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BACTERAEMIC SHOCK

and

THE MICROCIRCULATION.

(Experimental Studies and
Clinical Observations)

THESIS SUBMITTED BY ADRIAN LITTON TO THE UNIVERSITY
OF GLASGOW FOR THE DEGREE OF MASTER OF SURGERY

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PREFACE.

This thesis presents observations on experimental and clinical aspects of shock associated with infection caused by gram-negative micro-organisms.

The work involved in this dissertation was largely carried out in the Department of Surgery, Peter Bent Brigham Hospital and the Laboratories of Surgical Research at the Harvard Medical School, Boston, during the year 1963-1964.

It is a pleasure to acknowledge the interest and advice of Dr. Francis D. Moore, M.D., Moseley Professor of Surgery at the Harvard Medical School and Surgeon-in-Chief, Peter Bent Brigham Hospital.

I should also like to thank Dr. Carl W. Walter, M.D., Clinical Professor of Surgery at Harvard Medical School, Dr. Ruth Kundsin, Sc.D., Microbiologist, Department of Surgery at Peter Bent Brigham Hospital, and Dr. Herbert J. Berman, Ph.D., Research Professor of Biology at Boston University, for their help and interest throughout this work.

Preliminary papers on which this thesis is based have already been presented at different meetings.

A) In September, 1964, at the Autumn Meeting of the American Physiological Society, I read a paper on "The Quantitation of the Microvasculature of the

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Hamster Cheek Pouch", the abstract of which has been published in the Physiologist, (1964).

B) At a Workshop on "Septic Shock", held in Washington, D.C. in September, 1964, at the National Academy of Science, National Research Council, I read a paper entitled "Septic Shock and Terminal Sepsis in Critically Ill Surgical Patients". This paper was an interim report of the cases studied and presented in the clinical section of this thesis. The collected papers of the Washington meeting have been published in the proceedings of the Workshop. (Septic Shock. Edit. J.G. STRAWITZ, and N. GROSSBLATT. National Academy of Sciences - National Research Council, Washington, D.C. (1965).

C) At the Fourth European Conference on Microcirculation held at Cambridge University (June-July, 1966) I read a paper entitled "The Action of Vasoactive Substances on the Microvasculature of the Hamster Cheek Pouch". The manuscript of this paper has been accepted for publication in the proceedings of the Fourth European Conference. (Bibliotheca anatomica, Publishers, Karger).

BACTERAEMIC SHOCK AND THE MICROCIRCULATION.

PART I. EXPERIMENTAL STUDIES.

SECTION I.

A) Introduction.

B) Outline of the scope of the thesis.

BACTERAEMIC SHOCK AND THE MICROCIRCULATION.

(A) INTRODUCTION

Shock and infection constitute two of the major hazards that confront the surgical patient and where they co-exist the combination is frequently lethal.

Since the time of Lister and the introduction of antiseptics into surgical practice, great progress has been made in the understanding, prevention and control of infection. Even today, however, infection is still a major hazard and the danger of hospital-acquired infection is frequent.

Shock has also been a grave complication to the surgical patient. Today with the better understanding of the haemodynamic changes associated with shock many forms of shock can be either anticipated and prevented, or treated efficiently at their onset. For example, haemorrhagic shock can be rapidly overcome by replacing the volume of blood that has been lost, and the oligaemic shock of severe burns can be treated with intravenous crystalloid solutions and plasma.

Irreversible shock, a term which when applied to man can be used with certainty only in retrospect, is reserved for those forms of established shock which are

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unresponsive to energetic therapeutic measures. The criteria for defining irreversibility are vague. In animal studies, in controlled experiments where haemorrhage is carried out to achieve hypotension of a known degree, and where after a calculated interval of time, in spite of re-transfusion the animals succumb, the term 'irreversibility' can be defined with statistical accuracy. Even here the pathological and physiological changes which occur are not yet clearly understood. Shock associated with infection, especially by the gram-negative micro-organisms, has a high mortality, and up to the present, therapeutic measures to counteract such shock have been very unsatisfactory.

There does not appear to be any simple explanation for shock. When the cardiovascular system is upset many compensatory mechanisms try to restore normality. Once these feed-back mechanisms fail, "vicious cycles are produced with a downhill spiral in the viability of the organism". (CROWELL and GUYTON, 1961). Many biochemical constituents of the blood can be measured and their altered concentrations may appear to be the cause of the circulatory failure, but in reality may merely reflect the disorganisation of the integrity of the cell produced by peripheral circulatory failure and

consequent tissue hypoxia.

There have been several theories to explain irreversible shock, and those currently acceptable emphasise different aspects of this general cardiovascular failure.

FINE (1962) believed that all irreversible shock was due to endotoxaemia. In shock, the bowel becomes ischaemic due to sympathetic and catecholamine overactivity; organisms from the intestinal lumen escape through the devitalised mucosa and are absorbed by the portal vascular system. Due to the failure of the reticulo-endothelial system to clear those bacterial toxins, generalised endotoxaemia results with secondary 'septic shock'. The mode of action of endotoxin in the production of shock is still uncertain. Several neurohumeral vasoactive substances have been implicated as mediators in shock; these include catecholamines, histamine, serotonin, and the vasoactive polypeptides.

GUYTON and CROWELL (1961) emphasised that all forms of irreversible shock ultimately bring about failure of the myocardial muscle which produces the irreversibility. They have measured the effects of oxygen lack with precision and found that when oxygen debt was less than 100 ml. oxygen per kilogram of tissue,

independent of the duration of shock, the animal recovered. However, when oxygen debt exceeded 140 ml. per kilogram of tissue, recovery was impossible. Direct measurements of oxygen lack require sophisticated methods not readily available in clinical work, and indirect measurements of hypoxia assessed on the associated metabolic acidosis have been used e.g. blood pH, lactic acid, pyruvic acid pO_2 and pCO_2 levels and calculations of 'base excess'.

SCHAYER (1960) suggested that there was a balance between sympathetic activity and catecholamine release on the one hand and endogenous histamine production on the other. The teleological response of the animal or man to a failing blood pressure, (e.g. due to haemorrhage) is to cause peripheral vasoconstriction; this in turn produces diminished blood flow to the periphery with tissue cell hypoxia. Endogenous histamine is released causing peripheral arteriolar dilatation in an attempt to increase local blood flow. When this catecholamine-histamine balance is upset signs of 'decompensated' or irreversible shock follow.

HARDAWAY (1961) has been one of the main protagonists of the theory of disseminated intravascular coagulation as the cause of the irreversible shock state.

At first he noted a hypercoagulable state of the blood and, due to this, and the slow rate of flow in the microcirculation, intravascular thrombosis then occurred in the minute vessels - especially in the minute post-capillary venules. This caused sequestration of many factors required for blood coagulation and there then followed a hypocoagulable state with resultant haemorrhagic manifestations and evidence of increased fibrinolytic activity. Hardaway has shown in clinical observations of shock, many defects in the haemostatic mechanisms, and in post-mortem specimens of tissues and organs from patients who have died in shock, multiple thrombi in the minute vessels.

THE MICROCIRCULATION.

The microcirculation is the site of metabolic exchange. The heart and large vessels are regulated by the vasomotor centre in the brain, and adjustments are produced by afferent neural pathways - e.g. via the baroreceptors and chemoreceptors of the great vessels. It is significant that these receptors are situated near the entrances of the major vessels to the heart and brain - areas which are relatively independent of sympathetic vasoconstriction.

Beyond the small arteries in the peripheral vascular

bed, the microcirculation is regulated by chemical substances usually liberated locally and often producing vasodilatation and increased capillary permeability.

In shock, especially in shock associated with infection, there appears to be marked peripheral pooling of blood in the various vascular beds. (GILBERT, 1960).

(B) OUTLINE OF THE SCOPE OF THE THESIS.

Part I. Experimental Studies.

In the study of shock related to infection the following experimental studies were carried out.

i) The morphology of the microvasculature of the hamster cheek pouch was studied in detail and an attempt was made to quantitate the blood volume distribution in the minute vessels.

ii) The range of response of the microvasculature to neurohumoral stimulation was assessed by using several vasoactive substances considered to be active in shock.

iii) The local and systemic effects of endotoxins, the purified lipopolysaccharides of gram-negative bacteria, were observed in the microcirculation and the action of endotoxin was compared with the effects of previously assessed vasoactive substances.

iv) A preliminary series of experiments was initiated to 'bioassay' the vasoactivity of plasma in normal persons and in patients with severe gram-negative bacterial infections.

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Part II. Clinical Observations.

A selected group of surgical patients who were critically ill was studied to see how the clinical manifestations of shock associated with overwhelming infection compared with the reported haemodynamic changes observed in the experimental animal given a highly purified endotoxin preparation.

SECTION II.

THE MICROCIRCULATION.

A) Introduction.

B) The Hamster Cheek Pouch.

C) The Effects of Anaesthesia.

THE MICROCIRCULATION.

(A) INTRODUCTION.

William Harvey discovered the circulation of the blood and his classical monograph "Exercitatio Anatomica de Motu Cordis et Sanguinis" was published at Frankfurt in 1628. Although Harvey deduced that the vascular bed was a closed system, the mystery of the communication between the smallest arteries and veins remained until four years after his death, when in 1661, MARCELLO MALPIGHI described the capillary vessels in the transparent tissues of the frog.

The first authoritative monograph on the capillaries was by AUGUST KROGH in 1922. Most other work on the microcirculation had been carried out by histological examination of fixed in vitro preparations (e.g. by MALL, 1888) or by indirect inference from physiological studies of the macrocirculation — capillary exchange being deduced from the quantitative and qualitative changes in the blood from major arteries and veins to a tissue, or from tissue volume changes as recorded by plethysmography.

Observations have been made on the minute vessels of living animals. Studies were originally made in the transparent tissues of the frog (MALPIGHI, 1661; LISTER, 1858). Mammalian preparations which have been

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used to study the living circulation are the skin flap of the mouse (ALGIRE, 1943), the transparent chamber in the rabbit ear (SANDISON, 1924), the wing of the bat (NICOLL and WEBB, 1946), and the cheek pouch of the hamster (FULTON et al., 1947). Observations on the microvasculature in the mesentery of the dog, rabbit, guinea pig, rat and hamster have been made (e.g. CHAMBERS and ZWEIFACH, 1946), but laparotomy is required, difficulty is experienced in achieving a steady state due to the unnatural conditions, and the time available for observation is usually limited to less than one hour.

Compared with the tissue area in the window of the rabbit ear chamber, the hamster cheek pouch is relatively large. In addition, careful preparation of the ear is necessary before microscopic observation is possible and the chamber cannot be maintained indefinitely. The cheek pouch on the other hand has normal physiological activity and repair and renewal are normal processes. The cheek pouch is unique in allowing direct observations of the microvasculature without causing damage to tissues. The bat is a difficult animal to handle, breed and maintain in captivity, and the wing is not so transparent as the hamster cheek pouch. The nail bed vessels and the conjunctival vessels are the only small vessels readily

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accessible to direct microscopy in man, but here the magnification achieved and the clarity of resolution are very limited.

The interchange between blood circulating in the minute blood vessels and the internal environment enables the circulatory system to maintain a relatively constant internal milieu. Because of our limited ability to measure the essential variables in the microcirculation, information regarding the characteristics of blood flow in these peripheral vessels is scanty.

Direct visual observation of the minute vessels is the only method which allows examination of the microvasculature under conditions which approximate to normal. Arteries, capillaries and veins in one tissue, can be studied simultaneously and their variations in diameters, cross-sectional areas, and volumes can be recorded and compared.

The pharmacological actions of drugs on isolated organs or tissues can be recorded, but there is a danger in their free application to the intact animal. Reliable methods for measuring simultaneously and quantitatively the reactions to drugs of all the peripheral segments of the circulation are still being exploited.

The terms vasoconstriction and vasodilatation can be misleading e.g. if a drug constricts both the arteries and the veins, the resultant haemodynamic effect could not be precisely predicted since a narrowing of the arteries would decrease, while constriction of the veins would increase, the venous return. There are difficulties in ascribing changes in the blood pressure and volume of blood flow to activity of the minute vessels on the results of indirect measurements. Direct observation of the minute vessels can offer a more precise explanation of the changes.

Flow through the vascular bed depends on the arterial pressure, the arterial and venous resistances, the viscosity of the blood and the extravascular tissue pressure. Net changes in the vascular volume will depend on location of the resistance increase on the morphology of the vascular network. In shock where it has been presumed that there is peripheral pooling in the various vascular beds measurements of vascular volume changes are important but extensive data are not yet available on such vascular changes.

In carefully controlled studies, (e.g. KNISELY, 1936; CHAMBERS and ZWEIFACH, 1944; and NICOLL and WEBB, 1946) results from direct visualisation of the terminal vascular bed have been employed in the analyses of the peripheral vascular changes.

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B) THE GOLDEN HAMSTER CHEEK POUCH.

The golden hamster cheek pouch seemed to be the most satisfactory model to study the microcirculation in vivo. The golden hamster (MESOCRICETUS AURETUS) has a pair of very vascular transparent cheek pouches which are cylindrical diverticula of the buccal mucosa /Figure I/. The cheek pouch is a thin transparent membrane covered with stratified epithelium but with no hair follicles or glandular structures. Although there is a rich vascular network in the cheek pouch, lymphatic vessels have not been observed (SHEPRO ET AL., 1963). The pouch is prepared for study by first anaesthetising the hamster and then everting the cheek pouch with forceps and pinning it out flat over a transparent windowon the microscope stage. This "double membrane" preparation can be used for microscopic observations, using a transmitted light source. A "single membrane" preparation which gives much clearer detail at higher magnification (up to 1200 times) can be readily prepared by cutting a semicircular opening in the upper epidermal layer, pinning it back and clearing the loose connective tissue, thus leaving a single epidermal layer with a single flat layer of attached vessels /Figure I.B./. In all measurements it was assumed that all vessels lay in the same plane and were circular in cross-section.

