FIG. 1.—Photograph of respirator.

2. A magnetically controlled valve which utilizes a flow of compressed air to build up and disperse an air pressure within the bottle, the alternating pressure cycle rhythmically compressing and releasing the breathing-bag and inflating and deflating the lungs. During deflation the compressed-air stream is used to create a venturi effect within the valve, the negative pressure produced being sufficient to overcome the inertia and resistances of the gas system and assist the pressure in the breathing-bag to return to the atmospheric level.

3. A device which enables the capacity of the system to be altered and permits the frequency of the respiratory cycle to be varied.

4. A self-regulating expiratory valve which allows any excess of anaesthetic gas to escape and ensures that the breathing-bag contains a constant volume of gas at the end of each expiration.

Provision is also made for varying the relative lengths of the inflationary and expiratory phases and for the retention of a positive pressure in the lungs throughout expiration if desired. Fig. 2 is a reproduction of one type of

FIG. 2.—A type of tracheal-pressure curve attainable with the machine.

tracheal-pressure curve which is attainable by ventilation with the machine. This follows closely the ideal form of curve described by Cournand *et al.* (1948). Should spontaneous respiration occur, the design of the valve makes it possible for the machine to respond to the resultant pressure changes and so follow the patient's respiratory pattern.

The rate of respiration may be adjusted within a range of 8 to 30 respirations a minute, and the pressure range available is from 5 to 25 cm. of water.

The water manometer used to record the pressure changes in the anaesthetic circuit also serves as a safety valve, the length of its tube limiting the inflation pressure that the machine can apply to 30 cm. of water. It is cut out of circuit when the three-way tap is turned to connect the patient to the hand-operated breathing-bag.

Features of the machine in use include simplicity of operation, a satisfactory performance at low inflation pressures,

the assistance given to deflation, and a "chattering" or increase in rate which gives audible warning (when the mechanism is suitably set) should an obstruction to respiration develop. The machine has been found to require very little attention in the way of maintenance, and the breathing-bag is easily removed for cleaning purposes.

Fig. 1 shows the appearance of the original apparatus, which is being developed and produced commercially by Medical and Industrial Equipment Ltd., London, under the name of the "Aintree respirator." A more detailed account of the machine may be found elsewhere (Esplen, 1952).

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THROMBOTIC MICROANGIOPATHIC HAEMOLYTIC ANAEMIA (THROMBOTIC MICROANGIOPATHY)

BY

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The condition described in this paper as thrombotic microangiopathy has attracted little attention outside the United States of America, where it is commonly known as thrombotic thrombocytopenic purpura. Clinically, the typical fully developed case presents a syndrome of fever, haemolytic anaemia, purpura, and fluctuating neurological disturbances; when this syndrome is present the diagnosis can be made at the bedside. Often, however, the most characteristic component of the syndrome, the *waxing and waning* neurological signs, appears only in the terminal stages of the illness; even in the earlier stages, however, identification by laboratory studies of the haemolytic nature of the anaemia and of the thrombocytopenia underlying the purpura should enable the diagnosis to be made, for the association of haemolytic anaemia and thrombocytopenic purpura is found in only a few conditions, most of which can be distinguished from thrombotic microangiopathy on other grounds. Unfortunately, the disease is not widely known and it is seldom considered in diagnosis: in most cases the correct diagnosis has first been made *post mortem*, by recognition of the pathognomonic disseminated lesions which occur only in vessels of microscopic calibre. No treatment has yet proved effective, and the disease has been fatal in all the recorded cases, usually within two to six weeks of its clinical onset. There are grounds for hoping that earlier diagnosis and treatment may lower the mortality. The following account of thrombotic microangiopathy is therefore presented, with a report of two new cases.

Historical

The first account of an undoubted example of this disease appears to have been given by Moschowitz (1924, 1925), who described a case of acute febrile haemolytic anaemia with petechiae and the development of neurological signs shortly before death; Libman is said to have recognized the condition clinically as a "new" disease. Histological examination *post mortem* showed hyaline thrombosis of terminal arterioles and capillaries. Moschowitz recognized that the wide dissemination of these lesions was unique; he thought that

the thrombi were formed of agglutinated erythrocytes and that the disease was caused by some powerful haemagglutinative and haemolytic poison. He mentioned that Lederer had seen four cases "clinically identical" with his case but recovering after a blood transfusion (Moschcowitz, 1925); unfortunately, this comment has led to misquotation of Moschcowitz's case as a fatal case of Lederer's anaemia and so to the erroneous statement that disseminated hyaline vasothrombosis is a characteristic of the latter (O'Donoghue and Witts, 1932; Whitby and Britton, 1950).

