the normal subject, as well as in the haemorrhagic anaemias, even though haemoglobin synthesis in the latter is retarded by lack of iron. In leukaemia, leucocytes accumulate a high concentration of ribonucleic acids in the cytoplasm and nucleoli which does not rapidly decline, as in the case of normal cells.

Desoxyribonucleic acids are an important constituent of chromosomes, being apparently attached at specific loci in the polypeptide chain which goes to make up the chromosome fibre; the amount differs at the different phases of chromosome division, and is noticeably abnormal in certain pathological states.

Under normal conditions there is more desoxyribonucleic acid in the chromosomes of the proerythroblast than the promyelocyte at the metaphase. In pernicious anaemia, however, the promyelocyte chromosomes contain very little desoxyribonucleic acid, and this leads to incomplete spiralization; the proerythroblasts and early megaloblasts, on the other hand, show an excess which consequently leads to over-spiralization. Over-spiralized chromosomes are associated with irregular division, multipolar spindles, and chromatoid bridges at the anaphase. In short, it would seem that mitotic abnormalities are closely associated with different distributions of desoxyribonucleic acid.

Conclusion

In this limited survey of some of the dynamic aspects of haemopoiesis I have naturally laid most emphasis on basic principles, some of which are now well established owing to the specific characteristics which the cells of the haemopoietic system possess. I have also paid some attention to the quantitative aspects of the subject and to some of the fallacies which may so easily intrude with hasty interpretation.

Simple quantitative aspects of haemopoiesis are indeed of such everyday application in clinical medicine that they are all too often accepted without critical analysis, without thought of possible alternative interpretation, or from a superficial viewpoint, to the neglect of fundamental principles.

Quantitative deductions cannot be accurate unless made upon unequivocal facts entirely free from ambiguity.

Leonard Huxley (1900) quotes Thomas Huxley, when writing to Charles Kingsley, as saying, "My business is to teach my aspirations to conform themselves to fact, not to try to make facts harmonize with my aspirations. Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly to wherever and to whatever abysses nature leads or you will learn nothing."

In no field of medicine is this more true than in haematology, which in its daily clinical application to the dynamics of haemopoiesis is largely quantitative and in which precise results require the most critical appraisal if they are to be properly and accurately assessed.

REFERENCES

- Ashburn, L. L., Daft, F. S., and Faulkner, R. R. (1947). *Blood*, 2, 451.
 Barer, A. P., and Fowler, W. M. (1937). *J. Lab. clin. Med.*, 23, 148.
 Cartwright, G. E., Wintrobe, M. M., Buschke, W. H., Follis, R. H., jun., Suksta, A., and Humphreys, S. (1945). *J. clin. Invest.*, 24, 268.
 Crosby, W. H. (1954). *Bull. N.Y. Acad. Med.*, 30, 27.
 Daft, F. S. (1947). *Publ. Hlth Rep. Wash.*, 62, 1785.
 Dahl, S. (1950). *Acta haemat., Basel*, 4, 65.
 Endicott, K. M., Kornberg, A., and Ott, M. (1947). *Blood*, 2, 164.
 Guggenheim, K., and Buechler, E. (1949). *Ibid.*, 4, 958.
 Hawkins, W. B., and Hahn, P. F. (1944). *J. exp. Med.*, 80, 31.
 Huxley, Leonard (1900). *Life and Letters of T. H. Huxley*, 1, 29. Macmillan, London.
 Hynes, M. (1949). *J. clin. Path.*, 2, 99.
 Japa, J. (1945). *Brit. J. exp. Path.*, 26, 111.
 Kline, D. L., and Clifton, E. E. (1952). *J. appl. Physiol.*, 5, 79.
 Laurell, C. B. (1952). *Pharmacol. Rev.*, 4, 379.
 Menkin, V. (1940). *Arch. Path., Chicago*, 30, 363.
 — (1949). *Blood*, 4, 1323.
 Moore, C. V., Dubach, R., Mirmich, V., and Roberts, H. K. (1944). *J. clin. Invest.*, 23, 755.
 Palmer, J. G., Kemp, I., Cartwright, G. E., and Wintrobe, M. M. (1951). *Blood*, 6, 3.
 Rosenthal, R. L., Etess, A. D., and Litwins, J. (1951). *Acta haemat., Basel*, 6, 174.
 Smith, D. R., and Hayhoe, F. G. J. (1951). *Acta haemat., Basel*, 6, 253.
 Thorell, B. (1947a). *Studies on the Formation of Cellular Substances During Blood Cell Production*. Kimpton, London.
 — (1947b). *Acta med. scand.*, 129, Suppl. 200.
 van Dyke, D. C., and Huff, R. L. (1951). *Amer. J. Physiol.*, 165, 341.
 Whitby, L. E. H. (1937). *Lancet*, 2, 871.
 — (1949). *J. roy. Inst. publ. Hlth*, 12, 19.
 — (1951). *West. J. Surg.*, 59, 178.
 — (1952). *Lancet*, 1, 623.
 — and Britton, C. J. C. (1953). *Disorders of the Blood*, 7th ed., p. 256. Churchill, London.
 White, J. C. (1947). *J. Path. Bact.*, 59, 223.
 White, L. P. (1954). *Blood*, 9, 73.