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C) ANAESTHESIA.

Anaesthesia was essential in studying the microvasculature of the cheek pouch of the hamster. The anaesthetic usually employed was intraperitoneal pentobarbitone. A fresh solution was made up each day by dissolving powdered pentobarbitone in sterile normal saline solution. The minimum satisfactory amount of anaesthetic agent was employed: the dose was usually 9 mgms. pentobarbitone per 100 G. body weight intraperitoneally. The "sleeping time" was 30-35 minutes. Anaesthesia could be prolonged indefinitely by subsequent graded smaller doses of drug (2.5 mgm. doses as 0.05 ml. of solution containing 50 mgm./ml.).

Effects of Anaesthesia.

Anaesthesia, per se, has a profound effect on the circulation through the vascular bed. (ZWEIFACH, 1948; WEIDMAN and NICOLL, 1953). In the hamster anaesthetised with intraperitoneal pentobarbitone, the blood pressure usually falls, the effect is most profound in the first 5-15 minutes and then progressively wears off in the next 45-90 minutes. This feature introduces an important but unavoidable variable which has to be taken into consideration during all experimental observations on the cheek pouch. General anaesthesia causes an upset of

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'vasomotion' in the microvasculature. The small vessels show intermittent phases of dilatation and contraction (KNISELY, 1935) and it has been observed that general anaesthesia causes the vasodilator phase to be predominant (ZWEIFACH, 1948).

LISTER (1858) observed that chloroform anaesthesia in frogs had such an effect on the microvasculature. He noted, "The anaesthesia appears to impair the functions of the spinal cord as a regulator of the calibre of the vessels and its administration is generally followed by their dilatation". SAUNDERS and KNISELY (1954) also noted vasodilatation associated with intraperitoneal pentobarbitone in mammals.

In all the observations in the cheek pouch of the hamster, it was considered that pentobarbitone, by its central action on the nervous system caused a diminution of sympathetic vasoconstrictor tone. All experiments were carried out under similar control conditions.

SECTION III.

QUANTITATION OF THE MICROVASCULATURE IN THE HAMSTER CHEEK POUCH.

A) Introduction and methods of study.

B) Results.

C) Discussion.

D) Summary.

Quantitation of the Microvasculature in the Hamster Cheek Pouch.

A) Introduction.

The importance of accurate in vivo measurements of lengths, diameters, numbers of vessels, anastomosès, blood volumes and endothelial surface areas lies in assessing the haemodynamic changes associated with blood flow and volume distribution in the microcirculation, the only part of the cardiovascular system associated with metabolic exchanges with living tissue cells. Few studies have been made to measure the minute vessels in the living animal. Values reported here are the results of direct observations in living tissues where it was possible to follow blood flow in its complete peripheral path from distributing artery through the capillary network into the collecting venous system.

METHODS.

The microvasculature has been quantitated in the cheek pouch of the living anaesthetised hamster. (MESOCRICETUS AURETUS). Camera lucida drawings were made of the general and detailed distribution of the vessels. Diameters and lengths of vessels were measured with a calibrated ocular micrometer. Calibration of the ocular micrometer was carried out using a stage-micrometer with different eyepieces and objectives. Total cross-

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sectional areas, endothelial surface areas and blood volumes were calculated for the different types of blood vessels. For each size of blood vessel at least 10 different hamsters were observed and the mean of at least 25 readings was recorded. Magnifications varied from 40x to 1200x depending on the vessels being measured.

10x, 15x and 20x eyepieces were used along with various objectives. For the higher magnifications 25x and 60x water immersion objectives were chosen.

The hamsters were anaesthetised with intraperitoneal pentobarbitone (Nembutal) - 9 mgm./100 G. body wt. When required for the study of the smaller vessels, single membrane preparations were made by cutting a window in the upper layer of the everted cheek pouch.

The cheek pouch was perfused from time to time with Ringer's solution. The stage was not heated but the environmental temperature was maintained at 70°F (±3°F).

B) RESULTS.

There were usually 3 or 4 main arteries entering the cheek pouch and a similar number of major veins leaving it. PRIDDY and BRODIE (1948) and POOR and LUTZ (1958) in careful dissections of the head region of the hamster have described the gross arterial and venous connections of the pouch. In the present study the

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largest vessels which could be seen at the most proximal part of the everted pouch were considered to be the main vessels. More proximal junctions could not be studied by transillumination of the cheek pouch on the microscope stage.

Main Table 1 shows the mean for the number and diameter size of the main arteries and veins at the origin of the cheek pouch. The total cross-sectional area of the veins leaving the cheek pouch is over seven times as great as the total cross-sectional area of the entering arteries.

Branches from the main arteries formed the main arterial arcades in the cheek pouch and those anastomoses recurred throughout the cheek pouch and ensured an even pressure distribution to the terminal arterioles and the capillary bed. The mean diameter of the arterioles forming the arcades was 28.6 microns.

The angle of branching of main arteries was observed and the two branches usually formed an acute angle to each other; this was in marked contrast to the terminal arterioles which usually branched from the small arteries at right angles. This morphological feature seemed to be important in regulating the flow of blood into these terminal vessels.

The areas within the anastomosing vessels varied

widely but on average were 3 mm. x 1.5 mm. Smaller arterial anastomoses occurred occasionally but their occurrence was infrequent with no regular pattern.

No arterio-venous communications were seen. The anastomosing channels on the venous side were much more numerous than on the arterial side and occurred at all levels from the second order of post-capillary venules up to the largest veins. This rich anastomosis, in addition to maintaining a uniform pressure gradient, and flow pattern, could also provide a large storage space for blood.

In the cheek pouch there were usually four orders of arteries, the capillary vessels, and five orders of veins. Main Table 2 shows the lengths and diameters of these vessels. The mean number of branches of each group of vessels was calculated and the total cross-sectional area of the various vessels was recorded in Main Table 3. The relative changes in total cross-sectional area are illustrated in Figure 3. This figure demonstrates that there is a gradual increase in cross-sectional area down to the small arteries; a threefold increase then occurs to the terminal arterioles and a further twofold increase to the capillary bed. It is in these two terminal orders of arteries that the maximum pressure gradients must occur.

In the present survey the capillary bed did not

possess the largest cross-sectional area. Further small but significant increases occurred in the first two orders of post-capillary venules and it was not until the third order of veins that the area fell below that of the capillary bed. Later venous vessels showed a gradual linear decrease in total cross-sectional area.

The capillary vessels formed a uniform network throughout the cheek pouch with arterial supply and venous drainage joining the network. A camera lucida drawing of the capillary bed is illustrated in Figure 2. The distance between adjoining capillaries had a mean value of 113 microns. In the cheek pouch under resting conditions only one third of the capillary vessels had active blood flow at any one time. No arteriovenous communications or thoroughfare vessels described by ZWEIFACH (1961) were seen in the cheek pouch.

The mean diameter size of the capillary was 4.84 ($\pm$ S.E. 0.12) microns. This luminal diameter of the capillary was less than the equatorial diameter of the non-deformed erythrocyte (5.6 $\pm$ S.E. 0.2 microns). If "clumping" of the red cells occurred in the arterioles, cells which entered the capillaries, separated from the aggregated mass and passed in single order through the capillary. They were deformed from biconcave discs into hollow paraboloid structures or less commonly were folded

over on themselves. This incongruity of size allowed maximum apposition of red cell membrane and vascular epithelium, perhaps important in blood and tissue gaseous exchange. During the passage through the capillary the red cells became deformed and with increased velocity the deformation was greater. It was noted that the internal diameter of the capillary was greatest when the flow was sluggish or stagnant and the internal capillary diameter was smallest when the flow was most rapid.

In the post-capillary venules the lumen of the vessel was much wider than the capillary and aggregation of the red cells could occur. When the flow rate was low, red cells became densely packed in aggregates in these small veins and even when rapid flow was resumed considerable time was necessary to overcome the venous stasis and cause disaggregation of the densely packed erythrocytes. The leucocytes were much larger and less numerous than the red cells. In the larger vessels they seemed to roll along the margins of the vessels and to possess amoeboid movements in the capillaries.

In the minute vessels as a whole, flow appeared to be periodic with frequent temporary cessation of flow or complete reversal of flow.

Blood Volume Distribution.

The blood volume capacity on the venous side was

much greater than on the arterial. The volume distribution in the different orders of arteries, capillaries and veins is listed in Main Table 4. A correction was made for the largest order of veins as these main veins appeared more like cones than cylinders. The angle of divergence of these large vessels was calculated. The range was 24' to 1°30'. As endothelial surface area is an important factor in the control of diffusion to and from tissues, calculation of the relative proportions of endothelium in the various vessels was made (Main Table 4). Although only 2.2 per cent of the total blood volume was in the capillaries, those vessels accounted for 14 per cent of the total endothelial area in the microvasculature. A comparison of the ratio of endothelium to volume (last column in Main Table 4) shows the unique advantages of the capillary vessel — being the vessels with the smallest luminal diameter, the capillaries have the greatest surface exchange area for the volume of blood that they contain. In addition, the thinness of the capillary wall relative to all the other minute vessels, increases this unique diffusing capacity of the capillary vessels.

Main Table 5 shows the comparison of volume and endothelium in all the arteries, capillaries and veins

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in the microvasculature of the cheek pouch.

C) DISCUSSION.

In the minute vessels there is only a small fraction (2.2%) of blood in the capillary network. The capillary vessel has no elastic tissue or muscle cells in its wall and, as such, distension is limited. KROGH (1929) showed that in muscle the variations in metabolic needs were served by only a small number of capillaries being perfused with blood in the resting stage, and by near maximum capillary perfusion during exercise.

If the volume of blood in the minute vessels is compared to the total blood volume in the animal or man the relative volume of blood in true capillary vessels is minute. J.G. GIBSON, II ET AL., (1946) have shown that less than 20 per cent (approximately 17%) of the total blood volume is in the microvasculature at any one moment. The present study shows that the majority of blood in the microvasculature is on the venous side, where considerable pooling can take place.

The precise values of lengths and diameters of the various vessels differ from tissue to tissue and also from species to species. Absolute values have little direct importance but are of great physiological interest in the relative volume distribution and velocity flow

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patterns that are observed in the peripheral vascular bed. As more precise information about the microvasculature becomes available experimental models, measuring, pressure gradients, viscosity and other haemodynamic factors can be analysed with variables comparable to conditions observed in vivo in the microcirculation. At present, viscosity studies of blood obtained from larger peripheral veins may have very little direct relationship to the everchanging conditions in the microvasculature. No method of study is more direct than visual microscopy of living tissues. Other techniques depend on the uptake by the tissue or deposition of foreign material in the tissue, or variation in oxygen or carbon dioxide tensions.

The cheek pouch does not possess any arterio-venous communications. This has been confirmed by FULTON (1962) and by POOR and LUTZ (1958). Similarly in the bat wing no A-V shunts have been observed. (NICOL and WEBB, 1946). In the fingers of man and in the ear of the rabbit, A-V shunts have been described and in these sites they appear to subserve temperature requirements rather than metabolic needs. (GRANT, 1930). In the rabbit lung IRWIN ET AL. (1954) observed infrequent A-V shunts but these communications did not exceed 20 microns in diameter and appeared to be more like the A-V preferential channels

first described by ZWEIFACH (1948) in the mesentery of the dog.

IRWIN ET AL., (1954) noted by direct cannulation experiments using micromanipulative techniques that the greatest pressure gradients in the rabbit pulmonary vascular system were in the arterial vessels below 50 microns in diameter. In the present study the greatest increase in the total cross-sectional area occurred in the smallest two orders of arterioles.

Capillary Vessels.

SAUNDERS and KNISELY (1954) by direct in vivo microscopy showed that the narrowest parts of the circulatory system, the bottlenecks, were the terminal arterioles at the junction with the capillaries. Their measurements made in various living animals are shown in Main Table 6. Other published in vivo measurements of capillary size are listed in Main Table 7. Such in vivo measurements show satisfactory agreement with the observed size of the hamster cheek pouch capillaries (4.8 microns in diameter). These values of the internal diameters of capillary vessels are considerably smaller than previously reported series most of which deduced capillary size from study of the size of erythrocytes or else from measurements of histological preparations of tissues.

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Direct microscopy, however, shows marked deformation of the erythrocytes during their transit of the capillary vessel. KROGH (1929) observed "the capillaries are so narrow that red corpuscles could pass through only at a slow rate with a change of form from the ordinary flat discs to elongated sausages".

The observed deformation of the erythrocytes seen in the hamster capillaries is illustrated diagramatically in a camera lucida drawing (Figure 4).

Venules.

The post-capillary venules had the same length as the capillary vessels but were twice as wide. It was in the smaller orders of veins that stasis and "sludging" appeared most marked.

FERNANDO and MOVAT (1964) in electron microscopic studies of the small venules showed those vessels to be lined with a single layer of endothelium on a basement membrane. Exterior to the endothelial layer was a discontinuous layer of pericytes and muscle cells. Occasional collagen and elastic elements were present. Lysosomes which were not common in the endothelium of the arterioles and capillaries, were frequent in the venules and pinocytic vesicles were large. Those electron microscopically discrete intracellular structures appear to be the site of

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production of vasoactive materials and enzymes, important in the regulation of diffusion of fluids and proteolysis.