No further case was described until Baehr *et al.* (1936) published a composite clinico-pathological study of four cases. They believed that the thrombi were composed of blood platelets, and that the associated thrombocytopenia was due to the available supply of platelets being used up in the formation of the countless lesions. One of their cases was also reported by Friedberg and Gross (1936); another was redescribed by Gitlow and Goldmark (1939-40). Since then only 25 unequivocal cases have been reported (Altschule, 1942; Bernheim, 1943; Trobaugh *et al.*, 1946; Carter, 1947; Engel *et al.*, 1947; Fitzgerald *et al.*, 1947-3 cases; Singer *et al.*, 1947; Muirhead *et al.*, 1948; Green and Rosenthal, 1949-2 cases; Gore, 1950-5 cases; Singer *et al.*, 1950; Wyatt and Lee, 1950; Goldenberg *et al.*, 1950; Clinicopathologic Conference, 1950; Meacham *et al.*, 1950, 1951-2 cases; Symmers and Barrowcliff, 1951; Rackow *et al.*, 1952), making a total of 30 cases, to which Case 4* in Pagel's (1949) paper on acronecrosis can be added.

The complicated case described by Norman, Brown, and Spitz (Clinicopathologic Conference, 1946) was possibly fundamentally of the same nature; unfortunately, the histological description is sketchy and there are no illustrations. Four other supposed cases have been published. One was attributed by Ehrich and Seifter (1949) to iodine intoxication; in the absence of adequate data the accuracy of their diagnosis is questionable. The Italian case of Vannucchi and Esente (1949) cannot be accepted as proved, as there was no histological study; the equivocal clinical and atypical haematological findings do not support the diagnosis, and the ophthalmoscopic observation of thrombosis of major retinal veins is contrary to the findings in every other recorded case, in which only vessels of microscopic dimensions have been affected. The clinical and pathological descriptions and the illustrations of Wallace's (1951) two Australian cases are not convincing.

Although only 36 cases or supposed cases have been reported, thrombotic microangiopathy is probably not as rare as this number might suggest. Familiarity with the condition is an unusually important factor in its recognition; no fewer than 17 of the first 25 cases were described by workers in only three centres (Mount Sinai Hospital, New York; Harvard Medical School and the Boston City Hospital; and the Armed Forces Institute of Pathology, Washington). Wider knowledge of its occurrence rather than an increasing incidence of the disease probably accounts for the fact that 23 unequivocal cases were reported in the six years 1946 to 1951, while only seven were recorded in the 20 years from 1924, when Moschcowitz first described the condition. Of the 36 published cases or supposed cases, 30

were reported from the United States and three from this country. Two further British cases are described in this paper, and the diagnosis has been made in at least two other cases in England (Smith, 1951, personal communication†; Lennox and Dacie, 1951). Case 56 in Gilmour's (1947) monograph was probably an example of this condition. The British literature contains a paper from America in which there is a brief account of two other probable examples of this disease (Keil, 1937), although the details are insufficient to warrant outright acceptance of the author's claim that his cases were probably related to the condition described by Moschcowitz.

Clinical Features

The following summary has been prepared from the clinical descriptions of the 31 indisputable cases previously published and the two new cases reported in this paper. The age of the patients ranged from 9½ to 74 years; the greatest incidence was in young adult life. Nineteen of the patients were female and 12 male. Six patients were of Negro race.

The onset of grave illness is usually rapid, with asthenia and haemorrhagic manifestations as the commonest presenting symptoms. There may, however, be a prodromal period of weeks or months of vague ill-health, sometimes with muscle or joint pains or urticaria. Sometimes the acute illness is prefaced by a febrile upper respiratory infection which leaves the patient unexpectedly exhausted, or by gastro-intestinal disturbance and vague abdominal pain. Neurological symptoms or mental confusion may precede other manifestations; one patient (Goldenberg *et al.*, 1950) presented with a severe psychosis which necessitated admission to a mental hospital.

The characteristic clinical features of the established illness are fever, haemolytic anaemia, purpura or other haemorrhages, and fluctuating neurological disturbances.

Fever.—Fever up to 100-102° F. (37.8-38.9° C.) usually occurs; there may be terminal hyperpyrexia.

Haemolytic Anaemia.—Anaemia has been present in every case and is usually severe; it develops rapidly and is usually manifest when the patient first comes under observation. It may precede the haemorrhagic manifestations, and its severity is essentially independent of the latter. Haemolytic jaundice was present in 24 cases.

Haemorrhagic Manifestations.—Haemorrhagic lesions are usually obtrusive and rarely (four cases?) absent; they are commonly present when the patient comes under observation, but may first appear at any time subsequently. Purpura is commonest; only a few easily overlooked petechiae in skin or mucosae may be present, or there may be severe widespread purpura which often develops in crops. The tourniquet test may be positive before there is spontaneous bleeding. There may be haemorrhage from any of the orifices of the body; haematuria was a presenting symptom in five cases.

Neurological Disturbances.—Neurological abnormalities are usual, although they may first appear late in the course of the disease. In a large proportion of cases they have shown a distinctive multiplicity and waxing and waning character. Paraesthesiae, dysphasia and related disorders, cranial nerve lesions, cerebellar signs, isolated paralyses or pareses, monoplegia or hemiplegia, and spasticity are among many recorded transitory manifestations of focal nervous damage. Often, however, the neurological symptomatology is not distinctive (generalized muscular weakness, incontinence, headache, vertigo, delirium, stupor, coma). Convulsions are rare. Electroencephalography showed changes consistent with "diffuse cortical disorder" in one case (Singer *et al.*, 1950) and suggested a cerebral tumour in another (Muirhead *et al.*, 1948).