ASSISTED CIRCULATION BY PUMP-OXYGENATOR DURING OPERATIVE DILATATION OF THE AORTIC VALVE IN MAN

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Interest in the clinical application of the various forms of pump-oxygenator (extracorporeal circulation or artificial heart-lung machine) is growing so rapidly, and the use of this type of apparatus in man has so seldom been followed by recovery, that it is customary for isolated examples of its use to be reported (Dennis *et al.*, 1951; Dogliotti, 1952; Gibbon, 1953; Dodrill *et al.*, 1953; Helmsworth *et al.*, 1953).

Three authors, Dogliotti (1952) in Turin, Gibbon (1953) in Philadelphia, and Dodrill *et al.* (1953) in Detroit, report survivors, and Helmsworth *et al.* (1952) have used an oxygenator for vein-to-vein perfusion in a case of fibrosis of the lung. The pump-oxygenator employed in the case here reported was that designed and developed by Melrose in the department of surgery of the Postgraduate Medical School. Melrose (1953a) has described the machine and Melrose *et al.* (1953b) have reported the animal experiments performed in the Buckston Browne Laboratories of the Royal College of Surgeons, which seemed to prove that the machine might be used with safety in man. The machine consists essentially of a rotating oxygenator and two rotary pumps. Its chief advantages are a high degree of efficiency in oxygenation (100 ml. of oxygen per litre of blood) and a low initial charge of blood.

The circumstances in which the machine might be used with profit in a clinical way have also been discussed (Aird, 1953), and the opinion was then expressed that the use of such a machine to by-pass heart and lung totally and to provide safely a dry heart for surgery was an aim not then immediately obtainable. We

now have evidence that with a machine of this kind the surgical approach to the interior of the heart and even to the mitral valve under vision may well be possible. We hope to approach this aim by using the pump-oxygenator as a form of assisted circulation during operation, gradually increasing the proportion of the total circulation for which it is responsible.

There are certain standard procedures in cardiac surgery whose performance at present carries the risk of a dangerous fall in the rate of flow in the coronary arteries and the development of a ventricular fibrillation or cessation of heart-beat which is sometimes irreversible. The maintenance of flow in the coronary arteries during such a procedure seems to lessen the risk of ventricular fibrillation, and its severity if it occurs. Notable among these procedures is an attempt to deal surgically with severe degrees of aortic stenosis. When a thoracic surgeon is faced during operation with a seriously low aortic pressure, decreased coronary flow, and loss of cardiac efficiency, he normally has recourse to cardiac massage, occlusion of the thoracic aorta, and gravity or pump transfusion of blood directly into the aorta above the clamp to maintain coronary and carotid flow, at least in part.

We decided that a more effective method of maintaining the mean aortic pressure at a level sufficient for an adequate coronary and carotid flow would be to apply the pump-oxygenator throughout operation in parallel with the patient's own heart and lungs as a form of assisted circulation which could function in emergency as a total replacement for heart and lungs if cardiac function should give rise to serious anxiety. The indication for its use should be, we feel, a patient seriously incapacitated by a form of cardiac disease amenable to surgery who would, without some form of assisted circulation, be refused operation as too great a risk. When a new apparatus is used in such cases and the patient does not survive it is extremely difficult to exonerate the apparatus from blame and to apportion responsibility fairly between the severity of the operation and the danger of the ancillary apparatus. Similarly, if the patient survives, it is difficult to say to what extent the machine was of benefit, and to disprove that the operation might perhaps have been performed without its use. Recovery does show, however, in what manner the apparatus may be used without doing the patient detectable harm.