COHNHEIM (1889) showed that venules were important in inflammatory reactions and that polymorphonuclear cells migrated across the venular wall. Recent electron-microscopic studies by FLOREY and GRANT (1961) have confirmed this leucocyte migration through the walls of the venules.

Measurements of vascular volume changes are important in shock where it has been presumed that there is peripheral pooling in the various vascular beds. In the hamster cheek pouch only 2.2 per cent of the blood in the minute vessels was found in the capillaries. Main Table 8 compares the result of microcirculatory blood volume distribution in the present study with previously published calculations.

D) SUMMARY.

Measurements of length, diameter, and number of branches of arterial, capillary and venous vessels were made in the cheek pouch of the living hamster. Calculations of total cross-sectional area, blood volume and endothelial surface areas were made for the different type of vessels.

The greatest increase in cross-sectional area occurred in the terminal arterioles and the capillaries.

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The greatest total cross-sectional area was in the post-capillary venules. The internal diameter of capillary vessels was less than that of the undeformed erythrocytes. Three quarters of the blood in the micro-circulation at any one time was in the venules and only 2.2 per cent of the microvascular blood volume was in the capillary vessels.

SECTION IV.

THE ACTION OF VASOACTIVE SUBSTANCES ON THE MICROCIRCULATION

A) Introduction

B) Materials and methods

C) Results

D) Discussion

E) Summary and general conclusions

THE ACTION OF VASOACTIVE SUBSTANCES ON THE MICROCIRCULATION

A) INTRODUCTION.

Seventy years ago E.H. STARLING (1896) suggested that the balance between the hydrostatic pressure in the capillary vessel and the osmotic pressure of the plasma proteins dictates whether there will be a net gain or loss of fluid from the vascular system.

LANDIS (1927) using a micromanipulative technique, measured directly the hydrostatic pressures in the arterioles, venules and capillaries of the frog.

Direct visualisation of the changes in diameters (and in cross-sectional areas) of the arteries and venules at each end of the capillary network allows the changes in cross-sectional area to be related to hydrostatic pressure changes in the capillary bed. In addition changes in the rates of blood flow in the minute vessel can be observed. In the microcirculation the controlling mechanisms are dominantly chemical in nature. Substances are liberated into the local tissue environment by metabolic activity of the cells. True capillary vessels have no muscular tissue and do not have direct neural control. A vasoactive substance may have a direct effect on the capillary endothelium altering its shape or porosity

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or by its action on the arteries and veins may bring about indirectly a change in the hydrostatic pressure gradient in the capillary bed. The following physical factors and endogenous substances have been suggested to be important in the control of the minute vessels.

Physical Factors.

Injury and mechanical effects.

Temperature.

Light and radiation.

Metabolic or Humoral Substances.

Lactic acid and pH changes.

Adenylic acid derivatives.

Carbon dioxide and oxygen tensions.

Electrolytes - e.g. Calcium, potassium and sodium.

Adrenaline.

Noradrenaline.

Acetylcholine.

Histamine.

Serotonin.

Angiotensin II.

Vasopressin.

Plasma Kinins (e.g. Bradykinin).

B) METHODS.

The effects of several vasoactive substances were

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studied in the microcirculation of the cheek pouch of the anaesthetised hamster. If the substance to be tested was dropped on to a double membrane preparation the effects on the vessels of the pouch were slow and often incomplete. This was considered to be due to the relative imperviousness of the upper epithelial layer and also to dilution, (the cheek pouch being moistened from time to time with Ringer's Solution).

DALE and RICHARDS in 1918 attempted to study the effect of histamine on the mesenteric vessels but their results were indecisive. ZWEIFACH and METZ (1955 discussed criteria and limitations of using the rat mesoappendix to study the action of vasoactive substances. A quantitative procedure was developed for such a study on the minute vessels of the hamster cheek pouch.

If a single membrane hamster cheek pouch preparation was made and a vasoactive substance applied locally, a prompt effect was observed due to early diffusion and action on the vessels. (c.f. AKERS and ZWEIFACH, 1955). Evaporation was prevented by covering the "single membrane preparation area" with a ring of filter paper covered with a glass coverslip. The remainder of the pouch was covered lightly with cotton wool moistened from time to time with Ringer's Solution.

A further satisfactory method was to inject the

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substance (in 0.05 ml. sterile Ringer's solution) into the cheek pouch with a fine No.30 gauge needle and a tuberculin syringe. The injection was carefully planned. An area in the upper layer of the pouch where the artery and vein pattern seemed suitable was selected and with the aid of the dissecting microscope the needle was passed obliquely through the upper epidermal layer and gently brought to rest at the chosen site. The solution was then injected carefully. A slight "blister" formed between the upper epidermal layer and the loose areolar layer and if the chosen arteries and veins remained in sharp focus this field was selected for study. The advantage of injecting into the pouch was that subsequent dropping Ringer's solution on to the surface did not appear to effect by dilution the action of the injected substance. All substances to be tested were made up in sterile Ringer's solution so that the required dose was contained in the same volume (0.05 ml.).

The room temperature was kept stable at $70^{o}F \pm 3^{o}F$ and changes in air currents were avoided. The microscope stage was not heated. Control experiments were performed to establish the stability of the preparation and the environment. A camera lucida sketch was made of each preparation and sites on 3 and 4 arteries and a similar number of veins were marked. Internal diameter size of

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these vessels at the marked sites was recorded, measurement being made with a calibrated eyepiece micrometer. Control readings of the internal diameters of the selected vessels were made on two occasions at ten minute intervals and if the vessel diameters were constant subsequent serial readings were made at 3, 6, 15, 30 and 60 minute intervals after the control solution or test substance had been applied. By the use of various oculars and objectives 120 - 200 magnifications were usually selected. Occasionally higher magnifications up to 500 times were employed.

Initial control experiments were carried out as follows:

Readings were made at 0, 3, 6, 15, 30 and 60 minutes during experiments where no injections were made, the cheek pouch being merely observed for spontaneous changes in vessel calibre. In a further group of control experiments 0.05 ml. Ringer's solution was injected without any additional drugs and the arteries and veins were measured. It was observed that if the injection was made suddenly or without due care the mechanical effect could produce immediate widespread constriction. Care was always taken to prevent this effect and to exclude any preparation where mechanical stimulation seemed to have occurred.

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Initially the topical application of drugs was studied. Later the same substances were given intravenously and the local effect on the cheek pouch vessels was studied.

Methods used in calculating and comparing vessel calibre changes.

As there were usually many more veins than arteries in a microscopic field, a peripheral part of the cheek pouch was chosen for the experimental observations where 3 or 4 arteries of suitable diameters were sited. Measurements were then made at carefully selected points on 3 or 4 arteries and on 3 to 5 veins. The rate of diffusion of a vasoactive substance applied to the cheek pouch affected different vessels to varying degree. Attempts were always made to choose vessels relatively near to each other (within 1 or 2 adjoining high power fields). It appeared that the smaller the diameter of a vessel the greater its vasoactivity. (Perhaps due to rapid and complete diffusion of the vasoactive substance throughout the vessel wall.)

Most arterial and venous vessels studied had internal diameters within the range 20-60 microns. It was not possible to select vessels of identical size on each occasion.

When an assessment of the average changes in vessels

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was made mean diameter values appeared to give undue importance to smaller vessels. Mean square root diameters improved this imbalance but as cross-sectional area changes seemed more meaningful both as regards blood volume distribution and blood flow measurements the total cross-sectional area was calculated by summation of the cross-sectional areas of all the arteries or veins observed in one experiment. Changes in this total cross-sectional area were compared with control values before the test solutions were applied.

In order to compare one experiment with another changes in total cross-sectional area were expressed as a percentage of the original control cross-sectional area. In this manner vessels in a field of study, — in the same range, but not of identical calibre were compared. Mean values and standard deviations of percentage changes in total cross-sectional areas were recorded in the tables of results.

Materials Used.

Ringer's Solution	- Abbott Laboratories.
Histamine diphosphate	- Eli Lilly and Co. Indianapolis.
Histamine dihydrochloride	- Nutritional Biochemical Corp. Cleveland, Ohio.
Epinephrine (Adrenaline)	- l-epinephrine hydrochloride (Adrenalin Chloride, Park Davis & Co.)

l-norepinephrine bitartrate	- Levophed Bitartrate. Winthrop Laboratories, N.Y.
Serotonin creatinine sulphate	- Nutritional Biochemical Corp. Cleveland, Ohio.
Acetylcholine chloride	- Nutritional Biochemical Corp. Cleveland, Ohio.
d, l-isoproterenol hydrochloride	- Isuprel, Winthrop Laboratories, N.Y.
Phenoxybenzamine hydrochloride	- Dibenzyline, Smith, Kline French Lab.
Phentolamine - Regitine Methanesulphonate	- Ciba Lab.
Cortisone Acetate (USP)	- Cortone Acetate. Merck Sharp and Dohme, Philadelphia Pa.
Lactic Acid	- Sigma Chemicals, St. Louis.
Angiotensin amide	- Hypertensin, Ciba, Summit N.J.

C) RESULTS.

Control Experiments.

The results of observation alone of the microcirculation are recorded in Main Table 9 and in Supporting Tables 1-3. The "vasomotion" observed by ZWEIFACH (1961) was not a prominent feature in the cheek pouch of the anaesthetised hamster. Blood flow occurred in only one third of the capillary vessels at any one time and blood

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flow through the vessels of the capillary bed was intermittent and occasionally reversed. In the smaller arteries and veins spontaneous change in the size of vessels did occur from time to time but such changes were slight. Temporary narrowing of one vessel was often off-set by a widening of a neighbouring vessel. Generalised constriction of a field could usually be produced by stroking a larger vessel with a fine needle. Reflex constriction of the arteries in the neighbourhood would then occur.

When normal Ringer's solution (0.05 ml.) was injected into the cheek pouch with a fine needle, care being taken to inject slowly and not to injure vessels by direct puncture, there was little change observed either in rate of flow or in vessel diameter. Main Table 10 (and Supporting Tables 4-8) shows the results of five control experiments; there was a slight decrease in the total cross-sectional areas of the arteries suggesting a small increase in arterial tone. There was little change observed in the venous vessels. The spontaneous changes observed or the degree of change which could be due to experimental error was within 10 per cent control reading, a level which seemed acceptable in the "in vivo" biological model which was employed. It was in comparison with these results that the changes produced by vaso-active substances were studied.

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Action of Histamine.

Histamine dihydrochloride and histamine diphosphate appeared to give similar responses. Six experiments were carried out using 10 micrograms histamine base and a further six experiments using 5 micrograms histamine base. The results are tabulated in Main Tables 11 and 12 (and in Supporting Tables 9-20). The changes in total cross-sectional areas in the arteries and veins are illustrated in Figures 5 and 6. Immediately after the histamine injection there was a transient constriction of the arteries. Because no similar initial arterial vasoconstriction was observed after acetylcholine or lactic acid it was deduced that this constriction could not be due solely to mechanical stimulation. Within 3-5 minutes after the administration of histamine arterial dilatation occurred and this dilatation persisted during the hour of observation. Unlike the arterioles, however, the veins constricted slightly and this constriction was maintained. The capillary bed became very prominent owing to the increased arterial inflow and the post-capillary venous constriction. When a double membrane preparation was used, difficulty was experienced at the end of one hour in achieving sharp definition of the vessels owing to the oedema of the extravascular tissues at the site of histamine injection.

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This capillary fluid exchange was also demonstrated by injecting 0.5 ml. 1 per cent aqueous solution of Trypan blue intravenously. A blue discoloration of the tissues at the site of histamine injection was observed. This discoloration, however, was not observable by the naked eye until 2-4 hours after the injection.

Action of Serotonin (5-Hydroxytryptamine).

Six experiments using 5 micrograms of serotonin were carried out on the cheek pouch. The results are tabulated in Main Table 13 (and in Supporting Tables 21-26). The relative changes in total cross-sectional areas produced by serotonin are illustrated in Figure 7. There was marked arterial constriction (but not as intense as with the catecholamines). The effect of a single dose was relatively long lasting. In the dose chosen there was only very slight venous constriction although with the greater arterial narrowing blood flow in the veins became very sluggish and in many places complete stasis with red-cell aggregation occurred.

Action of Acetylcholine.

Acetylcholine was applied to the cheek pouch in a single one microgram injection dose. Six experiments using this dose were carried out and the results are recorded in Main Table 14 (and in Supporting Tables 27-32).

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Total cross-sectional area changes in the resistance and capacitance vessels are shown in Figure 14. Acetylcholine is a dilator of both arteries and veins and both types of vessels have comparable changes in the dose chosen. The effects persisted for the 60 minutes of observation. With the increased blood flow, the total volume of blood in the microvasculature was increased.

Action of Angiotensin.

Angiotensin II was used in two different doses, 25 micrograms in four experiments and 5 micrograms in a further four experiments. (Main Tables 15 and 16 and Supporting Tables 33-40). Angiotensin was a very potent arterial constrictor. Its effect was comparable to that of adrenaline or noradrenaline but with a single dose the marked vasoconstriction was not maintained in the same way as with the catecholamines. The effect was maximal shortly after the application of angiotensin II and gradually wore off. At the end of 60 minutes the total cross-sectional area of the arterial vessels had returned to the normal control level (Figure 8). Unlike the marked effect on the arteries angiotensin II had very little constriction action on the veins. This selective constriction of the arteries diminished blood flow to the cheek pouch and caused marked slowing of the blood in the veins. This effect would allow inflow of tissue fluids

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back into the vascular system. It would seem that a tissue angiotensinase rapidly destroyed the pharmacological action of the locally applied angiotensin II. In order to maintain an increased resistance in the peripheral arteries, a continuous intravenous infusion of angiotensin II was given (into a femoral vein cannula). When the infusion was discontinued the vasoconstriction rapidly disappeared.