*I am indebted to Dr. Walter Pagel for allowing me to see sections from this case, which he agrees should be considered an example of thrombotic microangiopathy.

†I am indebted to Professor D. S. Russell, in the absence of Dr. J. F. Smith overseas, for the opportunity to examine the typical histological material from this London Hospital case.

Inconstant clinical findings include moderate enlargement of lymph nodes, spleen, or liver. Uraemia has been observed rarely. Arterial hypertension was recorded in two cases; both were uraemic. The pulse rate is usually proportional to the temperature, but there may be a considerably disproportionate tachycardia. One child showed electrocardiographic evidence of myocardial ischaemia (Engel *et al.*, 1947). Retinal haemorrhages and papilloedema may be present.

Laboratory Findings

Haematology.—Haematological examination typically shows severe haemolytic anaemia, thrombocytopenia, and a leucocytosis which may be leukaemoid. Exceptionally, any of these findings may be absent. The anaemia has commonly been described as normocytic and normochromic; hypochromia, microcytic anisocytosis, and poikilocytosis have been noted in some cases. Although the severity of the haemolytic process varies, erythrocyte counts of two million or less, with a proportional reduction of the haemoglobin level, are common at the first examination. There is usually a pronounced reticulocytosis, and nucleated red cells are commonly found; the number of reticulocytes and nucleated red cells tends to rise during the course of the illness, and counts of the latter have reached figures equivalent to more than 14,000 per c.mm. Erythrocyte fragility in hypotonic saline is normal or slightly increased; Singer *et al.* (1950) noted increased mechanical fragility in one case. Spherocytosis was observed in three cases, in one of which the proportion of spherocytes was noted to increase remarkably as the disease advanced. Sick cells were not found in any of the Negro patients. The direct Coombs test was negative in the three cases in which it was recorded (Singer *et al.*, 1950; Meacham *et al.*, 1951). Pigment studies usually show hyperbilirubinaemia with an indirect van den Bergh reaction; there is a correspondingly increased excretion of urobilinogen in the faeces and urine.

Leucocytosis with a shift to the left is found in most cases; usually it is of moderate degree, at least in the earlier days, although counts of up to 50,000 have been recorded. Myelocytes, premyelocytes, and myeloblasts may be found in the peripheral blood; the leukaemoid picture was observed in eight cases, in some of which it was transitory. Severe thrombocytopenia is usual and platelets may be practically absent. The thrombocytopenia may be progressive, or successive counts may swing between very low and normal figures; the number of platelets may be above the "critical level" even during an outcrop of purpura. Clotting-time and prothrombin-time are usually normal, whereas bleeding-time is prolonged and clot retraction markedly deficient.

Marrow examination shows normoblastic erythropoietic hyperplasia; myeloid hyperplasia may be associated with an increased proportion of immature cells. Megakaryocytes may be increased in number but are said to show no other abnormality.

Urine.—Protein and excess urobilinogen are usually present. There is no bilirubinuria. Occasional granular casts are often found; erythrocytes are almost always present microscopically and there may be gross haematuria. The urine may be completely normal.

Blood Chemistry.—Hyperbilirubinaemia is the commonest abnormality. Hyperglobulinaemia has been noted in five cases, with a normal or low total protein concentration and an albumin-globulin ratio of approximately unity. Positive cephalin-cholesterol flocculation and thymol turbidity tests have been reported. Non-protein nitrogen is raised in a few cases.

Cerebrospinal Fluid.—The cerebrospinal fluid was normal in nine cases. Six others showed protein concentrations of 40 to 176 mg. per 100 ml., a positive Pandy test, and occasional erythrocytes.

Other Investigations.—Serological tests for syphilis were negative in the 13 cases investigated. Serum agglutination reactions, blood cultures, and other bacteriological investigations have been essentially negative. Occult blood is inconstantly present in the stools.

Diagnosis

Thrombotic microangiopathy was diagnosed *ante mortem* in only three published cases (Engel *et al.*, 1947; Singer *et al.*, 1950; Meacham *et al.*, 1951); there is little doubt that a larger proportion of cases would have been diagnosed during life if the syndrome were more generally known. Indeed, the characteristic diagnostic tetrad of the fully developed syndrome identifies the patient's illness as thrombotic microangiopathy; judging, however, from the available case reports, this tetrad appears to have been complete in considerably fewer than half the published cases. In particular, the characteristically multifarious and fleeting neurological signs usually occur at a late stage, if at all: more commonly, the neurological symptomatology is not diagnostic. Of much greater diagnostic importance is the association of haemorrhagic manifestations and haemolytic anaemia. The frequency of haemorrhage, particularly purpura, as a presenting or early sign of this disease makes it a cardinal diagnostic feature.

