abdominal rigidity and of shock. Even on the 12th day of the illness the blood pressure was 120/80, and both suprarenals had by then been affected. Temperature, pulse, and respirations were all normal during the first day. In Cases 4 to 10 both suprarenals were involved. It is obvious that in these cases the combined areas of pain each side of the umbilicus might be described as "epigastric." Actually it will be seen that 3 are so described—one as "diffuse," one as in the "left kidney region," and one as under the costal margin, left first and then right. The last—Case 10—had no pain, but was tender under the costal margin.

Now to summarize regarding the characteristics of the pain. The localization was definite and in an unusual site in the present case. From the 10 cases quoted, in 4 this same site is described and identifiable; in 5 others the word "epigastric" or "diffuse" is used. These words at least localize the pain to the front of the abdomen rather than the flanks, and inaccuracy of observation may well account for lack of more precise siting. In one the pain is described as in "the kidney region" only. It is my opinion that this area of suprarenal pain is definite and probably of as much diagnostic value as

pain and tenderness over MacBurney's point in the right iliac fossa. Observation of further cases will of course settle the issue. Pain in the loin is not as constant as in the anterior site.

The absence of rigidity is almost a constant finding in all the cases even after some days' duration, at a time when other abdominal catastrophes are almost certainly productive of this sign. Temperature, pulse, and respiration rate all remained normal in the majority of those cases in which they are recorded. In Pearl and Brunn's (1928) case fever is recorded on the 7th day. In Hall and Hemken's (1936) case

Differential Diagnosis

The main diagnostic problem is anatomical. In the case of infarction into the right suprarenal, diseases of the pleura, the gall-bladder, kidney, appendix, and alimentary tract are possible sources of diagnostic difficulty. In the case here described the uterus was enlarged by 8 months' pregnancy, and the provisional diagnosis made before laparotomy was that of a twisted ovarian cyst, or degenerating or twisted fibroid. A comparison of the picture described in the case history shows on retrospect the differences between most of these conditions

	Right Suprarenal		Right Suprarenal followed by Left		Both Suprarenals						
Case:	1	2	3		4	5	6	7	8	9	10
Sex	F	F	M		M	M	M	M	F	M	M
Age	32	17	45		72	30	46	40	44	?	74
Pain site	Below rt. C.M.	Epigastric	Rt. kidney Rt. C.M.	Lt. kidney Lt. ribs	Epig.	"Diffuse"	Epig.	Lt. kidney	Epig.	Lt. C.M. Rt. C.M.	Nil
,, degree	V. sev.	V. sev.	V. sev.	V. sev.	V. sev.	Sev.	V. sev.	V. sev.	Sev.	Mod.	—
,, nature	Persistent	Persist.	Persist.	Persist.	Persist.	Persist.	Sharp	—	—	Persist.	—
Tenderness site	Below rt. C.M.	Epig.	Present C.M.	Lt. C.M.	Epig.	Diffuse	—		Epig.	Under C.M.s	Under C.M.s
Rigidity	Nil	—	Nil	Nil	Marked	Slt.	—	Lt. abdo.	Slt.	—	Nil
Temperature	98°	—	102° } 9th	102°	98°	99°	—	104° (2nd day)	95°	97°	99°
Pulse	80	—	90 } day	90	104	90	—	—	120	100	80
Respirations	20	—	—	50	32	—	—	—	45	—	—
Vomiting	++	+	—	—	++	+	+	+	++	+	Nil
B.P.	120/80	—	120/80	120/80	140/95	—	—	—	—	—	—
Lungs	N.A.D.	—	—	—	Rales	—	—	—	Rales	—	—
Mental	Clear	Syncope	Clear	Dull	Clear	—	Clear	Clear	—	Clear	Clear
White cells	22,000	—	—	16,000	20,000	—	—	—	52,000	—	—
Haemorrhage: Purpura	Nil	—	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Haemorrhage: Elsewhere	Pulmonary	—	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Duration	12 hrs.	Hours	7 days	6 days	10 hrs.	4 days	? mths.	2 days	36 hrs.	21 days	14 hrs.
Remarks		11th day after burn			Carc. of bronch.				Pancreatitis too		Ch. nephritis
Reference	Keele	Arnaud	Pearl and Brunn		Altschule	Barsoum (1936)	Goolden (1857)	Hall and Hemken	Lavenson	Hektoen (1909)	Michaux and Mar set

Add 2 cases found in coma—both adrenals involved—and 2 cases in lunatics. C.M. = Costal margin.

fever of 104° F. was present terminally. The pulse rate remained below 100 in 5 out of 7 cases. In the one case (No. 8) where it was 120 there was accompanying pancreatitis.

