Summary

Five cases of canicola fever, diagnosed on clinical and serological evidence, occurred during a period of five years among piggery workers engaged in farms in the environs of Edinburgh.

A survey of 47 piggery workers in 12 Edinburgh farms showed from the results of serological examinations that 19 (40%) had at some time been infected with *L. canicola*. In addition to the five known cases this figure includes five others with histories of illness suggestive of canicola fever.

Specimens of blood from pigs from the two farms in which most of the cases occurred were found to contain antibodies to *L. canicola* in titres high enough to indicate a leptospiral infection. In one farm 46 out of 75 (61%) of the pigs were positive and in the other 40 out of 98 (40%).

Four out of six pigs newly introduced into one of the infected piggeries developed antibodies to *L. canicola* within three to eight weeks. On the 47th day after admission leptospores were being excreted in large numbers in their urine.

A hamster inoculated with the infected urine died after six days and leptospores were grown in culture from the heart blood. They were identified as *L. canicola*.

Six pigs were inoculated each by a different route with a virulent culture of *L. canicola*. Those which were inoculated subcutaneously and through a scarified area of skin developed antibodies to titres of at least 1 in 10,000 within 10 days. No obvious symptoms of disease followed the administration of the culture by any of the routes employed.

Pigs which were inoculated with urine from infected pigs subcutaneously and by scarification developed antibodies to *L. canicola* within 13 days. No symptoms other than a slight febrile reaction and a tendency to be less vigorous followed the inoculations.

The above evidence indicates that pigs may harbour *L. canicola* without showing any noticeable symptoms of disease. The organisms are excreted in the urine, and infection is passed from pig to pig. Human infection may result through contact with infected pigs.

The incidence of canicola fever in piggery workers is high, and this is in contrast to the recognized low infectivity rate among dog owners.

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REFERENCES

- Broom, J. C. (1951). *British Medical Journal*, 2, 689.
— and MacIntyre, A. B. (1948). *Vet. Rec.*, 60, 487.
Davidson, I. S. F., and Smith, J. (1936). *Quart. J. Med.*, 5, 263.
McIntyre, W. I. M., and Seiler, H. E. (1953). *J. Hyg. (Lond.)*, 51, 330.
Nisbet, D. I. (1951). *J. comp. Path.*, 61, 155.
Stuart, R. D. (1946). *Vet. Rec.*, 58, 131.
Thiel, P. H. van (1948). *The Leptospiroses*. Universitaire Pers, Leiden.
Weetch, R. S., Colquhoun, J., and Broom, J. C. (1949). *Lancet*, 1, 906.
Williams, H. R., McCroan, J. E., Starr, L. E., and Ward, M. K. (1953). *Clin. Res. Proc.*, 1, 97.
Wolff, J. W. (1954). *The Laboratory Diagnosis of Leptospirosis*. Springfield, Illinois.
— Dam, R. van, and Minkenhof, J. E. (1951). *Lancet*, 1, 1100.

NORADRENALINE IN SHOCK DUE TO
VISCERAL PERFORATION

BY

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In states of shock survival of the patient ultimately depends on removing the cause of the shock. Some temporary measure to tide the patient over the hypotensive crisis is, however, often necessary to prevent the vicious circle of progressive irreversible shock, and may be absolutely essential if the patient is to survive a major surgical procedure.

The following three cases of shock associated with visceral perforation all responded only temporarily to the infusion of moderate amounts of blood and dextran, and the early use of a continuous noradrenaline infusion over a period of days appeared to play a necessary part in maintaining an adequate blood pressure and in ensuring the recovery of the patients from the condition of circulatory failure. The cases described are three consecutive cases of this type that were admitted to the Central Middlesex Hospital.

Case 1

A woman aged 66 collapsed at noon on December 22, 1955, with very severe pain in the left iliac fossa, the pain soon radiating across the whole abdomen. When seen she was grey and very ill. Her blood pressure was 95/70 and her pulse volume was poor.

An intravenous infusion was set up and 1 pint (570 ml.) of dextran was given. Her general condition improved, and immediately prior to operation (six hours after the onset of symptoms) her systolic blood pressure was 125.