As the purpura is practically always accompanied by thrombocytopenia, the differential diagnosis is essentially that of thrombocytopenic purpura in general (Singer *et al.*, 1947; Dameshek, 1947). When the haemolytic nature of the accompanying anaemia is recognized, the number of conditions to be considered in diagnosis is reduced still further, and the correct diagnosis should be attainable in a large proportion of cases. Singer *et al.* (1950) pointed out that thrombocytopenia may be associated with haemolytic anaemia in thrombotic microangiopathy, "idiopathic" acquired haemolytic anaemia, toxic haemolytic anaemia (caused by sulphonamides, etc.), symptomatic haemolytic anaemia (malignant reticuloses, leukaemias, carcinomatosis, etc.), familial haemolytic anaemia in crisis, paroxysmal nocturnal haemoglobinuria, severe liver disease, and untreated pernicious anaemia. Of these, only the "idiopathic," toxic, and symptomatic acquired haemolytic anaemias cannot readily be differentiated by clinical and laboratory study from thrombotic microangiopathy; the leukaemoid blood picture of some cases of the latter is particularly likely to lead to confusion with the symptomatic group unless it is transient. Immunological methods may have diagnostic value, as the Coombs test is usually positive in the "idiopathic" and symptomatic haemolytic anaemias (Singer and Motulsky, 1949) and has been negative in the three published cases of thrombotic microangiopathy in which it was performed.

The ultimate proof of the diagnosis is histological. Biopsy was first suggested by Bernheim (1943), yet its value has scarcely been investigated. A few authors recorded failure to find the lesions in biopsies of marrow, although they were recognized in splenectomy specimens by Green and Rosenthal (1949) and Meacham *et al.* (1951). Little is known about the incidence of the typical vascular changes in tissues accessible to biopsy, and appropriate post-mortem studies would be valuable; lesions were numerous in the skin and in the vastus lateralis examined *post mortem* in one case (Smith, 1951, personal communication; see footnote on page 898). I have made the diagnosis in one case on the basis of a positive skin biopsy in association with the typical clinical picture; permission for a necropsy was not obtained.

Electrocardiography and electroencephalography may be of diagnostic value in demonstrating visceral changes.

Prognosis and Treatment

The disease has been fatal in every recorded case. The period between the first symptom of ill-health and death was less than six weeks in two-thirds of the cases, and less than a fortnight in eight cases. The longest durations were 15 weeks, 6 months, 10 months (two cases), and 3½ years. Although transient clinical improvement lasting a few days is common in the early stages, longer remissions have been recorded in only three cases. In the case described by Engel *et al.* (1947) withdrawal of sulphonamide therapy was followed by such marked improvement that the patient was

able to return home; five weeks later she developed a fatal relapse, which was not preceded by further drug therapy; test doses of sulphonamides had been shown to cause a febrile reaction, with tachycardia and leucocytosis but without evidence of haemolysis or haemorrhage. In another case (Symmers and Barrowcliff, 1951) the patient gradually recovered sufficiently to leave hospital, but relapsed a week later. A much more striking remission, with important therapeutic implications, was observed by Meacham *et al.* (1950, 1951); the patient remained in reasonably good health for 28 months after splenectomy, although arterial hypertension developed during that time. Mental deterioration then began, and six months later she was readmitted in coma. A 23-day course of 20 mg. of A.C.T.H. daily was given (the method of administration is not recorded); her condition improved remarkably during the first ten days, but relapsed on the thirteenth day, and she died ten weeks later.

Blood transfusions have been given in 20 cases, with transitory or no benefit; Singer *et al.* (1950) pointed out that transfused cells appear to be as rapidly haemolysed as those of the patient. Christian's (1951) statement that transfusion of platelets has been reported as a successful treatment is erroneous; the case to which he referred (Hirsch *et al.*, 1950) was one of thrombopathic thrombocytopenia, a condition which is not related to thrombotic microangiopathy.

Penicillin has been tried in five cases and aureomycin in one case without any demonstrable effect. It is doubtful whether streptomycin was responsible for the remission which followed in the one case in which it was given (Symmers and Barrowcliff, 1951). Sulphonamides appear to have been seldom used; they have been either without effect or possibly detrimental (Engel *et al.*, 1947; Fitzgerald *et al.*, 1947).

Splenectomy was performed in six cases. The patients were already severely ill, and four died during or shortly after the operation; one survived for six days, and showed no improvement during this time. The sixth case was that of Meacham *et al.* (1951); the long remission following this splenectomy suggests that the operation deserves further trial at a stage before the patient's condition makes surgery unduly hazardous.

A.C.T.H. has been tried only in the case of Meacham *et al.* (1951); although this patient's second remission may not have been due to the treatment, trial of A.C.T.H. or cortisone in future cases is obviously indicated. The nature of the primary lesion of the vascular wall suggests a relationship between this disease and the so-called collagen diseases and encourages the hope for benefit from treatment with these hormones; it is similarly relevant that they are said to have caused remissions in some haemolytic anaemias (Selye, 1951). The dosage given by Meacham *et al.* (1951) was small; they suggested that larger doses might cause ischaemic complications. This objection is possibly fallacious; its basis was the observation of multiple small infarcts in cortisone-treated cases of polyarteritis nodosa, due supposedly to over-rapid healing of the vascular lesions. Infarcts are not in fact necessarily numerous in cases of polyarteritis so treated (Symmers and Litchfield, 1952); moreover, only the smallest vessels are affected in thrombotic microangiopathy, so that there is more opportunity for maintenance of adequate collateral circulation, and the vessels involved are by no means always completely occluded.