Action of Catecholamines.

Adrenaline caused marked constriction of the small arteries. With a pharmacologically large dose (one microgram) the arterial bed was almost completely shut off and this effect persisted for up to 60 minutes when observation was discontinued. The response of the veins was always more delayed than the arterial response and was usually not so great. Nevertheless the venoconstriction produced by adrenaline (and noradrenaline) was greater than with any other substance tested. Venous stasis was marked. In a series of experiments, at 30 minutes the persistent constriction caused by adrenaline was relieved by a local injection of phenoxybenzamine or phentolamine (Main Table 17 and 18 and Supporting Tables 41-46). The dramatic increased flow resultant to the adrenolytic effects of these latter drugs is shown in Figures 9 and 10. Noradrenaline, in a similar dose to adrenaline had

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an almost identical effect on the arteries and veins of the cheek pouch and its effect was also promptly neutralised by the addition at 30 minutes of an alpha-receptor blocker (phentolamine or phenoxybenzamine). (Main Tables 19 and 20 and Supporting Tables 47-52). The arbitrarily chosen doses of the alpha-receptor blockers appeared to produce a satisfactory pharmacological action neutralising the vasoconstrictor effects of one micro-gram of adrenaline or noradrenaline (Figures 11 and 12).

When phenoxybenzamine and phentolamine were given by themselves as a local injection into the cheek pouch, these drugs did not appear to have any direct vasoactivity. This effect was in contrast to their marked adrenolytic action when given subsequent to an injection of adrenaline or noradrenaline (Main Tables 21 and 22 and Supporting Tables 53-58).

Action of Isoproterenol.

This catecholamine is a beta-cell receptor activator and as such should cause dilatation of the vessels. In all the experiments with isoproterenol on the cheek pouch (Main Tables 23 and 24 and Supporting Tables 59-67) the veins dilated promptly but the arteries uniformly con-stricted. The constriction, was not maintained but gradually wore off (Figure 13). It was of interest to note that most substances used caused a parallel action

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on the arteries and veins. Isoproterenol however caused a dissociated action on the arteries and veins of the cheek pouch and in this respect was the mirror-image of histamine which dilated the arteries and constricted the veins. These two substances (Histamine and Isoproterenol) were the only ones studied which produced dissociated effects on the arteries and veins.

Action of Lactic Acid.

The action of lactic acid on the microcirculation is recorded in Figure 15 and the results of three experiments using 100 micrograms lactic acid are recorded in Main Table 25 and in Supporting Tables 68-70. Lactic acid caused vasodilatation of both arteries and veins and the dilatation was proportionally equal in both the capacitance vessels and resistance vessels. Whether the dilatation of the microvasculature was due to lactic acid itself or was merely a function of the pH change was not discovered as other physiological acid substances were not used.

Action of Cortisone.

In the acute experiments lasting up to one hour, cortisone applied locally to the vascular bed did not appear to have any direct vasoactive effect. The results are recorded in Main Table 26 and in Supporting Tables 71-73. No composite experiments were carried out to see

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whether cortisone given at the same time as a vasoactive substance may alter the effect of the accompanying substance or "protect" the vascular wall from its action.

Intravenous Administration of Drugs.

All the drugs employed above were also given intravenously (into a femoral vein cannula) and the same effects were observed in the cheek pouch as in the topical injection. With intravenous administration the response was not so prompt as the locally applied substance. This slight delay could be explained by the circulation time from the site of injection to the cheek pouch and the pharmacological effect would be diluted as the injected drug became mixed with the circulating blood volume.

D) DISCUSSION.

Blood flow through an organ of tissue is a function of the vasoactivity of the artery and vein. Where the arteries constricted relatively more than the veins (e.g. after angiotensin II) stasis was observed in the post-capillary venules, encouraging transcapillary exchange of fluids from tissues to capillary lumen. When venous constriction was associated with arterial dilatation (e.g. after histamine) the capillaries became distended and transcapillary exudation of fluids into

the extravascular space occurred. The results of vaso-activity of certain drugs are recorded in the Tables of Results as changes in the cross-sectional areas of arteries and veins. In considering the haemodynamic implications associated with such drug action the effects of changes in flow would be proportionately very much greater than mere changes in area infer (POISEUILLE, 1842, showed that the flow was proportional to the fourth power of the radius).

Although the drugs applied to the cheek pouch appeared to have a direct action on the blood vessels their action must always be considered in relation to the tissue or organ being studied and the species of animal employed. Anaesthesia affects the neurological control of the micro-vasculature by abolishing or minimising sympathetic vaso-constrictor tone of the arteries (LISTER, 1858; NICOLL and WEBB, 1948; ZWEIFACH, 1961). This complication, however, seemed to remove the difficulty of spontaneous vasomotion observed by ZWEIFACH, (1937) and KNISELY (1935) in their studies. In the control experiments in the cheek pouch of the anaesthetised hamster, vasomotion was not a prominent feature.

Catecholamines.

ALQUIST (1948) found that catecholamine substances had a variable effect on the vasculature and to explain

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the variations in responses speculated two different receptor mechanisms, arbitrarily named alpha-receptor which constricted and beta-receptor which dilated. Adrenaline had both an alpha and a beta effect. In small doses the beta-effect would dominate and dilatation would occur (ALQUIST, 1948). With larger pharmacological doses the alpha-response dominated and vasoconstriction would be observed. FOLKOW (1955), BARCROFT and SWAN (1953) and GREENFIELD (1963) have shown that in skin and subcutaneous tissues alpha-receptors are present and that beta-receptors are present mainly in muscle tissue. Noradrenaline is mainly an alpha-receptor activator and most reports show little or no beta-effect. Isoproterenol has been shown in most reports (COBBOLD ET AL., 1960; FOLKOW, 1960: PARRATT, 1965) to be a beta-receptor activator with little action on the alpha-receptors. In the cheek pouch, a subcutaneous tissue, it would seem that alpha-receptors would dominate, few if any beta-receptors being expected in the arterial vessels.

The sympathetic tone which normally is present in the arteries is diminished with general anaesthesia. The absence of the sympathetic vasoconstriction was confirmed in the cheek pouch of the anaesthetised hamster — when the alpha-receptor blockers (phentolamine and phenoxybenzamine) were used alone there was no

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appreciable dilatation of the vessels, an effect which would have been expected if the sympathetic nervous system was causing increased vasoconstrictor tone. In addition when phentolamine and phenoxybenzamine were used following the application of adrenaline a response similar to that following noradrenaline was recorded. If beta-receptors were present in the cheek pouch arterioles, the addition of an alpha-blocker would cause the adrenaline to produce dilatation above the resting control level. Such an effect was not observed.

Most pharmacological studies of isoproterenol (a catecholamine which does not occur naturally) have demonstrated its beta-receptor action (COBBOLD, 1960; FOLKOW, 1960) and many believe that it has no alpha-receptor activity. The experiments on the cheek pouch using isoproterenol confirmed the dilatational effect on the veins. There was however arterial vasoconstriction and this effect would have suggested an alpha-receptor stimulation in the relative absence of beta-receptors. A recent report (NAKANO and KUSAKARI, 1965) using a pure beta-cell blocker (propranolol) suggested that isoproterenol may have an alpha-receptor effect but that this effect is usually masked by the dominant beta-receptor response. The results recorded above in the cheek pouch would confirm this suggestion that

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/isoproterenol is not a pure beta-receptor catecholamine but that it also possesses weak alpha-receptor action. In the subcutaneous tissues of the cheek pouch where arterial beta-receptors are scanty or absent a vaso-constrictor response was observed in the arterial vessels when isoproterenol was injected. This effect was not as great or as prolonged as that of adrenaline or noradrenaline. The marked venous dilatation produced in the cheek pouch venous vessels suggests that these subcutaneous veins have a very rich beta-receptor supply — readily responsive to the action of isoproterenol. (Subcutaneous veins must also have a rich supply of alpha-receptors as constriction occurred with adrenaline or noradrenaline).

Angiotensin II.

Angiotensin is a powerful arterial vasoconstrictor and increases systemic arterial blood pressure (PEART, 1964). The effect of a single dose of angiotensin II was however relatively transitory and the arterial vessels promptly returned to their previous calibre. In order to maintain a lasting effect a continuous supply of angiotensin II is required. The rapid destruction of angiotensin by angiotensinase will allow the vaso-constriction to be withdrawn promptly as soon as the renal ischaemia motivating the activation of angiotensin II /

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is removed. The relative immunity of the veins to the action of angiotensin II has been shown previously by several reports (FOLKOW ET AL., 1960; HADDY ET AL., 1962; De PASQUALE ET AL., 1963; LISTER ET AL., 1963).

Serotonin and Histamine.

Serotonin and histamine are liberated from injured platelets (HUMPHREY ET AL., 1954; WAALKES ET AL., 1957), and their action in the microcirculation can motivate changes directly at the site in the peripheral vascular system where the response is required. In the hamster cheek pouch there appeared to be a relative immunity of the venous vessels to serotonin. In contrast, in man SHARPY-SCHAFER and GINSBURG (1962) found marked venoconstriction with serotonin. The venoconstriction appeared to be greater than the arterial constriction and transcapillary exudation of fluids into the tissues occurred. Histamine is produced by mast cells and pericytes which are localised very near the endothelium of the minute vessels (UVAS, 1964). The mast cells of the cheek pouch are numerous and were well displayed by the injection into the cheek pouch of a 1 per cent aqueous solution of methylene blue. The endothelium itself may be the site of histamine production. SCHAYER (1962) has shown a high concentration of histidine decarboxylase in the endothelial cells of minute vessels; this enzyme is

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present in high concentration when histamine is being formed.

Histamine was the only substance which caused dilatation of the arteries and constriction of the small veins. This unique property of histamine increased the capillary blood volume and the hydrostatic capillary permeability with an exudation of fluid into the tissues. DALE and LAIDLAW (1919) in their early study of histamine shock demonstrated a rising haematocrit level in animals given a large dose of histamine.

<u>Vasoactive Polypeptides</u>.

STARLING (1896) in his original paper, believed that the capillary wall was relatively impermeable to the plasma proteins and that the osmotic pressure of the plasma proteins was important in regulating inflow of fluids from the tissues at the venous end of the capillary. DRINKER (1937) however, showed that there was an appreciable escape of plasma proteins from the capillary vessels into the tissue spaces and that return of the large molecule proteins to the vascular system was gained indirectly by way of the lymphatic vessels.

With the increased capillary permeability produced by histamine, plasma protein escape can be more marked and in the tissue spaces other potent vasoactive substances can be activated (e.g. bradykinin).

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Bradykinin was first isolated and identified by ROCHA e SILVA ET AL.(1949). It is a "second phase" mediator of the inflammatory response. In the first phase histamine causes increased capillary permeability. Some plasma protein enters the tissue space and kallikrein which is produced in damaged tissue cells enzymatically releases bradykinin from its inactive precursor in the $alpha_2$ globulin of the plasma (MITCHELL, 1964). This substance is one of the most potent vasodilators known and unlike histamine which produces a capillary filtrate relatively protein free bradykinin causes a marked increase in protein escape from the plasma in the minute vessels.

E) GENERAL CONCLUSIONS AND SUMMARY.

A method for directly assessing the response of arterial and venous vessels to vasoactive drugs and indirectly of capillary filtration was developed for the hamster cheek pouch.

There was a continuous variation in the calibre of the minute vessels in the hamster cheek pouch, but under anaesthesia with standard control conditions those changes were negligible. Vasoactive substances, by their relative action on the arteries and veins brought about changes in the hydrostatic pressure gradient in the capillary bed. Blood flow and overall fluid movement in a tissue or organ is therefore a function of the vaso-activity of the artery and vein. In the hamster cheek pouch the responses to histamine, acetylcholine, lactic acid, serotonin, angiotensin II, cortisone, and the catecholamines were observed. A differential effect of histamine, serotonin, angiotensin II and isoproterenol on arterial and venous vessels was noted.

SECTION V.

ENDOTOXINS.

A) Introduction and general review of the literature.

B) Experimental studies of the action of endotoxin on the microcirculation.

i. Introduction

ii. Materials and Methods.

iii. Results.

iv. Discussion.

v. Summary and Conclusion.

ENDOTOXINS

A) INTRODUCTION AND GENERAL REVIEW OF THE LITERATURE.

Endotoxins were first isolated from the capsules of gram-negative bacteria by BOIVIN ET AL., (1933). Exotoxins, produced from gram-positive organisms are heat labile and produce a highly specific antigen — antibody response and usually have a very specific action. The diphtheria exotoxins, for example, act on nervous tissue and myocardial muscle. The symptoms of tetanus are highly characteristic and are produced by the exotoxin, the tetanus bacillus usually remaining localised in the wound. In sharp contrast endotoxins, which are relatively heat stable, produce non specific symptoms, (pyrexia, rigor, malaise, vomiting).

Endotoxins are complex lipopolysaccharides with a molecular weight — greater than one million — (RAVIN, 1963). WEIDEL ET AL., (1960) demonstrated that the capsule or cell wall of Escherichia coli consisted mainly of three layers — an outer shell of lipoprotein, a middle layer of lipopolysaccharide, (the endotoxin), and an inner layer of mucopeptide. Destruction of the cell wall was necessary for the release of endotoxin.

Extracts were originally made by BOIVIN (1938) using a trichloracetic acid extract and later WESTPHAL ET AL.,

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/(1952) used a phenol method of obtaining endotoxin. In normal saline, endotoxin is insoluble and forms an opalescent suspension. In a non-electrolyte solution (Dextrose 5% or distilled water), BRAUDE (1964) found that endotoxin was more soluble. A highly purified lyophilised lipopolysaccharide extract (Difco Laboratories, Detroit, U.S.A.) is available for experimental use and in recent years many properties and actions of endotoxins have been reported.