Respirations in the present case were not raised until operation, when the patient showed distress under the anaesthetic. In the only other cases in which the rate is quoted it was 50, 32, and 45 per minute. These high rates suggest the presence of pulmonary congestion, though limited to a stage not revealed, as in the present instance, by profuse pulmonary haemorrhage. Basal rales were found in 2 cases. Vomiting of severe degree formed a prominent feature of the syndrome in 8 of the cases. It is mentioned as severe in 3 cases, and in only 2 is it omitted. Blood pressure is recorded in only 2 instances. Such readings as 120/80 and 145/95 correspond with the absence of the signs of shock found in most cases. In the present case it is probable that there was little change from the pressure of 120/80 taken before the illness. The mental state of all patients was clear, except in Case 2 after a week's illness. This contrasts with 4 other cases quoted—two by Arnaud and Laignel-Lavastine in which the patients were found in coma, and two occurring in lunatics (Munson, 1907; Severn, 1923)—a melancholic and an idiot. The white cell count has been found raised in all 4 cases in which it has been recorded. Figures of 24,000, 16,000, 20,000, and 52,000 raise the question of infection, but are equally well accounted for by infarction. Haemorrhage, either purpuric or from other organs, has been absent in all cases, except in the present one, in which it was terminal from the lungs. There was no evidence of any haemorrhagic diathesis in the case of D. V. K. Tonsillectomy had been performed 8 years previously, being followed by a miscarriage without abnormal haemorrhage. The absence of purpura in all cases is a point of interest, bearing in mind its constancy as a part of the Friderichsen-Waterhouse syndrome.

The duration of the illness has been variable. In 4 of the 10 cases death has occurred in less than 24 hours. In the others the illness has lasted from 36 hours to a period of months. This indicates that there must be all degrees of infarction. In fact, it is known that sometimes blood cysts are formed. Arnaud quotes a case in which a cyst weighing 4 lb. was found post mortem. The suprarenal tissue was entirely destroyed. The patient had had attacks of pain for a period of years, presumably due to repeated haemorrhages.

and suprarenal infarction. These differences lie in the characteristics of the pain, which is not like a colic, and the site of which does not correspond to gall-bladder or renal pain, and is too high for the pain of appendicitis. The strict localization and the absence of radiation are both positive evidence of the suprarenal origin of the pain. The vomiting suggests intestinal obstruction, and such a diagnosis may be disproved only by laparotomy.

Exploratory laparotomy was performed in 4 cases. In none was the diagnosis made at this time. This raises, in my opinion, the most important feature of all. In an exploratory laparotomy, if the usual sites of acute abdominal conditions are found to be normal then the suprarenals should be examined. In most cases palpation alone will suffice, since when there has been haemorrhage the gland is the size and consistency of a large plum. If doubt still remains it would be possible to inspect the region. Retroperitoneal haemorrhage will be visible as well as the plum colour of the infarcted gland itself.

Arnaud, in his classification of the picture of suprarenal haemorrhage in adults, describes three clinical types: (1) Peritoneal type, into which fall the cases here discussed with abdominal pain and vomiting. (2) Asthenic type, characterized by asthenia alone, leading to death: the exitus of the two psychotic cases suggests this type. (3) Nervous type, in which the patient is found in coma or delirium, and is seen post mortem to have no cerebral lesion, but bilateral suprarenal haemorrhages: into this group fall the two cases of Arnaud and Laignel-Lavastine mentioned above. Differential diagnosis in Groups 2 and 3 must be considered impossible. Lavenson (1908) and Keith Simpson (1937) add the type in which sudden death occurs with no ascertainable cause and in which bilateral suprarenal haemorrhages are found post mortem. All these types occur in adults. In none of the cases quoted is there evidence of infection being the causative factor.