Anaesthetic induction and maintenance was with nitrous oxide, trichlorethylene, and oxygen. Orotracheal intubation with a cuffed tube was performed under suxamethonium relaxation. Gallamine, 40 mg., was given, and later a suxamethonium drip was set up. Operation revealed faecal fluid and also solid faeces in the peritoneal cavity, due to a rupture of the sigmoid colon. Distal to the rupture there was an annular thickening of the wall of the bowel, this almost certainly being neoplastic in nature. The peritoneum was cleaned of faeces so far as possible and the perforated gut was delivered as a loop colostomy. After operation intensive antibiotic therapy with penicillin, streptomycin, and oxytetracycline was instituted.

After induction the systolic blood pressure rose to 130, but thence gradually fell during the course of the operation even though a further $\frac{1}{2}$ pint (284 ml.) of dextran was infused. The pulse volume became very poor and eventually the systolic pressure was barely 80. The patient was cold and very pale. Intravenous injection of 14 mg. of methylamphetamine hydrochloride ("methedrine") in two divided doses produced only a slight and very transient improvement in the blood pressure. A blood infusion was then started, but no immediate improvement followed.

In order to raise the blood pressure intravenous noradrenaline was given at the conclusion of the operation. A strength of 4 mg. of the bitartrate in 1,000 ml. of dextrose-saline was used, and at 60 drops a minute the systolic blood pressure rose from 80 to 125 within a matter of minutes (Fig. 1).

Back in the ward the intravenous noradrenaline was temporarily discontinued, one hour after its commencement, to see if the blood pressure would be maintained. At this time the patient had had a total of $1\frac{1}{2}$ pints (850 ml.) of

dextran and nearly 1 pint (570 ml.) of blood. There was an immediate fall in blood pressure to 90 systolic and the pulse rate rose from 140 to 160. Consequently the intravenous noradrenaline was recommenced. The blood pressure immediately rose and the pulse rate fell again.

Two hours after its commencement, the infusion was doubled in strength to 8 mg. of noradrenaline per 1,000 ml., and was utilized at this strength for the next 13 hours at a rate that varied between 32 and 80 drops a minute. Notwithstanding this, the systolic blood pressure sometimes fell to 75 and remained there at one period for four hours. The pulse volume remained very weak and the condition of the patient was poor.

Fifteen hours after operation the strength of the infusion was again doubled (now 16 mg. of noradrenaline per 1,000 ml.). At varying rates up to 60 drops a minute the systolic pressure was maintained at about 85 for the next

FIG. 1.—Chart showing the response of the systolic blood pressure to noradrenaline infusion (Case 1).

five hours. At 20 hours from operation the pressure rose to 100 and was maintained between 100 and 120 at 40 to 60 drops a minute. The general condition of the patient now showed some definite improvement.

Still later the strength of the infusion was increased to 32 mg. of noradrenaline per 1,000 ml. At a drip rate varying between 30 and 60, the systolic pressure was maintained fairly constantly in the region of 100. The pulse rate was 110 and the condition of the patient was now much improved.

At 40 hours from operation the drip rate was slowed to 10 and finally stopped about 47 hours after operation. Subsequently the systolic pressure was well maintained at over 110, and later became stabilized in the region of 130. The pulse rate remained about 100. The patient continued to gain strength day by day.

No further blood or dextran was given to the patient other than that received before, during, and immediately after the operation—a total of $1\frac{1}{2}$ pints (850 ml.) of dextran and 1 pint (570 ml.) of blood.

The urinary output during the first post-operative 24 hours was only 8 oz. (227 ml.). During this period the systolic blood pressure was for long periods between 75 and 90. Urinary output during the second 24 hours was 33 oz. (938 ml.). During this period the systolic pressure was maintained between 100 and 130 for most of the time. Urinary output during the third 24 hours was 84 oz. (2,387 ml.).

A further operation, at a later date, revealed that the carcinoma was inoperable, and the patient went home with a permanent colostomy. Her general condition, however, was remarkably good.

Case 2

A man aged 49 on January 6, 1956, gave a history of sudden onset of acute central abdominal pain. When

admitted he was in great pain and in a shocked condition. His blood pressure was 93/55 and pulse rate 140.