Anticoagulant therapy has not been used in any recorded case; its trial in patients with such a severe haemorrhagic tendency would require a difficult decision (Singer *et al.*, 1950).

Morbid Anatomy and Histopathology

Apart from evidence of severe anaemia and more or less widespread haemorrhages, which are usually petechial, there is little to be found macroscopically at necropsy. Some cases show small necrotic foci or infarcts in the viscera. The spleen may be moderately enlarged.

The microscopical findings are diagnostic. The characteristic histological feature is a very widely disseminated thrombosis of the smallest calibre blood vessels. Although the lesions may not be constantly present in any particular organ, they are particularly frequent and numerous in the myocardium, the capsular zone of the adrenals, and the renal cortex, and particularly rare in the lungs, where only the bronchial vasculature may be affected. The hepatic and adrenal sinusoids escape involvement.

The affected vessels are partly or completely occluded by granular or hyaline eosinophil material. Since the work of Baehr *et al.* (1936) it has usually been assumed that the occlusive masses are platelet thrombi (Editorial, 1950), although this remains unproved and the results of histochemical studies are equivocal (Orbison, 1952). The thrombus is often propagated free within the lumen for a considerable distance from its attachment to the vessel wall. It becomes covered by endothelium, and often a narrow crescent of lumen remains patent. Vessels which were completely occluded may be reopened by shrinkage of the thrombus away from the wall over part of its extent, or the thrombus may be canalized by endothelium-lined spaces. The older thrombi are more compact and may be invaded by endothelial cells or fibroblasts. The obstructed vessels may be much dilated and their walls very thin; Orbison (1952) showed that the dilatations are fusiform aneurysms involving the arteriolo-capillary junctional zone predominantly. Hyaline or sometimes fibrinoid material may be found beneath the endothelium of vessels of the size in which the thrombi form; this mural alteration has been described as the primary or prethrombotic lesion of the disease (Gore and Friedman, 1948; Gore, 1950), endothelial damage over the hyaline material leading to the deposition of platelets and so to the development of the characteristic thrombotic masses. There is doubt about the nature of hyaline projections into the lumen which may be seen in some cases; they may be focal protrusions from the hyaline prethrombotic lesion or they may possibly be old, shrunken, hyalinized thrombi. Further study of the mural changes is needed before this question can be decided. Endothelial hyperplasia is common even in vessels which are otherwise normal. Absence of any accumulation of inflammatory cells is characteristic; occasionally there is adjacent haemorrhage, but petechiae often seem to occur independently of demonstrable vascular lesions.

Small arteries, arterioles, and capillaries may be involved, although the arteriolo-capillary junctional zone is most often affected. Venules may contain the typical thrombi, although this is exceptional, and some authors claim that the supposed venules are dilated arterioles which have been misidentified. In the most heavily involved tissues the majority of the vessels may be affected, yet necrotic foci in the parenchyma are usually few and minute, and may be absent. Bernheim (1943) and others suggested that the relative paucity of ischaemic lesions could be explained by the incomplete occlusion of many affected vessels; collateral circulation through uninvolved vessels and recanalization of thrombi are other likely factors. In the kidneys the juxtaglomerular portion of the afferent arterioles is most often affected; glomerular capillaries are often obliterated by hyaline material which is not clearly thrombotic in nature but appears rather to represent a change in the capillary wall. A focal proliferative "glomerulitis" has been noted. The neurohistological changes have been described by Adams *et al.* (1948).

Differential Histological Diagnosis

The lesions of anaphylactoid purpura are easily distinguished from those of thrombotic microangiopathy by the cellular inflammatory reaction around the affected vessels in the former. Vascular lesions in some cases of "primary" amyloidosis may resemble the hyaline lesions of thrombotic microangiopathy fairly closely; their true nature is indicated by the changes elsewhere.

Lesions indistinguishable from the recanalized complete occlusions of thrombotic microangiopathy may be found in arterioles following occlusion of their parent arteries; such lesions are often seen in the vicinity of older arterial lesions of polyarteritis nodosa and occur particularly frequently in the subcutaneous tissue in arteriosclerotic gangrene and in acro-necrosis associated with subacute bacterial endocarditis (Pagel, 1949), Raynaud's syndrome, and similar forms of peripheral ischaemia. The thrombi in these conditions are composed of erythrocytes and fibrin, unlike those of thrombotic microangiopathy, and it is interesting that they undergo identical morphological changes (hyalinization, retraction, surface endothelialization, recanalization). Similar lesions, also probably originating as banal thrombosis, are seen in the vasculature of some gliosarcomata and occasionally in metastatic tumours in the brain; it is noteworthy that endothelial hyperplasia is a recognized characteristic of the vasculature of some of these tumours. Identical changes were shown in vessels occluded by agglutinated erythrocytes in experimental intoxication with certain snake venoms (Amorim *et al.*, 1951). Such observations suggest that the reparative process following thrombotic occlusion of these smallest-calibre vessels is similar, whatever the nature of the occlusive mass.