Clinical Features

The patient with whom this report was concerned was 32 years of age. She had contracted rheumatic fever first at 13 years, with chorea thereafter, a second attack of rheumatic fever at 23 years, and progressive dyspnoea from 1948. Since 1949 there had been attacks of winter bronchitis, and in July, 1952, an attack of carditis with congestive heart failure. Consequent upon this there was anginal pain on the slightest exertion, and when the patient presented she had been bedridden for six to eight months. Before operation the heart was fibrillating slowly, the pulse was small and slow-rising, and there were clear signs of mitral incompetence and aortic stenosis.

The pre-operative electrocardiogram, the patient being on digitalis, showed slow auricular fibrillation. There was no evidence of ventricular hypertrophy or infarction.

It is perhaps clear even from so abridged a clinical description that an operative attempt to dilate the aortic valve would carry an extremely heavy risk of serious coronary inadequacy developing during operation unless some artificial method of maintaining a satisfactory aortic pressure were available. Before it was available, operation

had in fact been refused on grounds of risk to life, and an attack of acute appendicitis had been treated conservatively (July, 1953) because of the high risk even of appendicectomy.

Operative Details

Operation (W. P. C.) was undertaken on December 9, 1953. After premedication with promethazine hydrochloride and pethidine, anaesthesia (Dr. John Beard) was induced at 2 p.m. with thiopentone and maintained with nitrous oxide, oxygen, and relaxants.

At 2.20 p.m. the superficial femoral artery and saphenous vein were exposed in the upper part of the right thigh. Seventy mg. (1 mg. per kg.) of heparin was then injected slowly. A 4-mm. (internal diameter) "polythene" catheter with multiple perforations was passed up the saphenous vein for a distance of 30 cm. so that its tip should lie in the inferior vena cava just above the diaphragm. On insertion of this catheter quite rapid bleeding occurred, through the perforations, before all the perforations lay within the vein. An obturator has now been devised for this catheter to prevent bleeding during its insertion and to be withdrawn when the venous catheter is in place. The venous catheter was held in place by a ligature around the vein, the distal vein being ligated. The artery was then controlled by two tapes and opened by a transverse incision. The arterial catheter, 2.5 mm. in internal diameter, was then passed up the femoral artery to a distance of 45 cm. so that its tip should lie within the arch of the aorta. A tape around the proximal artery and catheter was kept tight as a temporary ligature by an artery forceps. The distal artery was controlled by a bulldog clamp. Both catheters were in place at 2.40 p.m. and at 2.43 the pump was started at a rate of 500 ml. a minute; the pulse was not palpable at the wrist at this time. The chest was entered through a postero-lateral incision in the fifth intercostal space. Bleeding was not excessive, though the clotting-time was 30 minutes. At 3.10 the pericardium was opened to reveal a moderate excess of pericardial fluid and a very large tense left ventricle. The left atrium was aneurysmal and exhibited well-marked systolic pulsation. A systolic thrill was felt on the atrial wall below the inferior pulmonary vein, a coarse systolic thrill on the ascending aorta. Aortic valve closure was not palpable. The heart rate was now 84 and the radial pulse was just palpable and irregular. The pump rate was increased to 600 ml. a minute.

At 3.16 p.m. the heart was opened through the auricular appendage to reveal free mitral incompetence through a circular valve opening approximately 3 cm. in diameter. There was no stenosis of the mitral valve.

At 3.23 p.m. left ventricular cardiomy was performed, using a purse-string suture and Rumel's tourniquet. A guide wire was inserted through the ventricle and aortic valve into the aorta. The valve was fully dilated on three separate occasions with the triradiate Bailey dilator. No noticeable disturbance of heart rate or rhythm or any alteration in the force of the beat was detectable during these manoeuvres. The heart rate was 50-60 with periodic extra beats. The pump rate throughout this manoeuvre was maintained at 800 ml. a minute. At 3.30, after the dilatation, the aortic systolic thrill was noticeably less. Re-examination of the mitral valve did not reveal any noticeable alteration in the regurgitant flow of blood through the valve. At 4 p.m. both cardiomy wounds were closed with interrupted sutures and the pericardium was loosely stitched. The blood pressure in the arm was now 100 mm. Hg and the radial pulse was palpable. The rate of extracorporeal circulation was slowed progressively from 800 ml. to 500 ml. during closure of the cardiomy incision and was decreased still further to reach 300 ml. a minute at 4.20, when it was discontinued, after the pump had been in operation for 97 minutes.