He was given morphine, $\frac{1}{4}$ gr. (16 mg.), and an infusion of dextran was started. Immediately prior to operation (about nine hours after the onset of symptoms) he had had 1 pint (570 ml.) of dextran and his systolic blood pressure was 100.

Anaesthetic induction and maintenance was with nitrous oxide, trichlorethylene, and oxygen. Orotracheal intubation with a cuffed tube was performed under suxamethonium relaxation. Later gallamine, 80 mg., and further suxamethonium were given. Operation revealed a large quantity of faecal fluid and lumps of solid faeces in the peritoneal cavity. There was a rupture in the wall of the sigmoid colon. The peritoneum was cleansed, the distal colon emptied of faeces, and the rupture in the sigmoid colon sutured. A transverse colostomy was performed. Following operation antibiotic therapy with penicillin and streptomycin was instituted.

Six minutes after induction the systolic blood pressure rose from 100 to 120, but thereafter there was a steady fall in pressure even though another full pint (570 ml.) of dextran was infused fairly rapidly. Towards the end of the operation the systolic pressure was 90 and infusion of blood was started. Two-thirds of a pint (380 ml.) of blood was given in 35 minutes before the patient was returned to the ward; the systolic pressure was then 100. Back in the ward the remainder of the blood was given, and the blood pressure rose to 115/70. A total of 2 pints (1,140 ml.) of dextran and 1 pint (570 ml.) of blood had then been given. The patient received no further intravenous dextran or blood.

Subsequently, however, the blood pressure progressively fell and in 75 minutes had dropped to 70/50. Intravenous noradrenaline was then begun one and a half hours after the end of the operation, and the blood pressure was raised to 100/60 in 30 minutes using a strength of 8 mg. of noradrenaline to 1,000 ml. of dextrose-saline running at 25 drops a minute. Later the drip rate had to be increased to 60 to keep the systolic pressure between 90 and 110, and at nine hours after operation the rate had to be increased to 80.

Eleven hours after operation the infusion strength was increased—to 24 mg. of noradrenaline per 1,000 ml. At 20 drops a minute the pressure fell to 70/50, but at 36 drops it was maintained fairly constantly at 100/70. The general condition of the patient was now improved.

Twenty-six hours after operation the infusion strength was again increased—to 32 mg. of noradrenaline per 1,000 ml., and a drip rate of about 40 maintained the blood pressure at approximately 115/70. Forty hours after operation the drip rate was cut down to 25 and later reduced still further. The blood pressure was maintained about 125/70 and the general condition of the patient was now fairly good.

Sixty hours after operation the noradrenaline infusion was discontinued. Although the patient had been weaned off

FIG. 2.—Chart showing the relationships of the blood pressure and the urinary output to the noradrenaline infusion (Case 2). Following the cessation of noradrenaline infusion there was a 24-hour period of hypertension.

this fairly gradually there was a fall in blood pressure to 90/60 and later to 80/50, the period of hypotension persisting for about 24 hours. As the condition of the patient was then good and he showed no other signs of shock it was decided not to restart the noradrenaline infusion. The blood pressure eventually rose above 100 systolic and became stabilized about 110/65.

The urinary output during the first 24 hours following operation was 13½ oz. (383 ml.) and during the second 24 hours was 33 oz. (938 ml.). Twenty-four hours before the cessation of the noradrenaline infusion the output was 43 oz. (1,221 ml.) but fell to 16 oz. (454 ml.) for the 24 hours during the period of hypotension following its cessation (Fig. 2). The input during this latter period was greater than the input of the previous 24 hours.

The colostomy was later closed and the patient eventually left hospital fit and well. A pathological state that could have accounted for the rupturing of the colon was never found.

Case 3

A man aged 75 awakened in the early hours of the morning of January 18, 1956, with severe epigastric pain which rapidly spread to the rest of the abdomen. When seen about six hours later he was in great pain and was pale and shocked. His blood pressure was 86/50 and his pulse 102.