Aetiology

The cause of thrombotic microangiopathy is unknown. No infective agent has been found. Allergy has been suggested, without good evidence, although urticaria and joint pains have occurred prodromally and nasopharyngitis may precede the acute illness. Sensitivity to sulphonamides was suggested in one case (Fitzgerald *et al.*, 1947) and demonstrated in another, in which the evidence for its causal relation to the disease was equivocal (Engel *et al.*, 1947). The direct Coombs test was negative in the three cases in which it was performed, suggesting that haemolysis was not mediated through a globulin antibody. Reticulocytosis, leucocytosis, and the normality of megakaryocytes exclude "hypersplenism." No familial cases have been reported, although one patient's brother had idiopathic thrombocytopenic purpura without thrombotic lesions (Baehr *et al.*, 1936). Baehr *et al.* looked upon thrombotic microangiopathy as a variety of idiopathic thrombocytopenic purpura, but Klemperer (1951) has since accepted its primarily vascular nature.

Although it does not bring one much nearer to understanding the cause of the disease, the evidence for a relationship to the so-called collagen diseases is considerable, as Beigelman (1951) indicated. The morphology of the primary vascular lesion suggests such a relationship. One case of polyarteritis nodosa has been recorded in which widely disseminated lesions of thrombotic microangiopathy were also present, although there were no ante-mortem observations which could be related unequivocally to their presence (Symmers and Gillett, 1951). A family history of polyarteritis nodosa (Bernheim, 1943) and of disseminated lupus erythematosus (Singer *et al.*, 1950) has been reported. Relationship between disseminated lupus erythematosus and thrombotic microangiopathy has been much disputed, and was strongly denied by Klemperer (1948); while there are no close clinical or pathological similarities between them, "wire-loop" glomeruli have been noted in the latter, and three cases (Baehr *et al.*, 1936; Engel *et al.*, 1947; Meacham *et al.*, 1951) presented verrucose vegetations on the heart valves, resembling those of disseminated lupus erythematosus. One patient with thrombotic microangiopathy had had discoid lupus erythematosus of the scalp for ten years (Meacham *et al.*, 1951).

Jones and Loring (1951) suggested that thrombotic microangiopathy was merely an unusually severe form of capillary thrombosis such as occurs in the glomeruli and occasionally elsewhere in some cases of bacterial infection or circulatory disturbance, possibly through toxic or anoxic damage to the endothelium. Their argument is unconvincing.

Any aetiological theory must explain not only the primary vascular change which leads to thrombosis and thrombocytopenia but also the leucocytosis and haemolysis. Studies of many more cases during life are essential before the cause and nature of the disease can become clear.

Nomenclature

None of the names which have been used for this disease is satisfactory. Thrombocytic acroangiostrombosis (Fitzgerald *et al.*, 1947), thrombocytopenic thrombocytic microangiostrombosis (Lunedei, quoted by Vannucchi, 1949), generalized blood platelet thrombosis (Green and Rosenthal, 1949), and platelet thrombosis syndrome (Beigelman, 1951) assume the still unproved thrombocytic nature of the occlusive masses in the vessels. Moschcowitz's syndrome (Lennox and Dacie, 1951) shares with Beigelman's (1951) term the advantage of stressing the occurrence of a definite clinical picture, but has the objection of being eponymous. The most popular name, thrombotic thrombocytopenic purpura (Singer *et al.*, 1947), is inappropriate for those cases in which thrombocytopenia or purpura is absent. All these names neglect the characteristic haemolytic anaemia.

Thrombotic microangiopathic haemolytic anaemia, or, for brevity, thrombotic microangiopathy, is suggested as a suitable substitute for the names previously used. It indicates the location and the most striking feature of the characteristic histological lesions without mentioning inconstant and controversial features of this clinico-pathological entity.

Case 1

A previously healthy man aged 32, of independent means, had a febrile cold in February, 1946. He recovered in a few days, but a week later began to suffer from vague aching in the back and limbs. He felt off colour, was easily tired, and began to lose appetite. A few days later he noticed transient slurring of his speech on several occasions. One week later, on March 1, he was noticed to be fidgety, and confused about the identity of people whom he met. His doctor saw him next day and found him to be mildly disoriented; examination showed nystagmus and slight ataxia, a non-haemorrhagic urticarial rash, and a trace of protein in the urine. Two days later he seemed to be quite well, although it was noticed that a purpuric eruption appeared distal to the sphygmomanometer cuff. On March 10 he called on his doctor socially and fainted twice during the visit. He was admitted to hospital on the same evening.

On admission his temperature was 101° F. (38.3° C.) and pulse 140. He was pale and slightly jaundiced, and there were a few purpuric spots on his limbs. No other abnormality was found on systematic examination. His blood pressure was 135/75.