Causes of suprarenal haemorrhage may be classified as follows: In children two main types occur:

1. *Haemorrhage into the Suprarenals in the Newborn.*—Birth trauma is undoubtedly the cause here. Of 8 cases described by Levinson (1935) 6 were breech deliveries and 2 Caesarean sections: the latter two infants had been slapped on the loins to revive them. Owing to the involution of foetal cortex about the time of birth and its replacement by vascular tissue in a

loose stroma, haemorrhage is facilitated at that stage by trauma. Even in this type, however, operation proved successful in the case of Corcoran and Strauss (1924), in which laparotomy was done for a mass palpated in the left loin and left iliac fossa, and a bleeding-point ligated. This case establishes the fact that operation is feasible in cases of haemorrhage into the suprarenal. It is probable that small haemorrhages occur which heal and finally end in calcification of the suprarenal or in fibrotic change.

2. *Friderichsen-Waterhouse Syndrome.* — This syndrome occurs in older children. It is typified by the following case, the first of its kind to be seen by me.

> L. R., aged 5 months, was noticed by the mother to be restless and feverish in the night. In the morning a blotchy rash was observed on the forehead ; no vomiting ; drowsiness was present during the last hour. Examination showed extreme cyanosis, large purpuric patches all over the body ; pupils unequal and fixed ; tachycardia about 150 ; vomiting. Within an hour the child went into coma and died. Necropsy showed bilateral haemorrhage into both suprarenals. The brain and other organs were normal, except that there was congestion of both lungs. Blood culture was not done and the veins were not examined for thrombosis.

This clinical picture is in contrast to the syndrome in the adult due to infarction where there is no purpura, cyanosis, or delirium. The Friderichsen-Waterhouse syndrome occurs also in adults, and recently I have seen a typical case in a man aged 23, who came into hospital with purpuric patches, confluent on the feet and some 2 in. in diameter on legs and arms. This patient became comatose while being examined, at which time his blood pressure was only 70 mm. Hg systolic. Blood culture showed meningococci. He recovered on sulphapyridine therapy. This picture cannot be confused with the cases of primary infarction of the suprarenal gland. The purpura is in these cases the result of injury to capillary walls by the meningococci, which can be cultured from the purpuric patches. The two comatose cases described by Arnaud and Laignel-Lavastine might well fall into this fulminating meningococcal group.

Thrombosis of the suprarenal veins may occur in such patients and give rise to abdominal symptoms, which, however, will be obscured by the patients' mental state. Other organisms besides the meningococcus may produce suprarenal haemorrhage with purpura—but very rarely.

3. *Thrombosis of the Suprarenal Vein.*—This, according to Hall and Hemken, is the commonest cause of suprarenal haemorrhage in adults. It presents the syndrome of suprarenal infarction here described.

4. *Any Generalized "Haemorrhagic" Condition.*—This may show haemorrhage into the suprarenals. Such is the case, described by Lewis (1921), in an infant of 3 weeks which died of convulsions 5 hours after an operation for hare-lip. At necropsy, haemorrhage was found into pancreas, lungs, suprarenals, and other organs.

From this description of the types of suprarenal haemorrhage it will be seen that each presents a fairly distinctive clinical picture. These four groups summarize the clinical pictures in cases of fatal suprarenal haemorrhage. It has been shown by Snelling and Erb (1935) that in the newborn death does not always ensue on haemorrhage. Suprarenal glands examined later in life have shown calcification and haemosiderin deposition—i.e., evidence of previous haemorrhage. This calcification may be visible radiologically.