The chest was kept open for three-quarters of an hour after completion of the cardiomy until the rather persistent oozing, noticed towards the end of the operation,

had ceased. At 5 p.m. the catheters were removed from the saphenous vein, which was ligated, and from the femoral artery, which was repaired with 00000 arterial silk. The groin incision was closed in layers, and 70 mg. of protamine sulphate was given intravenously as a 0.01% solution in isotonic saline. The clotting-time after operation was 6–8 minutes. The estimated blood loss during operation was 6 pints (3.4 litres); and 7½ pints (4.3 litres) of blood, 4 pints (2.3 litres) of them freshly drawn, were given by transfusion. The pharyngeal temperature was 36.4° C. at the end of operation.

The mixed venous blood during the running of the machine showed an oxygen saturation of 78 to 76%, and a carbon dioxide content of 47–45 volumes %.

The serum potassium arose from a pre-operative level of 3.7 mEq/l. to a maximum of 6 mEq/l. during operation, falling again to 4 mEq/l. on the evening of operation.

At 6 p.m. the patient was returned to the ward already conscious; at 6.5 she asked what time it was.

Electrocardiographic Studies During Operation

A continuous E.C.G. tracing was run during the operation, and some 40 feet (12 metres) of this was recorded. We are indebted to Dr. J. F. Goodwin and Dr. L. G. Davies for its interpretation. At the beginning of the operation the electrocardiogram showed, as it did before operation, slow auricular fibrillation. This continued until 3.16 p.m., when during exploration of the left atrium the E.C.G. showed occasional ventricular ectopic beats from multiple foci, and auricular fibrillation. At 3.23, during dilatation of the aortic valve, there were various multifocal ventricular ectopic beats, some T-wave inversion following normal QRS complexes, and auricular fibrillation. At 3.30, following aortic-valve dilatation, occasional ectopic beats were seen. The QRS complex lost its Q and developed a deep S wave, with T still upright and taller than before. This was thought to be due either to a clockwise rotation around the long axis of the heart or perhaps to a diminution of left ventricular strain. Auricular fibrillation was still present. At 4 p.m. auricular fibrillation was still present, but there were no ectopic beats and the T waves had increased in height. No further change in the E.C.G. occurred while the chest was closed. At 10 p.m. slow auricular fibrillation was present as before operation, and the QRST complex had returned to normal.

Post-operative Course

On the evening of operation there was slight cyanosis of the lips, but the patient was fully conscious and in possession of all faculties two hours after operation. Cyanosis faded within four hours of the end of the operation.

Subsequent progress was uneventful, only 26 oz. (740 ml.) draining from the chest, but there was extensive ecchymosis of the chest wall round the thoracotomy incision and around the stab drain. Clinically the aortic systolic murmur is now softer and the patient has not experienced anginal pain such as was her chief complaint before operation. Convalescence has proceeded satisfactorily apart from a thrombophlebitis of the catheterized saphenous vein. Pulses did not return in the ankle of the limb whose femoral artery had been catheterized, but the limb remained warm and identical in appearance and temperature with its fellow of the opposite side. An improvement in exercise tolerance permits the climbing of 48 steps without undue distress. Previously completely bedridden, the patient can now walk many hundreds of yards. She has returned home and her exercise tolerance still improves daily.

Bleeding

Dr. S. J. Baker, of the department of haematology, has been our adviser on this subject, and has provided this report.

All workers in the field of extracorporeal circulation experience trouble with haemorrhage, both in experimental

animals and in human subjects. In this patient excessive bleeding occurred especially towards the end of the operation, even after the administration of adequate amounts of protamine to neutralize the heparin. This bleeding is explicable, at least in part, by the development of a thrombocytopenia. The platelet count (direct method) fell from a pre-operative level of 217,000 to 44,000 per c.mm. in the first half-hour after application of the machine. It remained at this level until several hours after the completion of the operation. Over the next eight days it gradually returned to the pre-operative level.

Immediately after operation the one-stage "prothrombin time" was normal, so factors V and VII were apparently still present in adequate amounts. Antihæmophilic globulin and Christmas factor were not tested for in this case, and it is possible that these may have been reduced.