Distribution and Degradation of Endotoxin.

In the study of the action, distribution and degradation of endotoxin, the lipopolysaccharide has been labelled by different means. CREMER and WATSON (1957) and RUBENSTEIN ET AL., (1962) used fluorescein; BRAUDE ET AL. (1955) used radioactive iodine, and SCHRADER ET AL., (1964) used tritium as a marker for endotoxin.

When endotoxin is injected intravenously into an experimental animal and after blood is withdrawn and centrifuged, the plasma and erythrocyte layers were found to be free from endotoxin which was localised in the buffy layer (CAREY ET AL., 1958). Further studies showed that the endotoxin was present almost exclusively in the platelet fraction and not in the leucocytes (HERRING ET AL., 1963). The endotoxin is removed finally from the blood and is taken up by the reticulo-endothelial system, most of the

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endotoxin becoming localised in the Kupffer cells of the liver, the spleen, and the small vessels of the lung (SCHRADER ET AL., 1964; BRAUDE ET AL., 1955). RUBENSTEIN ET AL., (1962) showed by a fluorescein label that an appreciable amount of endotoxin was taken up by the endothelium of the smaller peripheral vessels.

The Action of Endotoxin on Experimental Animals.

In all species of experimental animals which have been studied, endotoxin caused hypotension. The action of endotoxin in the dog has been studied in greatest detail. (FREEDBERG ET AL., 1944; LILLEHEI and MacLEAN, 1958; WEIL ET AL., 1956). In the dog the intravenous administration of endotoxin produces a rapid fall in systemic arterial pressure; the pulse becomes rapid; rigors, pyrexia, vomiting and blood stained diarrhoea occur. Pooling of blood in the hepatic circulation is most characteristic. There is a prompt sharp rise in portal venous pressure unaccompanied by any increase in hepatic or central venous pressure. In addition to the pooling of the blood in the liver there is relative stasis of the circulation and pooling of blood in the mesenteric circulation. The haematocrit reading rises and the plasma volume falls, LILLEHEI and MacLEAN, 1958). The venous return is poor and cardiac output is lowered. Generalised vasoconstriction occurs in response to maintain central

arterial blood pressure. This recovery from hypotension is only temporary as in the later stages, the small arterial vessels lose their vasoconstriction and dilate. The constriction of the venules, however is maintained and stasis in the capillaries and small venules is marked.

In the cat the arterial hypotension is associated with hyperpnoea and pulmonary oedema (HINSHAW ET AL., 1958). In the rabbit dyspnoea and prostration follow the administration of the intravenous endotoxin (BOQUET ET AL., 1947; BRAUDE ET AL., 1955). In sheep (HALMAGYI ET AL., 1963), and in calves (TIKOFF ET AL., 1966), the lung appears to be the main target organ for endotoxin. Pulmonary arterial pressure becomes very high. Recent studies in the primate (HINSHAW ET AL., 1965; VICK, 1964) show hypotension and a generalised peripheral vascular pooling not limited to any particular organ site.

The guinea-pig, rat, mouse and hamster — animals which are too small to monitor the haemodynamic changes in detail in separate organs, all show signs of shock after endotoxin administration. Dyspnoea, dia rrhoea, respiratory failure and occasional convulsions occur (ROBERTS, 1949; ROSS, 1957; GILBERT, 1960).

Pyrogenic Reaction to Endotoxin.

In doses considerably smaller than those required to produce haemodynamic changes, endotoxin can elicit a

marked temperature response. In some animals (e.g. rabbit, dog, cat) which respond to endotoxin by an elevation of temperature, the relative lethal dose of endotoxin is much smaller than in species (e.g. rat and mouse) which respond by hypothermia (ATWOOD and KASS, 1964). In the rabbit which is particularly sensitive to the pyrogenic action of endotoxin, the lethality of endotoxin can be diminished by shaving the animal's fur to increase heat loss and lower the temperature (ATWOOD and KASS, 1964). Previously it was believed that elevation of temperature had a protective action in zymotic disease. BANNISTER (1960) showed that when environmental and body temperatures were increased in man, the toxic action of endotoxin was much greater than the same dose of endotoxin administered at normal temperatures. Today varying degrees of hypothermia are being employed in clinical practice. BLAIR ET AL., (1964) used hypothermia as an adjuvant to therapy in bacteraemic shock in man. ATKINS (1960) in a comprehensive review of the action of pyrogens emphasised the importance of endotoxin. Although endotoxin itself may have a direct effect on the hypothalamus (KASS ET AL., 1964) most recent work suggests that the main pyrogenic action of endotoxin is indirect and is brought about by releasing an endogenous pyrogen from polymorphonuclear leucocytes (BEESON, 1948;

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KING and WOOD, 1958; HERION ET AL., 1961; KAISER and WOOD, 1962).

Action of Endotoxin on the Nervous System.

DELAUNAY ET AL., (1948) believed that endotoxin produced its toxic effects by a direct action on the central nervous system.

PENNER and KLEIN (1952) in cross-circulation experiments in dogs, using Shigella endotoxin found that endotoxin had a direct effect on neural cells. WEIL ET AL., (1956) attempted to repeat this work and were unable to find any direct neural effect of the endotoxin. Indeed WEIL carried out cordotomy and vagotomy and found no direct action of endotoxin on the central nervous system. TARDIEU (1942) on the other hand, demonstrated that endotoxin was more potent when injected directly into the third ventricle.

FINE (1961) supported the view that endotoxin acts centrally and suggested that the toxic action of endotoxin was due to the relentless vasoconstriction caused by the action of endotoxin on the sympathetic nervous system. Blocking the coeliac ganglia with local anaesthetic had a protective effect on animals given endotoxin. REILLY ET AL., (1934) were among the first to suggest that the site of action of endotoxin was the autonomic nervous system and recently KASS ET AL., (1964) demonstrated that endo-

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toxin may act by a direct action on the hypothalamus.

Vasoactive Substances.

Several neurohumoral vasoactive substances have been implicated as mediators in the early stages of endotoxic shock.

SPINK ET AL., (1964) showed that histamine is released early in endotoxaemia. HINSHAW (1961) and SCHAYER (1960) also showed a high blood level of histamine after endotoxin. GREISMAN ET AL., (1964) studied the course of typhoid fever in man and found that endotoxin induced an increased vascular reactivity to catecholamines. ZWEIFACH ET AL., (1956) had previously demonstrated in the rat mesentery a similar marked hypersensitivity to catecholamines after intravenously administered endotoxin, and THOMAS (1956) used this hypersensitivity to adrenaline as a bioassay skin test for endotoxaemia. In addition to the increased sensitivity of catecholamines there was also an increased production of catecholamines from the adrenal glands (NYKIEL and GLAVIANO, 1961), which was suppressed by spinal cord section (EGDAHL, 1959). Serotonin release with increased concentration in the blood has been found after endotoxin administration (ARMIN and GRANT, 1957; WAALKES ET AL., 1957; DAVIS ET AL., 1959). Bradykinin, a vasodilator polypeptide is released by proteolytic enzymes and

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THAL and SARDESAI (1965) confirmed that such proteolytic activity is produced by endotoxin. SHERRY (1961) demonstrated that shock in general promotes proteolytic enzyme action.

Direct Action of Endotoxin on Vessels.

ZWEIFACH ET AL., (1956) suggested that endotoxin may act directly on the vessel wall. FROHLICH ET AL., (1962) administered endotoxin directly into the coronary circulation and did not demonstrate any diminution in blood flow. They concluded that endotoxin did not have a direct effect on the vasculature of the coronary vessels. VICK (1965) using isolated strips of vessels found that endotoxin did not have any in vitro effect on the smooth muscle of the vessel wall unless associated with blood as a perfusing fluid.

Changes in the Blood.

Blood Volume. In the early stages of hypotension secondary to endotoxin administration there was no change in the blood volume (GILBERT, 1960). In the later stages however, in some species, the total blood volume decreases. LILLEHEI and MacLEAN (1958) and PENNER and BERNHEIM (1942) showed a reduction in the plasma volume and a progressive rise in haematocrit in dogs. Recently in man, HOPKINS ET AL., (1965) have monitored the haemodynamic changes in shock. In human haemorrhagic shock there was a considerable

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reduction in blood volume. In septic shock, on the other hand, there was no definite pattern, the blood volume did not bear a direct correlation with the degree of shock and in the majority of cases there was no appreciable change in blood volume.

Haematological Effects. Several reports (e.g. DONALD ET AL., 1958) show that endotoxin produces a temporary leucopenia shortly after the endotoxin has been administered. This is subsequently followed by a polymorphonuclear leucocytosis which may be marked. In addition to its effects on the leucocytes, endotoxin causes a marked thrombocytopenia (STETSON, 1951; DAVIS ET AL., 1960; GREISMAN ET AL., 1964). Endotoxaemia produces a general upset in the clotting mechanism (MacKAY ET AL., 1958; THOMAS and WESSLER, 1964). Within minutes after intravenous endotoxin, the blood is hypercoagulable and later this is followed by a prolonged hypocoagulable state. HOROWITZ ET AL., (1962) showed an increase in platelet factor 3 after endotoxin. The vascular effects of endotoxin may be brought about by obstruction of the minute vessels with plugs of platelets, leucocytes or fibrin aggregates, the circulating level of these being acutely depressed in endotoxaemia (WEIL and SPINK, 1957; HARDAWAY ET AL., 1961).

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Metabolic, Enzyme and Hormone Changes.

Endotoxin has a marked effect on carbohydrate metabolism. WOODS ET AL., (1961) observed that endotoxins exert a stimulating effect on cell glycolysis remarkably similar to that of insulin. At first there is a marked increase in glycolysis. The liver glycogen is decreased (FUKUDA, 1963), and the blood glucose level rises. In the later stages there is a marked hypoglycaemia. It was previously believed that endotoxin had a direct effect on carbohydrate metabolism, but more recently SANFORD ET AL., (1960) have shown that the glycolysis is mediated by catecholamines released during endotoxaemia.

SCHAYER (1960) has demonstrated an increase in histidine decarboxylase, and BERRY and SMYTHE (1963) found a decrease in plasma tryptophan pyrrolase concentration. KONTTINEN ET AL., (1964) found an increase in the serum enzyme activity of glutamic oxaloacetic transaminase, lactic acid dehydrogenase and alpha-hydroxybutyric dehydrogenase and suggested that liver damage produced by endotoxin was the most likely source of the enzyme release.

In endotoxin shock in animals there is disruption of liver cell lysosomes with release of their contained enzymes (e.g. acid phosphatase, and B-glucuronidase). This leakage of enzymes from lysosomes can be prevented

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by pretreatment with cortisone. The permeability of liver cell lysosomes in endotoxaemia allows the activation of proteolytic enzymes with their dissemination causing tissue injury and contributing to the irreversibility of bacterial shock (JANOFF ET AL., 1962; 1963).

Lactic and pyruvic acid concentrations are both increased in endotoxaemia where there is tissue hypoxia and anaerobic metabolism. This metabolic acidosis appears common to many forms of shock (HUCKABEE, 1958).

EGDAHL (1959) and NYKIEL ET AL., (1959) demonstrated an increase in catecholamines in the adrenal vein after endotoxin and most previous reports have shown an increased output of adrenocortical hormones during endotoxaemia (e.g. MELBY ET AL., 1957). Rapidly fatal meningococcal septicaemia was believed to be associated with acute adrenal failure produced by adrenal haemorrhage (Waterhouse - Friderichsen syndrome). Recently however LEVIN and CLUFF (1965) demonstrated that the adrenal haemorrhage was the result of shock associated with endotoxaemia and was not the cause of the shock. The adrenal cortex was found to be very sensitive to damage when actively engaged in the manufacture of steroids. Haemorrhage when present, was mainly in the zona fasciculata of the adrenal cortex.

Immunological Aspects.

Although endotoxin has many pharmacological

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properties associated with the release of several vaso-active substances it is still difficult to assess whether endotoxin possesses an intrinsic toxicity or whether the initiating mechanism of endotoxic shock is an immunological response of the classical antigen-antibody type. The early rise in histamine concentration in the blood, noted by several workers after the experimental injection of endotoxin is also frequently observed during an antibody-antigen reaction (WEIL and SPINK, 1957).

LAWFORD and WHITE (1964) have demonstrated abnormal serum components in endotoxin treated rats. GILBERT and BRAUDE (1962), using E. coli endotoxin in rabbits noted a decrease in complement. They believed that the initial stage of endotoxic shock in dogs, involved an immune mechanism with decrease in complement and histamine release. An initial depression of serum properdin level was followed by increased values which in mice persisted for a few days (LANDY and PILLEMAR, 1956). Properdins are macroglobulins and ROWLEY (1964) suggested that properdins and natural antibodies may be identical.

The Role of the Reticulo-Endothelial System.

The reticulo-endothelial cells are specialised vascular endothelial cells adapted to remove colloidal, foreign or noxious particles from the blood. Endotoxin is cleared from the blood by the reticulo-endothelial

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system (BRAUDE ET AL., 1955). Tolerance to endotoxin results from the more rapid clearance of endotoxin by the R.E.S. (BEESON, 1947). ROWLEY (1960) noted an increased phagocytic activity of the peritoneal macrophages of mice after intraperitoneal endotoxin and LEE (1962) observed an inhibition of the R.E.S. clearance of fibrin caused by endotoxin.