Investigations.—Erythrocytes 3,200,000 per c.mm.; reticulocytes, 22%; haemoglobin, 9.3 g. per 100 ml.; leucocytes, 12,800 per c.mm., with 75% (9,600) neutrophils, 2% (256) eosinophils, 18% (2,304) lymphocytes, and 5% (640) monocytes; 12 normoblasts were noted in counting 300 leucocytes; platelets, 84,000. The serum bilirubin was 6.5 mg. per 100 ml.; plasma proteins, 6.2 g. (albumin 3.2 g., globulin 3 g.); blood urea 34 mg. per 100 ml. Urine: protein ++; urobilinogen ++; no bilirubin or reducing substance; many erythrocytes and occasional granular casts in centrifugate.

On March 11 his temperature was 102° F. (38.9° C.) and pulse 140. He complained of stiffness of the left hand. The left biceps and triceps reflexes were exaggerated; the tendon reflexes of the right arm and of both legs were normal, although there was an extensor plantar reflex on the right side. During the day purpura became widespread and there was frank haematuria. Successive platelet counts at intervals of a few hours were 210,000, 34,000, and 78,000. On March 12 he was stuporous; the reflexes were now normal, but a partial left facial paralysis was noted and the right pupil was contracted and immobile. His condition

deteriorated rapidly; his temperature rose to 107° F. (41.7° C.) shortly before death and both pupils became widely dilated. Investigations within a few hours of death showed 4.1 g. haemoglobin, 1,400,000 erythrocytes, with 36% reticulocytes, 4,000 platelets, and 23,000 leucocytes. No myelocytes, premyelocytes, or myeloblasts were seen; 49 normoblasts were counted per 300 leucocytes. The blood urea was 36 mg. per 100 ml.

Necropsy.—The noteworthy macroscopical findings were anaemia, jaundice, and widespread purpura in the skin, serosae, and urinary and intestinal tracts; permission to examine the brain was withheld. **Microscopical findings:** The histological appearances were typical of thrombotic microangiopathy (Fig. 1). Lesions were particularly numerous in the outer third of the ventricular myocardium, and in the adrenals, renal cortex, and pancreas. There were a few minute foci of necrosis in the myocardium, without any cellular infiltration.

Comment.—The clinical picture illustrated the characteristic features of this disease, and the diagnosis could have been made during life.

FIG. 1.—Case 1. Irregular dilatation and partial or complete thrombotic occlusion of arterioles and capillaries in myocardium. Endothelization and partial organization of some of the granular or hyaline thrombi. (Haematoxylin and eosin. $\times 100$.)

The illness probably dated from the "cold," a month before death, although the patient seemed to be in good health when he fainted, 46 hours before he died. While it is now recognized that the histological findings were typical of thrombotic microangiopathy, it should be admitted that two years passed before they were identified. Many pathologists saw the sections and, while all

appreciated the seemingly unique nature of the vascular changes, none was acquainted with the disease. Only later, when illustrations of identical lesions were found in a paper about this condition, was the diagnosis made.

Case 2

A wood machinist aged 27 had an inguinal herniorrhaphy on July 31, 1951; previously his health had been excellent, and he seemed to be perfectly well when he was discharged home on August 9. On August 18, while he was sitting quietly at home, he suddenly threw up his arms and said, "Send for a doctor." He made no complaint, but repeated his demand several times before collapsing on to the floor, where he vomited and then lay still. His doctor found him deeply unconscious; his limbs were flaccid, although the plantar responses were extensor. Within a few minutes the coma became less deep and he responded to some commands. He was admitted to hospital a few hours later.

On admission he was semiconscious. He resisted examination, answered some questions and ignored others, and on one occasion let himself fall to the floor with seemingly deliberate care to avoid hurt. His general behaviour suggested hysteria, but it was observed that there was paralysis of movement of the left eye to the right, a pin-point left pupil, and no pupillary reaction to light on either side. All reflexes were brisk; the plantar responses were now flexor and muscle tone was normal. Examination of the other systems showed no abnormalities except for regular coupling of the pulse beats; the pulse rate was 64, the blood pressure 110/70.

Investigations.—Urine: trace of protein; no sugar. Lumbar puncture: clear colourless cerebrospinal fluid under normal pressure; 70 mg. of protein per 100 ml; Lange curve 0012100000; no cells found.

When re-examined an hour after admission both pupils were moderately dilated and reacted to light. There was now spontaneous nystagmus to the left and no evidence of ocular palsy. He was stuporous until his death on August 20, 54 hours after he collapsed at home. While in hospital he was noticed to become increasingly pale; the blood was not examined. There was no jaundice or pyrexia. His pulse rate ranged between 50 and 80; coupled beats were not found after the first few hours of observation. An electrocardiogram on the day of his death showed sinus rhythm, rate 50, with occasional ventricular extrasystoles and left axis deviation.