There are three factors which may produce a deficiency of coagulation components: (1) the operation itself—coagulation factors, especially platelets, are sometimes reduced during major surgical procedures; (2) the "dilution" effect of replacing a considerable proportion of the patient's blood by stored "bank" blood, which contains no platelets and will probably be deficient in antihæmophilic globulin and factor V, to an extent depending on the length of storage; and (3) the machine, which, although lined throughout by silicone, causes marked loss of platelets presumably by adhesion to foreign surfaces and/or by mechanical destruction.

The most effective available method of correcting the thrombocytopenia in a patient at the end of a procedure such as this would appear to be the transfusion, or replacement transfusion, of a substantial quantity of platelet-rich blood freshly drawn into siliconed apparatus, or the use of a direct platelet transfusion. Bell and others (Bell, 1953; 1954) in Gibbon's unit have made an extensive survey of coagulation disorders arising after massive simple transfusion, and also during the course of extracorporeal circulations. Their work suggests that, apart from the thrombocytopenia, the "dilution" effects could be prevented by the use of blood not more than 48–72 hours old; but this may be difficult to achieve.

Conclusions

The pump-oxygenator previously described has been shown at least not to be productive of serious immediate toxic effects, and no delayed effects can be predicted on theoretical grounds.

It is our impression that the machine has been helpful when used to assist the circulation of a human patient throughout a severe cardiac operation which would not have been attempted without some kind of artificial help. Throughout the operation no anxiety was felt concerning the coronary circulation, as measured by the visible contraction of the ventricle and the electrocardiogram. Previous experience without the use of the machine has shown that even less severe aortic dilatations performed in patients less debilitated have been accompanied sometimes by irreversible disturbances of cardiac rhythm. There was never any threat in this case of cardiac cessation or ventricular fibrillation during two explorations of the left atrium and mitral valve, and three separate forcible dilatations of the aortic valve.

We have previously stated that the chief therapeutic use we saw immediately for this machine was its application to extreme cardiological emergencies, and we propose to apply it to this purpose, for it is capable not only of increasing oxygenation but of reducing the blood carbon dioxide to any desired level, so avoiding the dangers of present methods of oxygen therapy in heart failure. We consider now, however, that this machine may also be used to open the way gradually towards the ultimate aim of a pump-oxygenator for routine total replacement at surgical operations. Rare congenital defects in infants are susceptible to open repair under vision with the assistance of cooling. In adults, selected cases of aortic stenosis may be treated

with every chance of improvement without the use either of cooling or of the extracorporeal circulation, but the most important aim of modern surgery is the direct correction under vision of the adult mitral valve, and this can be attained only by some form of assisted circulation.

It may be that one way of progressing towards this aim of a dry adult heart for the routine performance of surgery on its interior may be the use of an assisted circulation to take over in successive cases more and more of the circulation.

Experience will show what amount of aortic flow per minute is required for the maintenance of an adequate coronary and carotid circulation, but previous experience with pressure perfusion of the clamped aorta in emergency, by quantities of blood per minute small in proportion to the output of the pump, suggests that the necessary flow may not in fact be particularly high. On this occasion a flow of 500 to 800 ml. was maintained for a total period of 97 minutes, and it might be estimated that in that time there was a total flow of 70 litres through the machine. Alternatively, it might be said that the patient's total volume of circulating blood passed through the machine about 15 times, or that, for 97 minutes, the machine was responsible for 20 to 30% of the total cardiac output.

Bleeding during and after the operation is the most serious problem which we have to face, but we prefer the risk of bleeding as we experienced it in this patient to the still greater risk of clotting around the tubes of the machine at some critical stage of operation during which the patient's life might depend upon the efficiency of the artificial circulation. It seems reasonably certain that the bleeding we experienced was due in the main to platelet loss, though the effect of operation, transfusion of foreign blood, and the machine on clotting function is highly complex, and other factors certainly operate too. Methods are being developed for the collection of fresh blood rich in platelets; even fresh blood, drawn by routine methods, loses a high proportion of platelets in collection.

All the data collected concerning the effect of the machine have not been presented here—much of the material cannot be fully analysed until a series of cases is available for study. The management of collecting devices and the drill for the timing of samples require a large team of medical and technical staff, and the arrangements and control of apparatus, especially collecting apparatus in an operating-room already occupied by a complex surgical team, have been the subject of prolonged study and experiment.