The majority of the reticulo-endothelial cells are in the liver (KUPFFER cells), the red pulp of the spleen and in the lungs. At times the ordinary endothelial cells can take over the specialised R.E.S. activity. (This property was noted by ASCHOFF who first described the phagocytic principles of the reticulo-endothelial system). The R.E.S. can be blocked with thorotrast, colloidal carbon, or trypan blue. FINE ET AL., (1959) noted a diminution in the competence of the R.E.S. in haemorrhagic shock. An assay of the functional capacity of the R.E.S. was measured by the clearance of injected particles of carbon (BIOZZI ET AL., 1953) and p^{32}-labelled endotoxin (HOWARD ET AL., 1958).

The Shwartzman Phenomenon.

Shwartzman (1928) first described a reaction which consisted of an area of local necrosis of the skin at the site of injection of certain bacterial filtrates, when a similar filtrate was injected intravenously about

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twenty-four hours later. This reaction was known as the local Shwartzman Reaction. If both injections, similarly timed were given intravenously, a general reaction resulted with bilateral cortical necrosis of the kidneys as the most characteristic feature. LEE (1964) postulated a hypothesis of intravascular coagulation to explain the generalised Shwartzman Phenomenon. An initial intravenous injection of endotoxin activated the blood coagulation mechanism and resulted in a continuous formation of fibrin. The R.E.S. appeared competent to remove the fibrin no matter how large the primary dose of endotoxin. However, after a second intravenous injection 12-24 hours later, the phagocytic ability of the R.E.S. was impaired and generalised intravascular fibrin aggregates occurred, especially in the renal glomeruli, with subsequent ischaemia causing bilateral cortical necrosis.

The local Shwartzman reaction, described mainly in the skin of the rabbit has also been described in the hamster cheek pouch (GUSTAFSON and CRONBERG, 1963).

Although two correctly spaced injections are required to produce a Shwartzman reaction, in certain species, pregnancy can produce susceptibility to a single dose of endotoxin (WONG, 1962; GALTON, 1964).

GALTON (1964) also showed a Shwartzman reaction in pregnant hamsters after a single injection of Colchicine

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and concluded that colchicine may involve endotoxin derived from the intestinal flora.

Endotoxin and Allergic Reactions.

The effects of endotoxin resemble anaphylaxis not only at the shock stage but also in the milder forms of reaction. Stetson (1951) studied the effects of intradermal injection of endotoxin as an antibody-mediated reaction and compared the effects with those of the tuberculin reaction in rabbits. The response to tuberculin is an allergic reaction and its hallmark is the delay in the onset of the local inflammatory reaction at the cutaneous injection site. The local effect becomes marked at twenty-four hours. In contrast, endotoxin causes a reaction to take place much faster and to disappear sooner. WEIL and SPINK (1957) considered that endotoxin produced an "anaphylactoid" reaction with the early production of histamine associated with a decrease in complement. In order to account for the differences of tolerance and hypersensitivity to endotoxin, SKARNES and CHENDID (1964) postulated that if the amount of antibody exceeded the dose of antigen, protection was evident, and if the dose of antigen exceeded the antibody, an increased sensitivity occurred. Endotoxin can produce similar pharmacological effects whether or not the animal has been previously infected by the bacteria. This has been considered by

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some, to be due to antibody production, produced by the gram-negative bacteria, endogenous to the lower alimentary tract. KOSTKA and STERZL (1962) noted that the serum of pigs removed from their mothers at birth, contained complement but no E. coli antibody, and that the addition of endotoxin to the serum of those pigs did not cause any inactivation of the complement. WHITBY ET AL., (1961) found that after endotoxin administration there was a general release of substance against the enterobacteria which showed the specific activity of antibody.

The antibodies to endotoxin appear to be 19S natural antibodies and are located mainly in the macroglobulin fraction of the plasma proteins (LO SPALLUTO ET AL., 1962). WOLF ET AL., (1964) by immuno-electrophoretic studies, showed that endotoxin produced a macro-globulin precipitation line that included several antibody specificities of which the antibody to the homologous endotoxin was merely one. The enhanced resistance to infection with other bacteria after administration of endotoxin may be due to the cell destructive action of endotoxin with the liberation of D.N.A. breakdown products which act as a general stimulus for antibody production (BRAUN and KESSEL, 1964).

There has been controversy about the intrinsic toxicity of endotoxin for experimental animals reared in

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a sterile environment. Recently KIM and WATSON (1965) reported that endotoxin had intrinsic toxicity independent of an antibody-antigen reaction. In experiments in colostrum-deprived pigs, kept in a sterile environment they were unable to detect immunoglobulins by serological and immuno-electrophoretic methods. Those pigs however were susceptible to the lethal action of endotoxin. In contrast, colostrum fed pigs, showed a significant level of immunoglobulins in their serum and had an increased resistance to the toxic effects of endotoxin.

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SUMMARY.

The precise chemical structure of endotoxin is not known. The endotoxin of gram-negative bacteria is a complex lipopolysaccharide with a high molecular weight. It is antigenic; in the experimental animal it evokes an antibody response. The antibodies produced, however, appear to be mainly in the 19S macroglobulin fraction of the plasma proteins. Although endotoxin is highly toxic, resistance and tolerance can be acquired. The reticulo-endothelial system plays an important part during endo-toxaemia. The Shwartzman reaction, first described in rabbits given gram-negative bacterial filtrates, appears to be mediated by an antigen-antibody reaction with fibrin deposition.

Minute doses of endotoxin produce a marked pyrogenic response in many species of animal. Carbohydrate metabolism and serum enzyme changes occur, and there are marked haemodynamic changes in experimental animals given endotoxin. Many vasoactive substances are released. In the blood an early leucopenia is followed later by a poly-morphonuclear leucocytosis. Thrombocytopenia occurs and multiple blood coagulation defects are observed.

B) EXPERIMENTAL STUDIES OF THE ACTION OF ENDOTOXIN ON THE MICROCIRCULATION.

i. Introduction.

Endotoxins, the lipopolysaccharides, produced in the capsules of gram-negative bacteria, have been used extensively in recent years in experiments to understand the pathogenesis of bacteraemic shock in animals and man. Intravenously administered endotoxin brings about a rapid fall of blood pressure in animals and man. The effect of the endotoxin appears to be dominantly in the peripheral vascular bed. GILBERT (1960) suggested that the peripheral pooling produced by endotoxin could be caused by either constriction of the outflow vessels or dilatation of the inflow vessels. Although several observers had studied the microcirculatory changes there had been no direct evidence for either of these mechanisms.

The immediate effect of endotoxin on the microvasculature may not be a direct effect on the vessel walls but may be mediated by means of an antibody-antigen reaction (STETSON, 1955) or vasoactive substances may be liberated through interaction with factors in the blood (VICK, 1963), in the tissue cells, or in mast cells near the endothelium of the vessel wall. Histamine, catecholamines, serotonin, acetylcholine, bradykinin, and neural factors have been suggested as important in the

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early stages of endotoxic shock (HINSHAW ET AL., 1960; DAVIS ET AL., 1961; JACOBSON ET AL., 1964; KOBOLD ET AL., 1964; VICK, 1964).

Direct visualisation of minute vessels, studied in vivo in animals given endotoxin may help to indicate the initial humoral mechanisms involved.

ii. Materials and Methods used in Experimental Studies.

Animals: Male Golden Hamsters (Mesocricetus auratus) weighing 90-110 G. were used in the experiments. They were housed individually in plastic cages and were given unlimited food (commercial pellets - Purina Laboratory) and free access to water. For the endotoxin studies only animals without previous experience of endotoxin were used. This precaution was necessary to prevent the complications of a Shwartzman reaction or of "adaptation" to endotoxin.

Endotoxin: Dessicated lipopolysaccharide endotoxin extracted from E. coli 026:B6 by the modified Boivin trichloracetic acid method was obtained from Difco Laboratories, Detroit, Michigan. The $L.D._{50}$ for the Webster Strain of white mice was less than 500 micrograms. The endotoxin was made up in sterile, pyrogen free Ringer's Solution (Abbot Laboratories). A crude extract of E. coli 026:B6 antigen and a further solution of a sterile filtrate of a week old pure culture of an E. coli

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obtained from the skin of a burned patient were also employed. The endotoxin preparations were injected in 0.05 ml. volumes into the cheek pouch and the local effects on the minute vessels observed. In additional experiments, a larger dose of E. coli endotoxin was given systemically (into the femoral vein) and the local effects in the Cheek Pouch were observed.

iii. Results.

Topical Action of Endotoxin. The results of the local applications of 100 micrograms 026:B6 lipopolysaccharide, 500 micrograms of the same endotoxin, 0.05 ml. of a crude antigen preparation, and 0.05 ml. of a sterile filtrate of an old culture of E. coli are given in Main Tables 27 to 30 and Supporting Tables 74-88. The changes in cross sectional areas of the arteries and veins caused by the injection of 100 micrograms of lipopolysaccharide are illustrated in Figure 16.

Endotoxin injected locally caused a dilatation of the arteries and constriction of the veins. Of the vasoactive substances which had been applied to the cheek pouch in previous experiments to assay their effects on the microcirculation, only histamine produced the same dissociated action on the minute vessels. Endotoxins used in different doses and as different types of preparation all gave

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similar effects when applied locally. There did, however, appear to be a quantitative response to the dose of endotoxin which was injected.

Action of Intravenous Endotoxin. When endotoxin (2 mgm. lipopolysaccharide E. coli 026:B6) was injected intravenously (into a cannula in the femoral vein) there was uniform constriction of the arterioles with a decrease in the blood flow to the capillary bed (Main Table 31, Supporting Tables 89-92, and Figure 17). Stasis of blood occurred in the capillary and post-capillary venous vessels. The veins constricted only slightly. This vasoconstrictive effect of intravenously administered endotoxin was in marked contrast to the topically administered toxin where the primary response was a vasodilation of the small arteries.

Action on Platelets of Intravenous Endotoxin. 2.0 mgm. E. coli lipopolysaccharide were injected intravenously in 0.5 ml. Ringer's solution. The injection was made after cannulation of the femoral vein. The hamster was anaesthetised and with the help of the dissecting microscope the femoral vein was cannulated just below the inguinal ligament. A polyethylene tube — "Intramedic" gauge P.E. 10 — was introduced and the intravenous injection made. Direct microscopy of the cheek pouch was carried out before and after the injection of the endotoxin.

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White aggregates were noticed in several of the post-capillary venules. These "platelet" aggregations increased in size and either completely blocked the vein or else — more frequently — parts of the mass broke off and were carried away as platelet emboli. In the larger vessels the broken fragments gathered speed. It was considered that owing to their size the emboli would be carried round the circulation and become impacted in the vascular capillaries of the pulmonary circulation. Marked dyspnoea was a uniform finding in all the hamsters after intravenous injection of endotoxin (2.0 mgm. was greater than the $L.D._{100}$ for the hamsters). Only one hamster died within one hour of injection. Death usually occurred between 12-36 hours after the injection. Showers of platelet emboli were observed in the cheek pouch on the venous side 5-20 minutes after the intravenous injection of endotoxin. By 30 minutes only a rare white embolus could be observed. Great effort was taken to try to observe white aggregates on the arterial side. No large aggregates were seen. Very occasional small masses were observed on the arterial side but these masses were observed as minute granules less than 5 microns in diameter. Endotoxin caused platelet aggregation and, in the post-capillary venules where the flow rate was slow, white clumps of adhesive platelets occurred. In addition, the marked vasocon-

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striction of the pre-capillary resistance vessels (described above) caused considerable reduction in the flow rate in the microvasculature. The sequestration of platelets which was observed in the cheek pouch was confirmed by carrying out platelet counts before and 30 minutes after the administration of intravenous endotoxin. Blood was collected by direct cardiac puncture and transferred immediately to an "unopette B.D." the platelet count being carried out on a Phase microscope using a double counting chamber, two counts being made on each specimen examined. The results (shown in Main Table 32) show a rapid reduction in the platelet count after the intravenous administration of endotoxin. The normal platelet count in hamsters was found to be 750,000 per c.mm.

iv. Discussion.

The action of endotoxin in animals or man is complex and has been the subject of considerable investigation in recent years. The numerous conflicting views about the mode of action are no doubt due to the multiple late chain reactions which occur when shock is well established. The initiating mechanisms which bring about the early changes which occur on the administration of endotoxin are difficult to assess as compensatory systemic reactions, are promptly produced masking the initial trigger mechanism.

If the endotoxin is given locally into the cheek pouch,

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the initial changes observed are unlikely to be due to changes caused by vasoactive substances produced at distant sites (e.g. in the adrenal gland). The molecular weight of endotoxin is large (mol. wt. 10^6) (RAVIN, 1963), and as there are no lymphatics in the cheek pouch (SHEPRO ET AL., 1963) the endotoxin must stay locally for a considerable time (SCHRADER ET AL., 1964) and not be carried away to produce secondary effects in distant organs or tissues. The endotoxin may act itself on the endothelium of the vessel walls, (ZWEIFACH ET AL., 1956; RUBENSTEIN ET AL., 1962) or, more likely in view of its large molecular size, may act indirectly by releasing vasoactive substances from the tissue cells, tissue fluid, endothelium or blood (GILBERT, 1960). From the visually recorded changes in the microcirculation, histamine, or a histamine-like substance appeared to be active in the very early stages after locally applied endotoxin. In 1919 DALE and LAIDLAW described the effects of the administration of a large dose of histamine. This histamine shock had many of the haemodynamic characteristics of endotoxic shock.