No similar case has been reported in adults, but now that cases of fulminating meningococcal septicaemia can be saved, as in the case described above, such haemorrhages may be expected, possibly with subsequent calcification visible radiologically. It should not be assumed that all cases of calcified suprarenal glands result from tuberculosis. The suggestion is tentatively put forward here that some cases of Addison's disease with "atrophic" or even calcified suprarenals are the result of old haemorrhage into the gland. No such case, so far as is known, has been recorded, but in a case of Addison's disease treated by grafting foetal suprarenal glands into the rectus sheath (Bailey and Keele, 1936) there was dramatic and successful response of blood pressure and symptoms, though not of pigmentation. This patient was last seen 6 years later, quite well. Relevant to the present thesis is that 6 months before her symptoms developed she had had cholecystectomy for abdominal pain. The gall-bladder appeared normal and the patient's symptoms were not improved. Were the symptoms produced by disease of the suprarenals?

Pathology

Post-mortem findings have been limited to changes in the suprarenals in most cases. Carcinoma of the bronchus was an associated finding in Case 4 (Altschule, 1939). Pancreatitis obscured the clinical picture in Case 8 (Lavenson's). "Chronic nephritis" was found in 2—those of Michaux and Marsset and of Lavenson. This association has probably more than coincidental significance, as it has been noticed by French workers (Michaux and Marsset, 1923), and recently such a case has been found by Dr. Robb-Smith (personal communication). Pulmonary haemorrhage was observed only in the present case, though congestion was mentioned in Case 8.

Unilateral infarction of the suprarenal has been found only in the present case and one other (Arnaud), in both instances on the right side. In Case 3 the right side was involved first. In Cases 7 and 9, however, the history suggests that the left side was involved before the right. In all cases the suprarenal glands have been replaced by blood, often clotted, contained inside a capsular layer, or (in 5 cases) infiltrating into the retroperitoneal tissues to a varying extent. This infiltration may be extensive and produce a palpable tumour in the flank. Such a case in an infant was operated on and cured (Corcoran and Strauss, 1924).

Histologically the medulla of the gland is completely replaced by blood. In most instances a layer of cortex remains. Thrombosis of the suprarenal vein is an important and frequent finding. In 6 of the 10 cases it is specifically described, and is not mentioned in the others. That this thrombosis of the vein is not a sudden event is shown by the fact that in the present case the thrombus in the main suprarenal vein projected into the inferior vena cava, and was estimated to be from 2 to 3 days old, whereas that in the small venous radicles was more recent. Thrombus had spread, therefore, from large vein to small, and infarction of the gland was so produced.

The cause of death in the present case was the diffuse bilateral pulmonary haemorrhage ; in the other cases it presumably was acute suprarenal insufficiency. In the post-mortem findings of cases of Friderichsen-Waterhouse syndrome pulmonary congestion is commonly mentioned, and in view of the present case it would seem that suprarenal insufficiency does produce some change in pulmonary circulation.

Pathological Physiology in Suprarenal Infarction

Symptom production in suprarenal infarction and biochemical changes that ensue are shrouded in mystery and complexity. The pain in the right side is of the "referred" type. Its accurate location corresponds with thoracic segment 10. It results either from afferent stimuli passing up from the medulla of the gland itself or from retroperitoneal irritation. The state of tension of the gland from which blood spurted post mortem and the mild degree of retroperitoneal infiltration would favour the first hypothesis in the present case. The medulla of the suprarenal receives a large number of sympathetic fibres that come from the coeliac ganglion and plexus, which incorporates the two splanchnic nerves on each side. Fibres to the suprarenal are plentiful and mostly preganglionic, and medullated. From the site of pain in the present case it seems justifiable to suggest that the segment from which the outflow occurs is Th. 10.

The vomiting is remarkable, and no easy explanation is available. One can only compare it with the crisis in Addison's disease, the mechanism of which is imperfectly understood. Pulmonary haemorrhage is even more difficult to account for, though it is obviously related in some way to the acute suprarenal insufficiency. To try to say how related would be merely to indulge in guesswork. It does appear, however, that there is no reason why this patient should have died if pulmonary haemorrhage had not occurred, since the other suprarenal was intact. But possibly it, too, would have become infarcted, as happened in Pearl and Brunn's case.