Necropsy.—There were four small petechiae in the skin and scattered petechiae in the serosae. The meninges, dural sinuses, and cerebral arteries were normal. A single fresh haemorrhage 0.3 cm. in diameter, was found in the left caudate nucleus; the brain was slightly oedematous but otherwise normal, and there was no trace of a pressure cone. No venous thrombosis, pulmonary embolism, or other noteworthy abnormalities were found, and the interatrial foramen was closed. The bladder urine gave strong reactions for urobilinogen and urobilin. **Micro-**

FIG. 2.—Case 2. Thrombosis of many smallest-calibre vessels in myocardium. (Haematoxylin and eosin. $\times 80$.)

scopical findings (Fig. 2): Typical vascular lesions of thrombotic microangiopathy were present in the brain, particularly in the subcortical zone and in the medulla, and also in the myocardium, portal tracts, and kidneys. In addition, many small arterioles which were not thrombosed showed segmental hyaline change or endothelial hyperplasia. Many glomeruli showed patchy hyaline obliteration of some loops, and there was some periglomerular fibrosis. No necrotic foci were found in any of the organs.

Comment.—This case was clinically atypical. There were no prodromata, and the total duration of illness was 54 hours. The presenting manifestations simulated hysteria, but abnormal neurological signs were present. While the latter were transient and to some extent fluctuating in localization, these qualities were not so pronounced as to be diagnostic. No haemorrhagic tendency was noted during life, and petechiae were not a striking feature at necropsy. While anaemia developed during the period of observation, it was not serious enough clinically to give rise to concern, and no evidence of haemolysis was noted before death, although the urine obtained *post mortem* contained excess urobilinogen.

Summary

Thrombotic microangiopathic haemolytic anaemia (thrombotic microangiopathy) is the name proposed for an unusual disease, possibly related to the so-called collagen diseases, and commonly referred to as thrombotic thrombocytopenic purpura. The fully developed clinical syndrome consists of fever, haemorrhagic manifestations, haemolytic anaemia, and multifarious fluctuating signs of neurological disorder. This tetrad

is diagnostic, but often is complete only in the terminal stages of the illness, and any component may be absent. The disease should be considered in the diagnosis of all cases which present the association of haemolytic anaemia and thrombocytopenic purpura; biopsy may be of value.

Examination of the tissues shows a unique histological picture of widely disseminated thrombosis of the smallest-calibre blood vessels, with endothelial hyperplasia, conspicuous dilatation of many of the affected vessels, and no inflammatory reaction.

The disease has been fatal in every case which has been reported. Treatment with A.C.T.H. or cortisone deserves trial, and splenectomy should be considered.

Two new cases are reported.

I wish to thank the many colleagues who have been patient with my interest in this disease, particularly Dr. D. F. Barrowcliff for his help in reviewing the literature, and Dr. D. R. Humphreys for allowing me to report the case of his patient (Case 2).

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NEWER SYNTHETIC ANALGESIC DRUGS

BY

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During the last ten years a group of new synthetic analgesic drugs has become available to the medical profession. The purpose of this paper is to present the results of a comparison made between the individual members of this group of new drugs, and between them and morphine. The drugs of the new series are:

Pethidine ("dolantin," "dolantal," "demerol," "meperidine") 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester hydrochloride.

Amidone ("physeptone," "miadone," "dolphine," "methadon") DL-6-dimethylamino-4:4-diphenylheptan-3-one hydrochloride.

Phenadoxone ("heptalgin," "heptazone") DL-6-morpholino-4:4-diphenylheptan-3-one hydrochloride.

Höchst 10581 (for purposes of convenience it will be referred to here as "hexanone") DL-6-morpholino-4:4-diphenylhexan-3-one hydrochloride.

Patients suffering from the following painful conditions were used: post-herpetic neuralgia, tuberculous cystitis, pubic osteitis, sciatic pain due to prolapsed intervertebral disk, rheumatoid arthritis, ankylosing spondylitis, lymphosarcoma with abdominal pain, and carcinoma of the cervix, vagina, colon, stomach, glosso-tonillar sulcus, larynx, breast, and bronchus, with metastases in the spine. The effect of these analgesics was not investigated on the following pains for the reasons given: the pains associated with coronary thrombosis, trigeminal neuralgia, burns, or childbirth, as the pain is insufficiently chronic; the pains associated with colic or peptic ulcer, as they are best treated with spasmolytic drugs; the pain of headache, as many different types of pain might be included under this heading, including psychogenic pain. The conclusions drawn in this work, then, do not refer to these pains. In most patients tested the pains were severe; only in those with rheumatoid arthritis and ankylosing spondylitis was this not so. In all patients the pain was chronic, and never disappeared spontaneously. Unless some analgesic drugs were given, sleep or occupations such as reading were impossible in all patients, except those with rheumatoid arthritis or spondylitis.

Morphine, being a well-known and effective analgesic, was compared with the newer group of drugs. It was given by injection intramuscularly, in the form of the sulphate or as papaveretum ("omnupon"), or by mouth as the hydrochloride, as "nepenthe," or as papaveretum. The new drugs were given orally in tablet form or intramuscularly.

The method of clinical assessment was that reported by Keele (1948), by Hewer, Keele, Keele, and Nathan (1949), and by Robson and Keele (1950). Trials were carried out on a few patients whose pains were constant over periods of weeks and who were able to keep pain charts. These patients were given various drugs and inert substances, and recorded hourly the state of their pain, using the categories severe, moderate, slight, or nil. The method is entirely subjective. The results obtained on