We wish to acknowledge our indebtedness to many colleagues and assistants who have been concerned in this work and in the management of the case here reported. To the cardiologists at Hammersmith Hospital, including Dr. J. F. Goodwin and Dr. R. I. S. Bayliss, we owe a great deal of day-to-day advice and the pre-operative investigation and management of patients who are considered for this and other forms of surgery. We are indebted for help and advice in our electrocardiographic studies to Dr. J. F. Goodwin and Dr. L. G. Davies. Dr. S. J. Baker, of the department of haematology, has given much time and thought to our problems of coagulation and haemorrhage. Dr. John Beard, anaesthetist for thoracic surgery in the Postgraduate Medical School and Hammersmith Hospital, has been a most important member of the operative team, and has collaborated most helpfully. Mr. Ralph Shackman and the staff of the Surgical Research Laboratories have given us constant help, and Mr. Gerald Rainbow and Miss Eva Bottoms particularly have been unwearied in the maintenance of the machine. With New Electrical Products Ltd. we have explored now for a long period, and very happily, the technique of liaison between surgical and technological research; and Mr. J. Brown of that company has not only devoted endless time and skill to the original construction of the machine but has attended and studied its performance in the operating theatre. A second phase of this prototype apparatus embodying improvements which the function of this machine has suggested is now under construction; the cost of its development is being borne by a grant from the Nuffield Foundation. We have had assistance from the National Research Development Corporation in our plans for the machine's development.

REFERENCES

- Aird, I. (1953). *British Medical Journal*, 2, 57.
 Bell, W. N. (1953). *Med. Clin. N. Amer.*, 37, 1851.
 — (1954). Personal communication.
 Dennis, C., Spreng, D. S., jun., Nelson, G. E., Karlson, K. E., *et al.* (1951). *Ann. Surg.*, 134, 709.
 Dodrill, F. D., Hill, E., Gerisch, R. A., and Johnson, A. (1953). *J. thorac. Surg.*, 26, 584.
 Dogliotti, A. M. (1952). *Bull. Johns Hopk. Hosp.*, 90, 131.
 Gibbon, J. H., jun. (1953). Personal communication.
 Helmsworth, J. A., Clark, Leyland, C., jun., Kaplan, S., and Sherman, R. T. (1953). *J. thorac. Surg.*, 26, 617.
 Melrose, D. G. (1953a). *British Medical Journal*, 2, 57.
 — *et al.* (1953b) *Ibid.*, 2, 62.

INSULIN RESISTANCE FOLLOWING HYPOTHALAMIC LESIONS AND REMOVAL OF THE ADRENAL MEDULLA

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It has long been thought that insulin-resistant diabetes might be associated with the presence of an insulin antagonist (Himsworth and Kerr, 1940). Resistance to insulin has been shown to develop in intact animals after the injection of purified growth hormone (Young, 1950) and of cortisone (Campbell *et al.*, 1950) over periods of some days. The work of Bornstein and Park (1953) has shown that neither of these hormones is an insulin antagonist, but that both are necessary for the development in the intact animal of the insulin antagonism found in alloxan-diabetic rats. Bornstein (1953) found that the insulin antagonism was confined to a specific lipoprotein fraction of the serum of such rats. The serum from a human subject rendered hypoglycaemic by a large dose of insulin also exhibited insulin antagonism, while that from a normal human subject and from normal rats possessed no such activity.

Section of those pathways from the hypothalamus to the brain stem which mediate autonomic function produced no change in insulin sensitivity (Beattie and Chambers, 1953a), but when the adrenal medulla was removed from these rats they developed marked resistance to insulin. These experiments are described below.

Material and Methods

Male albino rats of a single strain and weighing between 200 and 250 g. at the start of the experiment were used. For five weeks before the experiments began they were kept at a constant environmental temperature of 29.5° C. Rats of the series 1 experiments were kept at this temperature throughout the experimental period. Rats of the series 2 experiments were kept at 29.5° C. until day 12 of the experiment, when they were transferred to a cooler environment with a mean temperature of 18° C.

The rats of each series were divided into four groups. Group A rats were unoperated controls. Group B rats had brain lesions inflicted on day 0. The adrenal medullary tissue was removed from the group C rats on day 7. Group D rats had brain lesions made on day 0 and the adrenal medullary tissue was removed on day 7. All rats were killed on day 21.

Each group of rats in series 1 was divided into four subgroups. The first subgroup was used to obtain resting blood-glucose and resting liver-glycogen values. The second subgroup was given an intraperitoneal (I.P.) injection of insulin (1 unit per kg. body weight) on day 21. Blood-