After intravenously administered endotoxin there is both an increased production of catecholamines and also an increased sensitivity to the actions of catecholamines (ZWEIFACH ET AL., 1956; ROSENBERG ET AL., 1959). This increased sensitivity has been used as a "bioassay" test for

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the presence of endotoxin (THOMAS, 1956; FRITZ ET AL., 1962). Vasoconstriction caused by increased sympathetic tone or by release of catecholamines from the adrenal gland must be reactions, secondary to peripheral pooling of blood. If the catecholamines had a primary role, hypertension should be produced and not hypotension — which is a very early observed sign in all species of animals given endotoxin.

Microcirculatory Changes.

DELAUNAY ET AL., (1948) observed the effect of intraperitoneal endotoxin on the mesenteric and omental vessels of the rabbit and guinea pig. At first there was arterial constriction and later arterial dilatation and stasis in the capillaries and veins. ALGIRE ET AL., (1952) also observed the vascular effects of endotoxin in the microcirculation. In the skin flap of the mouse, arterial dilatation associated with stasis of blood in the microvasculature occurred after endotoxin. More recently ZWEIFACH (1964) observed that when endotoxin was injected into the wall of the small intestine of the rabbit, venous stasis and petachiae formation were produced. In the present study endotoxin, injected locally into the hamster cheek pouch produced a histamine-like reaction on the minute vessels — the arterioles dilated, the small veins

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became constricted and the capillaries and post-capillary venules appeared congested. After intravenous endotoxin, in response to the hypotension subsequent to peripheral pooling, vasoconstrictor substances were produced. SCHAYER (1962) suggested that homeostasis in the peripheral vascular bed is achieved by a balance between endogenous histamine formed in the peripheral vascular bed and systemic catecholamines. Histidine decarboxylase is present in the vascular endothelial cells and after endotoxin administration its concentration is increased. In the terminal stages of endotoxic shock, when the small vessels no longer respond to catecholamines the plasma concentration of histamine becomes high.

Endotoxin and Blood Coagulation.

With the administration of endotoxin there is a marked increase in the coagulability of the blood (McKAY and SHAPIRO, 1958). This hypercoagulable state of the blood is rapidly followed by a hypocoagulable state (TURPINI and STEFANINI, 1959; HARDAWAY and JOHNSTON, 1963). Thrombocytopenia, a lowered concentration of fibrinogen, and an increase in endogenous fibrinolysins can be detected.

BRAUDE ET AL., 1955 and HERRING ET AL., (1963), in experiments using labelled endotoxin showed that the platelets rapidly took up the endotoxin. Later the endo-

toxin was removed from the bloodstream by the reticulo-endothelial system and most was found in the liver, spleen, and lungs (BRAUDE ET AL., 1955; CREMER and WATSON, 1957).

In vivo studies, using systemically administered endotoxin reveal a marked sequestration of platelets, and thrombocytopenia. In 1949, YOUNGER and ALGIRE observed large whitish masses in the circulating venous blood of the transparent skin flap chamber of the mouse after injecting polysaccharide from S. marcescens.

SILVER and STEHBENS (1965) noted platelet aggregation in the ear chambers of rabbits after typhoid lipopoly-saccharide and ROBB (1965) noted platelet micro-emboli in the mesentery of rabbits given endotoxin.

In the hamster cheek pouch platelet aggregations were observed in the post-capillary venous vessels and micro-emboli were frequent 5-20 minutes after the injection of intravenous E. coli lipopolysaccharide. Platelet counts showed marked thrombocytopenia when the peripheral blood was examined 30 minutes after the intravenous endotoxin injection. Aggregations of platelets have been observed when endotoxin is added to plasma in vitro (DES PREZ, 1964; REAM ET AL., 1965).

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V. Summary and Conclusions.

When endotoxin was applied locally to the microvasculature of the hamster cheek pouch a histamine-like response was observed with arterial dilatation and venous constriction. Intravenous administration of endotoxin produced a vasoconstrictor response in the minute vessels. Platelet aggregations were observed in the minute vessels and venous emboli were frequent. Thrombocytopenia was noted.

SECTION VI.

BIOASSAY OF PATIENTS' PLASMA FOR VASOACTIVE SUBSTANCES.

a) Introduction.

b) Vasoactivity of serum and plasma of normal persons.

c) Vasoactivity of plasma of patients in shock associated with infection.

d) Vasoactivity of plasma of patients with severe dermal burns.

e) Discussion.

BIOASSAY OF PATIENTS' PLASMA FOR VASOACTIVE SUBSTANCES.

A) Introduction.

Blood which has been allowed to clot, or serum from normal animals or healthy human beings has long been known to have vasoconstrictor properties (STEVENS and LEE, 1884; RAPPORT ET AL., 1948). Plasma, however, shows a considerable variation in range of vasoactivity. Vasoactive substances appear in the blood to maintain the stability of the cardio-vascular system.

Bacteraemic shock produces a grave upset in the cardio-vascular system with marked peripheral pooling of blood (GILBERT, 1960). Several experiments were carried out to test the vasoactivity of plasma, especially in patients where shock was associated with overwhelming infection. In animal experiments endotoxins have been shown to produce a marked catecholamine response (GREISMAN ET AL., 1964). In patients in shock, vasopressor substances have been used frequently to restore normal systemic arterial blood pressure. If endogenously produced vasoconstrictor substances were already acting on the peripheral vessels, the addition of further vasopressors may be of doubtful value. The hamster cheek pouch was used as a model to assay the effect of plasma on the minute vessels.

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Methods.

Human serum was collected and tested. (Whole blood from healthy persons was allowed to clot spontaneously and then centrifuged.) Specimens of plasma used in the experiments were obtained by collecting blood from a large peripheral vein into a heparinised plastic syringe. The blood was spun immediately. Only the top layer of plasma was used, care being taken not to include any of the buffy layer. 0.05 ml. undiluted plasma was injected locally into the hamster cheek pouch and changes in the cross-sectional area of the minute vessels observed over a 60 minute period.

Results.

B) Normal Human Serum.

Normal human serum caused vasoconstriction (Main Table 33 and Supporting Tables 93-95). The initial vasoconstriction of the small arteries was prompt, and the vessels did not return to their control size during the 60 minutes of observation. There was, however, very little venous vasoconstriction. This vasoconstrictor activity has been shown to be due mainly to serotonin released from disintegrating platelets. (RAPPORT ET AL., 1948; HUMPHREY and JAQUES, 1954).

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Normal Human Heparinised Plasma.

In several experiments using heparinised plasma from healthy human volunteers, only slight arterial vaso-constriction was observed. Main Table 34 and Supporting Tables 96-98 record the activity of plasma from three persons. The sera from two of these healthy persons was also tested and was found to have much greater vaso-constrictor activity than the heparinised plasma.

Hospital Inpatients.

Heparinised plasma was obtained from patients in hospital. Some patients were post-operative and some were receiving medical investigation or treatment. None of these patients was in shock and no hypertensive patients was included. Only slight vasoconstriction was observed. The vasoactivity of plasma from these patients did not appear to differ from the vasoactivity of plasma from the healthy volunteers.

C) Patients in Septic Shock.

Heparinised plasma samples, taken from patients who were in shock, and who at the same time had positive blood cultures for gram-negative organisms were markedly vaso-constrictor (Main Table 35 and Supporting Tables 99-101). In the experimental bioassay of the plasma of one of these patients, phenoxybenzamine was added to the cheek pouch

at 30 minutes after the injection of the plasma. There was a prompt improvement in the circulation of the cheek pouch vessels but the arteries did not return completely to their control size.

Patient in Bacteraemic shock and receiving intravenous vasopressor.

The patient, a female aged 79 years, was admitted to hospital acutely ill with an empyema of gall bladder and acute pancreatitis. Cholecystostomy was performed. Post-operatively the patient was hypotensive. Blood cultures were positive for Klebsiella-aerobacter species. With an intravenous noradrenaline infusion the patient's systolic arterial blood pressure was maintained at 80 mmHg. There was profound coldness and cyanosis of the extremities. The vasoactivity of the plasma is shown in Figure 18, and in Supporting Table 106. The plasma (0.05 ml.) caused marked constriction of the arterioles of the hamster cheek pouch — the arterial blood flow almost ceased. There was little change in the venous diameters. With the arterial inflow considerably reduced and the venous capacity almost unchanged, there was marked stasis and aggregation of the erythrocytes in the minute vessels. Phentolamine (10 micrograms) was injected into the cheek pouch 30 minutes after the plasma injection. The arterial spasm showed

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immediate signs of being overcome and the venous flow commenced to speed up even although there was no change in venous calibre. The blood flow in the microcirculation, which was almost completely stagnant improved considerably after the adrenolytic drug. The calibre of the arterioles did not however return completely to control level.

D) Heparinised Plasma from Burned Patients.

Plasma samples from four persons who had received severe burns (30-55% body surface) were assessed for vaso-activity. The plasma was withdrawn from the patients 3-5 weeks after the burns. At the time of sampling all the patients had normal blood pressures and had adequate renal function. Although infection was a major problem at this time, the patients did not have any appreciable pyrexia. Blood cultures were negative and shock was absent. The plasma specimens of three out of four of these patients had most pronounced vasoconstrictor properties (Main Table 36 and Supporting Tables 102-105).

E) Discussion.

The identification of gram-negative bacterial endotoxins in blood and tissues cannot be achieved readily in clinical practice. Endotoxin is identified usually by its biological properties - e.g. by its ability to produce fever (KEENE ET AL., 1961), or dermal necrosis (THOMAS, 1956;

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LARSON ET AL., 1960; FRITZ ET AL., 1962), or death of the injected animal (FINKELSTEIN, 1964). Under experimental conditions endotoxin can be identified with greater precision by its radioactive or fluorescein label. (BRAUDE ET AL., 1955; RUBENSTEIN ET AL., 1962). That endotoxin is the cause of the cardiovascular collapse in patients with severe gram-negative infection has not been universally accepted. Nevertheless in man the action of endotoxin has been observed:

(a) after the administration of typhoid vaccine (ALTSCHULE ET AL., 1950).

(b) after administration of endotoxin for therapeutic purposes (BRUES and SHEAR, 1944).

(c) after experimental administration (BANNISTER, 1960; GREISMAN ET AL., 1964).

Profound cardiovascular effects have been observed after accidental transfusion of infected blood (BRAUDE ET AL., 1953). In the assay of the effects of endotoxin in patients' blood, the plasma may show varying types of vasoactivity during different phases of the endotoxaemia and shock. Several endogenous vasoconstrictor substances have been identified in plasma — catecholamines, serotonin, angiotensin. The precise nature and quantity of vasoconstrictor substances in plasma is sometimes difficult to determine.

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/ ZWEIFACH and METZ (1955) in studying the vaso-activity of the plasma of 90 hospital patients found that in some the plasma was vasoconstrictor and in others, non reactive or vasodilator.

PAGE (1943) demonstrated that the vasoconstrictor substance (adrenaline) present in the plasma of burned dogs, and in dogs subjected to haemorrhage, was different from the vasoconstrictor substance (angiotensin II) present in the plasma of hypertensive patients or dogs, and that each of these vasoconstrictors was different from the vaso-constrictor property or normal serum (serotonin). In experiments reported previously (see above) when endo-toxin was given intravenously there was aggregation of platelets in the small venules, and platelet emboli. Thrombocytopenia occurred. DAVIS ET AL., (1960) showed that in dogs after the intravenous administration of endotoxin, the serum serotonin level fell and the plasma serotonin level rose slightly. The low serum serotonin level could be explained by the associated thrombocyto-penia which was also observed.

ARMIN and GRANT (1955) used the denervated rabbit ear to assay the vasoactivity of blood from donor rabbits which had either been subjected to haemorrhage or had been stimulated by struggling. After haemorrhage the vaso-constrictor properties appeared to be due mainly to cate-

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cholamines as adrenalectomy diminished the vasoactivity. In the rabbits that had been struggling adrenalectomy was without effect, the vasoconstrictor appeared to be due mainly to serotonin release. In a later paper (1957) ARMIN and GRANT considered that the vasoconstriction of rabbit blood following endotoxin, resembled serotonin.

In the patients who were studied in the present report overwhelming sepsis associated with shock was accompanied by marked vasoconstrictor properties of the plasma. The vasoconstriction was relieved in greater part by the use of an alpha receptor blocker. Some vasoconstrictor activity, however, appeared to be due to non-catecholamine substances.

Use of Vasoconstrictor Drugs.

The use of the noradrenaline infusion in the ill patient in septic shock increased the systolic arterial pressure at the expense of tissue perfusion.

The almost complete cessation of blood flow observed in the hamster cheek pouch after the injection of the patient's plasma, was overcome by the use of phentolamine. It would appear that except for very urgent temporary use to maintain central arterial blood pressure, the use of vasoconstrictor drugs should be reserved for those cases where endogenous vasoconstrictor substances are inadequate. A bioassay of the vasoactivity of the plasma of all the

shocked patients in this study did not suggest, however, that there was any inherent defect in the production of vasopressor substances.

Burns. In three out of the four patients with severe burns marked vasoconstriction was associated with the plasma even although the patients' vital signs appeared stable. Similar constrictor properties, found by PAGE (1943) in the plasma of dogs that had been subjected to experimental burns, were considered to be due to an increased concentration of catecholamines.

Endotoxins.

In patients where severe gram-negative infections were associated with shock, the vasoconstrictor properties which were demonstrated in the plasma did not appear to be specific for endotoxin but rather to be the result of endogenous vasoconstrictor substances released in response to hypotension. The assay of these haemodynamic substances produced during the different stages of endotoxaemia may nevertheless allow a more rational approach to the use of vasoactive drugs in therapy.

BACTERAEMIC SHOCK AND THE MICROCIRCULATION.

PART II.

CLINICAL OBSERVATIONS.

SECTION VII.