Biochemically there is no evidence at all as to what changes are taking place in such acute suprarenal disease. In adrenalectomized dogs detectable changes in blood chemistry do not occur until the second day at the earliest. This applies to values of blood cholesterol, sugar, urea, sodium, potassium, and chloride ; nor does blood pressure fall or pulse rate rise until the second or third day. These findings are curiously

confirmed by the clinical normality of blood pressure and pulse in these cases of suprarenal infarction described.

The vascular supply of the suprarenal gland is remarkable. Three arteries converge to produce the most vascular organ per gramme in the body. The vein arises from sinusoids in the medulla. Its walls contain a considerable quantity of muscle, and the blood in it is oxygenated, being "arterial" rather than "venous." Occlusion of this large vein results in a haemorrhagic infarction of the gland, which starts in the loose medullary tissue, destroying it completely. The cortex is also destroyed, but often a thin rind of it escapes, helping to form a capsule round the haemorrhagic area. Later this may rupture, the blood spreading down into the perirenal fat and into the retroperitoneal tissues.

The cause of primary venous thrombosis is unknown, though it occurs as a rarity, the portal vein being the commonest of the visceral veins to be affected.

Pregnancy as a Factor.—One other case occurring in pregnancy has been found—in a girl aged 18 with hyperemesis gravidarum. No other clinical facts are given; but at necropsy it was seen that haemorrhage was into the left suprarenal more than the right. Thrombosis of the suprarenal vein was marked.

Summary

A case of haemorrhagic infarction of the right suprarenal gland is described. The clinical picture is compared with that of cases in the literature, and it is considered that this rare condition may be diagnosed in life. The characteristics of the pain—particularly its site, the repeated vomiting, and the remarkable absence of shock—present a well-defined but hitherto unrecognized syndrome.

Differential diagnosis is discussed, with particular attention to other clinical types of suprarenal haemorrhage: (1) haemorrhage in the newborn; (2) Friderichsen-Waterhouse syndrome; (3) haemorrhagic disease. Examples of these are described.

The failure of laparotomy to diagnose cases is noted and a plea put in for exploration of the suprarenals at operation if no other adequate pathological change is found; ligation of a bleeding-point or excision of the gland are measures which might be adopted.

I would like to put on record my deepest gratitude to Prof. Chassar Moir for his great skill and for his kindness to my wife in her illness and to me afterwards. He made available to me all his case notes, and his help has been invaluable. Dr. A. H. T. Robb-Smith has also been most generous in permitting me to have full details of the pathological findings, and in discussing them with me.—K. D. K.

REFERENCES

Altschule, M. D. (1939). *Amer. J. med. Sci.*, **198**, 17.
Arnaud, F. (1900). *Arch. gén. Méd.*, **186**, 5.
Bailey, H., and Keele, K. D. (1936). *Proc. roy. Soc. Med.*, **29**, 42.
Barsoum, H. (1936). *British Medical Journal*, **2**, 972.
Corcoran, W. J., and Strauss, A. A. (1924). *J. Amer. med. Ass.*, **82**, 626.
Goolden, R. H. (1857). *Lancet*, **2**, 266.
Hall, E. M., and Hemken, L. (1936). *Arch. intern. Med.*, **58**, 448.
Hektoen, L. (1909). *Trans. Chicago path. Soc.*, **8**, 87.
Lavenson, R. S. (1908). *Arch. intern. Med.*, **2**, 62.
Levinson, S. A. (1935). *Amer. J. Surg.*, **29**, 94.
Lewis, C. J. (1921). *British Medical Journal*, **2**, 706.
Michaux, J., and Marsset, H. (1923). *Bull. Mém. Soc. méd. Hôp. Paris*, **47**, 161.
Munson, J. F. (1907). *J. Amer. med. Ass.*, **49**, 19.
Pearl, F., and Brunn, H. (1928). *Surg. Gynec. Obstet.*, **47**, 393.
Ryle, J. A. (1936). *Natural History of Disease*, London.
Severn, A. G. M. (1923). *Lancet*, **1**, 647.
Simpson, C. Keith (1937). Ibid., **1**, 851.
Snelling, C. E., and Erb, I. H. (1935). *J. Pediat.*, **6**, 22.