A dextran infusion was started and morphine, ½ gr. (11 mg.), was given. Immediately before operation (about eight hours after the onset of symptoms) he had had 1 pint (570 ml.) of dextran and his systolic blood pressure was 110.

Anaesthetic induction and maintenance was with nitrous oxide, trichlorethylene, and oxygen. Orotracheal intubation with a cuffed tube was carried out under suxamethonium relaxation; later gallamine, 60 mg., was given. Further relaxation was provided by using intermittent suxamethonium. Operation revealed a large pyloric ulcer which had perforated. Several pints of free fluid and much gas were found in the peritoneal cavity. A partial gastrectomy was performed with moderate difficulty.

Fifteen minutes after induction the systolic pressure had risen from 110 to 120. As operation began a slow blood infusion was set up. However, within the next 35 minutes the systolic pressure had fallen to 80 and consequently the rate of the blood infusion was accelerated very considerably. There was an immediate response and the systolic pressure eventually rose to 140. Following cessation of the blood infusion, however (after 1 pint (570 ml.) had been given), there was a fairly abrupt fall in pressure down to 75 systolic. Intravenous methylamphetamine hydrochloride (8 mg.) raised the systolic pressure immediately to 130, but this was very transient and a further intravenous dose of 8 mg. had to be

given 20 minutes later, together with 12 mg. intramuscularly (Fig. 3). Again a good but relatively transient response was obtained.

At the conclusion of the operation voluntary respirations were relatively shallow, and while still intubated the patient suddenly collapsed, his radial pulse becoming impalpable. Whilst apparatus for a noradrenaline infusion was being assembled the patient was inflated with oxygen and recovered in under a minute, his systolic pressure returning to 110. Atropine, 1/100 gr. (0.65 mg.), and neostigmine, 2 mg., were given intravenously, and voluntary respirations definitely improved and soon appeared to be quite adequate. As the systolic pressure was being maintained over the next 15 minutes the noradrenaline infusion was withheld.

On return to the ward the patient's systolic pressure fell, and one hour after leaving the theatre was only 75—it remained about this level for two and a half hours. During this period a further ½ pint (284 ml.) of blood was infused, but no significant rise in the blood pressure occurred. A total of 1 pint (570 ml.) of dextran and 1½ pints (850 ml.) of blood had then been given. As the general condition of the patient was very poor a noradrenaline infusion was begun, a strength of 8 mg. of noradrenaline to 1,000 ml. of dextrose-saline being used. The infusion was run very slowly at first; the systolic pressure was gradually raised to 100 and was maintained fairly constantly at this level, running at 40 drops a minute.

Six and a half hours after the commencement of the infusion the strength of the noradrenaline was doubled (to 16 mg. of noradrenaline per 1,000 ml.) and the rate cut down to between 20 and 25 drops a minute. The systolic pressure was maintained fairly constantly at 100 to 110 and later between 110 and 120. The general condition of the patient showed marked improvement over the next 16 hours. Further steady improvement continued day by day.

The noradrenaline infusion was continued for a total of 40 hours; for most of the time the rate was approximately 20 to 30 drops a minute, the strength of solution being 16 mg. of noradrenaline per 1,000 ml. The infusion was discontinued fairly suddenly and the systolic pressure fell from a constant 120 down to 105. Within a further three hours, however, it was being maintained constantly between 115 and 120.

Twenty-seven hours after the commencement of the noradrenaline infusion the patient's pulse was noticed to be irregular. This was probably due to auricular fibrillation, but it might have been caused by multiple extrasystoles. No fall in the blood pressure occurred and the patient's general condition remained steady. Intravenous digoxin was given in the infusion. The irregular pulse persisted for over 24 hours after the time the noradrenaline was discontinued.

Owing to incontinence the exact urinary output during this period could not be accurately ascertained, but, apart from the first 24 hours, it appeared to be adequate.

On the twelfth day after operation the patient was very well and was beginning to eat a light diet. Unfortunately, in the evening he suddenly collapsed and died. Post-mortem examination revealed a pulmonary embolus.

Discussion

Although a systolic blood pressure below 70 or 80 mm. Hg may be tolerated for some considerable time in an otherwise fit individual, there is little doubt that in an ill and toxic patient such a hypoten-

FIG. 3.—Chart showing the response of the systolic blood pressure to rapid blood infusion, intravenous methylamphetamine hydrochloride, anoxia, and noradrenaline infusion (Case 3).

sion persisting for more than an hour or so must seriously prejudice the chances of recovery. Therefore in ill toxic patients every endeavour must be made to raise the systolic pressure to about 90 mm. Hg or above.

In the treatment of shock due to visceral perforation simple infusions of blood or dextran alone are usually effective in permanently maintaining an adequate blood-pressure level provided that the factors causing the shock are effectively treated. Therefore, in the first instance, infusions of blood or dextran should be instituted. Should such simple measures fail, then the early use of continuous noradrenaline infusion probably holds out the best chance of recovery.

In the three cases of this series the responses to intravenous infusions of blood and dextran were initially good, but in none of them was the blood pressure maintained permanently at a reasonable level even after the infusion of moderate amounts—2½ to 3 pints (1,400 to 1,700 ml.)—of these fluids. However, intravenous noradrenaline quickly brought up the blood pressures, and, by a regulation of the rates of infusion, maintained them, by and large, at a constant satisfactory level. In the absence of some such measure to maintain a satisfactory blood-pressure level, it is possible that none of these patients would have survived. Perhaps further transfusions of blood and dextran might have achieved similar results, but they could, at the same time, have led to a dangerous overloading of the circulation. Certainly the use of very large amounts of blood would appear to be a more unphysiological line of therapy notwithstanding the limitations of noradrenaline as a pressor agent.

Objection to the use of noradrenaline in hypotensive states has been made because it is thought that, although the blood pressure is raised, the blood flow to vital organs is, owing to the completely unselective nature of the vasoconstriction produced by the pressor agent, actually reduced. This is undoubtedly true when considering the effect of noradrenaline on normotensive individuals, or on shocked subjects whose symptoms are due to reduced blood volume, but the haemodynamic response that occurs when noradrenaline is administered to a subject whose shocked state is not associated with any significant oligæmia may not be at all times comparable, and clinical experience tends to confirm this view. The heightened level of consciousness often seen in such shocked patients as the blood pressure rises under noradrenaline therapy is strongly indicative of an increased cerebral blood flow. The vastly increased urinary output is, similarly, a strong indication that the renal blood flow has increased, although some increase in urinary output is theoretically consistent with a reduced blood flow if the filtration fraction is sufficiently increased.

No obvious change in the level of consciousness was noted in these patients, mainly, no doubt, because the infusions were started in the immediate post-operative period. A significant effect on the urinary output was, however, apparent in Case 2, and its effect on the output in the other cases was probably no less significant. In Case 2 there was a 24-hour period of hypotension following the cessation of the noradrenaline infusion (60 hours after operation), and during this period the urinary output fell dramatically notwithstanding the fact that the input was slightly greater than the input of the previous 24 hours (Fig. 2). It is therefore reasonable to infer that noradrenaline played an important part in the maintenance of an adequate urinary output, and that its effect in maintaining such an output was so great that it is reasonable to assume that renal blood flow, during the period of noradrenaline therapy, was greater than the blood flow in the period immediately after its cessation. The effect of noradrenaline on the blood flow to other vital organs was probably comparable.

The early promotion of an increase in blood flow to vital organs, including centres in the medulla, together with the correction of any myocardial ischaemia following an increase in coronary blood flow, almost certainly helps to prevent the

development of an irreversible phase, refractory to treatment (including noradrenaline therapy), and progressing rapidly to complete circulatory standstill.

The need to increase progressively the dose of the drug as the duration of its administration increases may be evidence of deterioration in the condition of the patient, but it may, on the other hand, be due to the patient developing an acquired tolerance to the drug. It was met with in Cases 1 and 2, but not in Case 3. It was so marked in Case 1, where there had been such a dramatic initial response, that the systolic pressure was allowed to fall dangerously low: the strength of the noradrenaline solution should have been increased earlier than it actually was. Should this diminished response to the drug be due to acquired tolerance then it is possible that the administration of cortisone or corticotrophin might prevent it occurring.