F. E. Maisel and E. Somkin (*J. Allergy*, 1942, **13**, 397) have published a preliminary report on the treatment of the asthmatic paroxysm with nicotinic acid. They found that (*a*) severe asthmatic attacks were controlled within 3 to 5 minutes, and improvement lasted 3 to 15 hours, in 16 of 21 patients by the intravenous injection of 0.1 g. of nicotinic acid; (*b*) 5 of 9 chronic asthmatic patients were benefited by 0.2-g. doses given orally three times a day before meals and on retiring; and (*c*) 11 of 18 patients receiving intravenous therapy followed by oral therapy showed decided improvement in their asthma. The patients experience a flush and a sensation of heat, then often begin to cough, and expel tenacious mucous plugs. The beneficial effect is thought to be produced by the strong vasodilator properties of nicotinic acid, relieving the bronchospasm or directly affecting the pulmonary vessels, and has no bearing on vitamin deficiency. The patients were mostly beyond middle life, often with a well-marked infective element and not responsive to ordinary allergic methods of therapy. No patient developed any disturbing symptom.

THE HERRING AS A SOURCE OF VITAMINS A AND D

A COLLABORATIVE INVESTIGATION

BY

A. L. BACHARACH
Biochemical Department, Glaxo Laboratories Ltd.
E. M. CRUICKSHANK
Dunn Nutritional Laboratory, Cambridge University and Medical Research Council
K. M. HENRY
National Institute for Research in Dairying, Reading University
S. K. KON
National Institute for Research in Dairying
J. A. LOVERN
Torry Research Station, Department of Scientific and Industrial Research, Aberdeen
T. MOORE
Dunn Nutritional Laboratory, Cambridge
R. A. MORTON
Department of Organic Chemistry, Liverpool University

Conditions determining Food Value

The importance of a food as a source of any particular nutrient depends primarily on two factors—the amount of the nutrient present and the quantity of the food eaten. Most recent books on dietetics and nutrition include the herring among the "protective foodstuffs," and justify this by referring to its excellence as a source of fat-soluble vitamins (cf. Plimmer and Plimmer, 1938; Bourne, 1941; McDonald, 1938; Mottram, 1938, 1940; McCarrison, 1941). Only Wokes (1941) appears to have had doubts.

Examination of the evidence for this belief is rather disconcerting. In the tables of Fixsen and Roscoe (1937-8, 1938-9) four references are given, and they derive from only three authors, one of whom was reviewing the physiology of the sterols and gave no experimental data of his own. More recent papers have been exceedingly scanty, both in number and in informativeness, though an exception on the latter score may be made for that by Lunde *et al.* (1937), who give values for the body oil of herring as under.

Condition of Herring	Vitamin (I.U. per 100 g. Oil)	
	A	D
Fresh, winter	200 to 2,800	9,000 to 15,000
Kippered	Unaffected	11,500 to 14,500
Canned and stored	Decreased	7,000 to 14,000
Canned, kippered	Trace	

These authors do not clearly differentiate between canned herrings that have been submitted to preliminary kippering and those that have not, but they remark that "since kippered herring contains about 12 to 13% of oil, the canned product is a food with . . . a high vitamin D potency." This seems to us to be a conclusion of little practical bearing unless consumption data are also taken into account, so enabling us to assess the importance of the herring as a source of vitamins A and D in the national diet.

From certain figures published by the Herring Industry Board for the year 1937, and made available to us by the kindness of Dr. Magnus Pyke of the Ministry of Food, an idea is to be had of the *per capita* consumption of herrings in this country. It amounted to approximately 1½ oz. a week, of which just under 0.6 oz. was fresh herring. One of us (J. A. L.) has been able independently to obtain a check on these figures, with very satisfactory agreement. The figures for the vitamin D content of herring-flesh oil have little nutritional significance without an accompanying statement as to the oil content of the flesh, which is known to vary considerably. Our own findings, given below, confirm this and cover a range from 3.6 to 20.2% in fresh herring.

The contribution to their average intake of vitamins A and D obtained by the population from herrings clearly cannot be satisfactorily calculated on the basis of published data. We