Following induction of anaesthesia there was in all cases a slight rise in the systolic blood pressure and a marked diminution of the facial pallor. This may have been due to the removal of one of the possible factors causing the shock—namely, the severe pain. However, it is possible that more efficient oxygenation, following induction and intubation, was responsible for the temporary diminution of the signs of shock.

The paramount importance of adequate oxygenation in the shocked patient is clearly illustrated in Case 3. Here the patient collapsed after operation because voluntary respirations were too shallow for full oxygenation. Vigorous inflation with oxygen alone led to recovery in a very short time (Fig. 3). This episode underlines the need for ensuring that any respiratory depression due to relaxant drugs has been fully counteracted before extubation, and poses the question whether long-acting relaxants should be avoided in cases of shock or in very ill patients.

The noradrenaline infusions were maintained for 47, 60, and 40 hours respectively. Toxic effects attributable to the drug were not noticed.

Summary

Three cases are described in which noradrenaline had to be used in order to maintain an adequate blood pressure after traditional methods of resuscitation had failed. The cases are consecutive ones of their type. The two patients with perforation of the large bowel recovered completely; the patient with peptic ulcer perforation showed a good immediate recovery but died 12 days later owing to a pulmonary embolus.

It is suggested that in these cases of shock traditional methods of resuscitation should be tried first, but if these methods fail the use of a continuous noradrenaline infusion should not be delayed.

Noradrenaline therapy is very far from being the complete answer to the problem of the treatment of the shock due to visceral perforation, but its early use in the shocked state probably produces an increase in blood flow to vital organs. This and the correction of myocardial ischaemia (following the increase in coronary blood flow) may be important factors in helping to prevent the development of an irreversible phase which is refractory to treatment and where noradrenaline therapy is of no avail and may possibly do more harm than good.

The paramount importance of adequate oxygenation in the shocked patient is stressed.

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BIBLIOGRAPHY

- Braude, A. I., Williams, D., Sieminski, J., and Murphy, R. (1953). *A.M.A. Arch. Intern. Med.*, 92, 75.
 Fremont, R. E., Luger, N. M., Surks, S. N., and Kleinman, A. (1954). *A.M.A. Arch. Surg.*, 68, 44.
 Gilmour, T. E. W. (1955). *British Medical Journal*, 2, 1248.
 Kurland, G. S., and Malach, M. (1952). *New Engl. J. Med.*, 247, 383.
 Luger, N. M., Kleinman, A., and Fremont, R. E. (1951). *J. Amer. med. Ass.*, 146, 1592.
 Miller, A. J., Shifrin, A., Kaplan, B. M., Gold, H., Billings, A., and Katz, L. N. (1953). *Ibid.*, 152, 1198.
 Moyer, J. H., Skelton, J. M., and Mills, L. C. (1953). *Amer. J. Med.*, 15, 330.
 Ritchie, H. D. (1956). *British Medical Journal*, 1, 371.
 Shanahan, E. F. (1955). *Brit. J. Anaesth.*, 27, 31.
 Skelton, J. M., Mills, L. C., and Moyer, J. H. (1952). *Fed. Proc.*, 11, 391.
 Wise, R. I., Shaffer, J. M., and Spink, W. W. (1952). *Proc. cent. Soc. clin. Res.*, 25, 961.

REPORT OF TWO SIBLINGS DIAGNOSED AS CASES OF ACUTE LYMPHATIC LEUKAEMIA

BY

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The cases described below concern a brother and sister in both of whom acute lymphatic leukaemia was diagnosed during life. In the sister the disease followed a classical course to an early death, but in the brother, although he too died after a short illness, certain unusual features were noted during life and at necropsy. This report is presented because of the rarity of familial leukaemia and because of the interest of the case of the brother.

Case 1

The patient, a housewife aged 38, was admitted to West Middlesex Hospital early in March, 1950, because of pallor, generalized pains and weakness developing during the last three months, epistaxes, and the passage of blood clots per vaginam apart from normal menstruation. There was nothing relevant in the past history. Results of blood examination on March 3 were: haemoglobin 53% (Haldane); R.B.C. 2,390,000 per c.mm. Total white cell count not available, but differential count showed polymorphs 12%, lymphocytes 71%, prolymphocytes 9%, and nucleated R.B.C. 8%.

Clinical examination revealed a pale woman with bilateral subconjunctival haemorrhages and suborbital bruising, petechiae, and bleeding gums. There was no lymphadenopathy, but spleen and liver were each enlarged to two fingerbreadths and were tender; two small haemorrhages were noted in the left optic fundus. Blood pressure was normal, the urine clear, and the temperature 99.6° F. (37.55° C.). Blood examination on March 10 showed: haemoglobin 34%; R.B.C. 1,200,000 per c.mm.; W.B.C. 50,700 per c.mm. (polymorphs 2.5%, lymphocytes 77%, lymphoblasts 20%).

The patient's condition rapidly deteriorated, with epistaxes, haematemesis, and melaena, and she died in cardiac failure on March 17, 1950.

Case 2

This patient, a brother of Case 1, aged 31, was admitted to King Edward Memorial Hospital, Ealing, on July 5, 1955. He had first complained of lumbar pain, with swollen inguinal and axillary lymph nodes, eight weeks previously, and at that time was thought to be suffering from glandular fever. There was no history of past illness. On June 8 a blood count revealed: haemoglobin 94%; W.B.C. 6,000 per c.mm. (polymorphs 10%, lymphocytes 89%, monocytes 1%), some large and atypical lymphocytes being similar to those seen in glandular fever.

Two weeks later severe gingivitis and some petechiae on the left arm developed. Cervical and submandibular

lymph nodes swelled and he became pyrexial. On June 24 the blood count was: haemoglobin 78%; W.B.C. 7,000 per c.mm. (polymorphs 56%, lymphocytes 36%, monocytes 4%, eosinophils 3%). No atypical "glandular fever" cells noted.

On his admission to hospital on July 5 the patient was pale and had visibly enlarged cervical and submandibular lymph nodes. There were no abnormalities in the cardiovascular or respiratory system. The tip of the spleen was just palpable, but the liver was not enlarged. There was

FIG. 1.—Case 2: Sternal marrow smear on admission to hospital. ($\times 180$.)

generalized lymphadenopathy, also generalized petechiae becoming confluent over chest and abdomen. Temperature was 101° F. (38.3° C.). Blood picture on admission: haemoglobin 57%; R.B.C. 4,400,000 per c.mm.; W.B.C. 3,400 per c.mm. (atypical non-granular immature cells 27%, neutrophils 6%, lymphocytes 67%); platelets 166,000 per c.mm. On sternal marrow puncture large numbers of primitive leucocytes (blast cells) and a very few normal elements were found (Fig. 1). Blood was transfused repeatedly, but no remission occurred. In view of the low total leucocyte count the patient was not given radiotherapy, or any drugs, apart from sedatives. He steadily became weaker, and on July 26 a severe throat infection with monilia occurred which did not respond to treatment.

By August 1 the lymph nodes had rapidly decreased in size and then remained so. Clinically the spleen did not appear to enlarge further. A swinging temperature—98°–101° F. (36.7°–38.3° C.)—was maintained throughout the illness. A blood count on July 27 showed: haemoglobin 70%; W.B.C. 2,400 per c.mm. (lymphoblasts 20%, polymorphs 14%, lymphocytes 64%, monocytes 2%); and on July 30: haemoglobin 57%; W.B.C. 1,400 per c.mm. (differential count as before). The blood picture continued to deteriorate, and on August 10 the figures were: haemoglobin 25%; W.B.C. 800 per c.mm. (lymphoblasts 8%, polymorphs 6%, lymphocytes 84%, monocytes 2%). The patient died two days later.

Comment

There is no other family history of leukaemia, but the father and a brother and sister, who are alive and well, state that the patients' maternal grandfather died of a "rare disease." Their mother was said to have died "at the menopause," and she lost three infants before the birth of the two patients and the surviving brother and sister, the cause of their death being unknown.

Unfortunately no post-mortem examination was held on the woman. The following is taken from the necropsy report (Dr. W. S. Killpack) on her brother: "Emaciated