BACTERAEMIC SHOCK - CLINICAL OBSERVATIONS

A) Introduction.

B) Methods of Study.

C) Clinical Findings.

D) Management and Therapy.

E) Discussion.

F) Conclusion.

BACTERAEMIC SHOCK - CLINICAL OBSERVATIONS

A) Introduction.

Since the introduction and widespread use of antibiotic therapy in hospital practice, certain bacterial species, previously considered to have little pathogenicity for man are now being recognised as causative agents of severe and sometimes fatal disease. At present among the more important "opportunist" pathogens are the gram-negative bacilli of the Escherichia, Klebsiella-Aerobacter, Proteus and Pseudomonas genera, many of which comprise a part of the normal bacterial flora of man. Recent reports (FINLAND ET AL., 1959; MAIZTEGUI ET AL., 1965) have confirmed the marked increase of gram-negative bacterial infections in hospital. Although hypotension has been described from time to time in association with bacterial infection (e.g. LAENNEC, 1838) it was WAISBREN, who in 1951 first indicated that a precise shock-like state could be seen in some patients with gram-negative bacteraemia. The mortality from gram-negative bacteraemia becomes very high when shock supervenes.

BORDEN and HALL (1951) and BRAUDE (1953) were the first to suggest that gram-negative bacteraemic shock was caused by endotoxin. That the shock-like state associated with bacteraemia is due to endotoxin cannot, however, be confirmed with certainty as there is at present no precise

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chemical method of assaying the endotoxin in the blood.

When purified endotoxins from gram-negative bacteria are injected intravenously into the experimental animal, several reactions take place, including fever, shock, peripheral vasoconstriction, leucopenia and then leucocytosis. Patients suffering from bacteraemia due to gram-negative infections similarly exhibit rigors, chills, pyrexia and leucocytosis.

Bacteraemic shock is more commonly seen in the elderly rather than the young, and in those who have intercurrent diseases, e.g. cirrhosis, diabetes or underlying malignant disease. This would suggest a predisposing immunological defect which makes the normal defence mechanisms more vulnerable to the bacterial toxins.

Manipulation, instrumentation (e.g. urethral catheterisation) or surgical treatment are frequently precipitating factors in the production of bacteraemic shock, caused no doubt by release into the blood stream of a sudden large quantity of bacteria or their toxins from a localised infective site. If bacteriological specimens or blood cultures are not obtained routinely in cases of hypotension where the cause is not obvious, bacteriological factors contributing to the hypotension may readily be overlooked.

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Clinical Observations on Bacteraemic Shock.

B) Methods of Study.

In the surgical intensive care unit of the Peter Bent Brigham Hospital, of the Harvard Medical School, Boston, many seriously ill patients were treated under the direction of the Surgeon-in-chief, Dr. Francis D. Moore.

Several selected studies were carried out on these patients by the clinical and research surgical staff. While parallel respiratory, metabolic, renal and haemodynamic studies were being carried out, I studied in detail the significance of bacterial infections in these ill surgical patients.

Bacteriological specimens from the patients were investigated in the surgical bacteriological laboratory under the direction of Dr. Carl W. Walter, M.D., Clinical Professor of Surgery and Dr. Ruth Kundsin, Sc. D., Microbiologist to the department of surgery. The nomenclature of the enterobacteriaceae isolated corresponded to the classification of EDWARDS and EWING (1962).

During the year, October 1963 - September 1964, among the patients treated and studied in the intensive care unit, there were 31 patients who had prolonged hypotension associated with bacterial infection. Twelve of these patients had been transferred from other hospitals.

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C) Clinical Findings.

Twenty-three (74%) of the thirty-one patients died. Main Table 37 gives the major site of disease in the patients. Unlike most previous series where bacteraemic shock was most common in elderly male patients with urinary infections, or in young women with septic abortions, in the present series, due to the selection associated with the admission of patients to the surgical intensive care unit, a wider variety of conditions was found with related bacteraemic shock.

The largest group of patients, (twelve cases) had abdominal injuries, peritonitis, or abdominal complications as sequelae to surgical procedures. Eight patients had sepsis associated with extensive burns. Urinary tract disease (two cases), biliary disease (three cases), and conditions affecting the female reproductive tract (two cases) were included. In a final group of four patients who were on maintenance immunosuppressive drug therapy following renal or hepatic homotransplantation, overwhelming bacterial infections played a major part in the final stages of the patients' illnesses. In this complicated group it was not possible to separate the important contributing effects of chemotherapy and "host-versus-graft" immunological rejection phenomena, from the obvious toxic action of severe intercurrent infection.

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Bacteraemia.

The thirty-one patients were selected for study as episodes of hypotension appeared to be associated with severe infection as the evident clinical cause. Blood cultures revealed a bacteraemia in twenty of the thirty-one patients. Main Table 38 lists the positive blood culture findings. The one gram-positive organism was a staphylococcus aureus. (Phage type U.C. 18). KUNDSIN ET AL., (1964) have shown that U.C. 18, a newly identified phage lyses many hospital-acquired staphylococci which were untypeable by the usual phages in routine use.

Nineteen of the positive blood cultures (96%) were gram-negative organisms. Escherichia coli was the commonest organism. In only one case were two organisms identified in the blood cultures (Pseudomonas aeruginosa and Klebsiella-Aerobacter species).

Bacteriological Data.

In all the patients included in the clinical study cultures from respiratory and urinary tracts, skin, wounds and blood, were obtained routinely. Additional bacteriological specimens were taken during operative procedures or as indicated by the patient's progress.

At post-mortem examination, bacterial cultures of lung, heart blood and other organs and tissues were taken and compared with the bacteriological cultures obtained

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during life. Main Table 39 lists in detail the bacteriological data of all the patients. Several organisms were frequently isolated from multiple sites in one patient. Although it was sometimes difficult to assess quantitatively, the importance of the different genera of bacteria isolated, one species was frequently found to be dominant and if blood cultures were positive it was commonly the dominant organism which was isolated.

Clinical Features.

Twenty-nine of the thirty-one patients in the present series developed shock in hospital. Symptoms were usually preceded by manipulation or surgical operation. The "initiating" event preceded clinical signs by 12-48 hours. At the onset chills and rigors were characteristic and later pyrexia occurred. The skin was cold and clammy; cyanosis and mottling were present in the later stages. Vomiting and diarrhoea, although frequent, were not always present. In four cases deep jaundice occurred and the mechanism of its production was not easily explained on clinical observations. Most of the patients remained conscious and alert. Later however, mental confusion or stupor was noted. Death usually supervened within two to three days of the onset.

Sex and Age.

In the selected group of patients with bacteraemic

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shock there were nine females (six of whom died) and twenty-two males (seventeen of whom died). Ages ranged from twenty-four years to eighty-three years, and the median age was fifty-eight years.

Renal Function.

In bacteraemic shock, renal insufficiency was a cardinal problem. Of the thirty-one patients, twenty-one had renal impairment, manifest as oliguria or anuria associated with a blood urea nitrogen (BUN) level above 50 mgm. per 100 ml. (A blood urea nitrogen level of 50 mgm. per 100 ml. is equivalent to a total blood urea concentration of 103.5 mgm. per 100 ml.) Figure 20 shows the BUN concentration in the patients at the time of shock. In one case of renal failure peritoneal dialysis was carried out and in other five cases haemodialysis was performed, sometimes on two or three occasions. There was however only one survivor in the group where dialysis had been employed.

A careful watch on renal function was maintained and where the hourly output of urine fell below 30 ml. energetic measures were taken to attempt to overcome the renal failure. A trial dose of mannitol was sometimes effective in improving renal function but where shock proved resistant to therapy, urinary output decreased progressively and at post-mortem examination acute tubular necrosis was a prominent feature.
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Respiratory Complications.

In the shocked state respiratory problems were common and in most cases were the major immediate cause of death. Hypoxia was frequent. It was necessary to carry out tracheostomy in eleven patients and endotracheal intubation in an additional four patients, to assist or control respiration because of progressive hypoxia. Immediate, though temporary, improvement in the blood gas status was usually achieved by tracheostomy associated with controlled respiration. In four patients tracheostomy had been carried out in the terminal stage of the illness; in the other seven cases serial tracheal cultures were carried out. Gram-negative bacterial infection of the trachea was common and in five patients, the same gram-negative organisms which were isolated from endotracheal swabs were later isolated in blood cultures. Although tracheostomy appeared to be immediately life-saving in cases of severe oxygen lack, when the tracheostomy was maintained for several days in association with artificial mechanical respiration, severe tracheitis and infection frequently supervened, pulmonary compliance progressively decreased with hypoxia and hypercarbia, and death occurred finally from respiratory and circulatory failure.

In shock associated with bacterial infections in the

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early stages where a metabolic acidosis was found, there was compensatory respiratory alkalosis (hypocarbia). In the later stages however when respiratory function became impaired there was a final mixed respiratory and metabolic acidosis.

At post-mortem examination the pulmonary lesion was usually a combination of tracheobronchitis, broncho-pneumonia and atelectasis. Multiple small peripheral emboli were frequently found and there was sometimes evidence of aspiration. Pulmonary oedema appeared to be a common terminal phenomenon.

Haematological Findings in Bacteraemic Shock.

Blood Volume Measurements.

Blood volume estimations were carried out frequently in the patients during hypotensive episodes. The plasma volume was estimated either by using Evan's Blue (T1824) or 1^{131}albumen. The large vessel (venous) haematocrit was measured and on the assumption that the total body haematocrit was 0.90 of the large vessel haematocrit (MOORE, 1959), the total blood volume was calculated. Occasionally the red cell mass was estimated independently by labelling the patient's own red cells with Cr^{51} and retransfusing the autogenous isotope-labelled cells. A semi-automatic machine (the 'Volemetron') was used at the bedside on some occasions to give an immediate direct

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reading of blood volume using I^{125}-labelled albumen.

The results of blood volume measurements taken in fifteen patients at the time of shock is illustrated in Figure 21. The observed results were plotted against the expected blood volumes which were obtained from a nomogram giving the blood volume as a function of the patient's age and weight (DAGHER ET AL., 1965). In septic shock the observed blood volume did not appear to be lower than the expected volume. On the contrary there appeared to be an expansion of the vascular space and the effective blood volume to maintain an adequate arterial blood pressure was sometimes considerably in excess of the expected normal value. Main Table 41 shows the changes in the blood volume of a patient in shock associated with generalised peritonitis. Intravenous fluids were given in an attempt to restore systemic arterial blood pressure without causing undue elevation of the central venous pressure. On the second post-operative day when the blood pressure became stable the blood volume had expanded to 6,720 ml. In the course of the following five days, as clinical improvement progressed, the blood volume fell to 4,700 ml. being about the expected normal blood volume for the patient. The central venous pressure had been monitored throughout the period of hypotension and had never exceeded 15 cm. water.

<u>Leucocytosis</u>.

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Leucocytosis.

Eighty-two per cent of the patients in bacteraemic shock had a leucocytosis over 10,000 cells per c.mm. (43% having a white cell count over 20,000 per c.mm. and 18% over 30,000 per c.mm.). The leucocytosis was due to an increase in the polymorphonuclear leucocytes. The median white blood count was 18,000 per c.mm. and the highest recorded leucocyte count was 43,000 per c.mm. In only one patient was leucopenia noted at the time of hypotension — the patient was on immuno-suppressive drug therapy following renal homotransplantation. In this patient the leucocyte count remained under 2,000 per c.mm. for the five days preceding death from overwhelming sepsis.

Coagulation Mechanisms.

Prothrombin estimations:- Prothrombin content of the blood was estimated by (modified) Quick's method and the concentration present was expressed as a percentage of the normal control. In the twenty-one patients where the prothrombin content was estimated, values varied from 10-84 per cent of normal. The median value was 40.5 per cent.

Fibrinogen:- Fibrinogen levels were assessed only in those patients with haemorrhagic manifestations. In two patients the fibrinogen concentration was less than 100 mgm. per cent.

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Thrombocytopenia.

Platelet counts were carried out in eighteen cases. Eleven patients were considered to have thrombocytopenia (platelets being less than 150,000 per c.mm.). In five cases the thrombocytopenia was severe (platelets less than 25,000 per c.mm.). Two of the cases of severe thrombocytopenia were cases on immuno-suppressive therapy following organ homotransplantation. They had, despite chemotherapy, maintained high platelet counts until severe gram-negative bacterial sepsis supervened.

Biochemical Changes in Bacteraemic Shock.

In the patients with bacteraemic shock, renal failure was common and the blood urea nitrogen levels were high (Figure 20). Associated with an elevated blood urea nitrogen the serum potassium level was usually raised. Serum sodium and chloride levels were low except where there was evidence of dehydration and haemoconcentration (as seen in some of the burns cases).

Like most other forms of shock where poor tissue perfusion and cell hypoxia were common features, in the cases with sepsis, when shock was present, there was a metabolic acidosis, the degree of which was proportional to the duration and severity of the shock.

Blood lactate and pyruvate levels, pH, pCO_2 and 'base excess' data were obtained from patients in shock associated

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with sepsis. Main Table 40 tabulates the biochemical data and in Figure 22 the relationship of excess lactate to base excess in patients in shock is illustrated. The high degree of correlation between the base deficit and the excess lactate ($P < 0.001$) demonstrated that the base deficit could be accounted for almost exclusively by increased concentration of lactate (accumulated during anaerobic tissue metabolism).

Enzyme Changes.

In shock, anaerobic glycolysis and anoxic damage to body cells was reflected in the elevation of total serum lactic dehydrogenase (L.D.H.). The concentration of this enzyme in the serum was usually raised, the range being 90-1400 units per ml. A similar though not always parallel elevation was noted in the serum glutamic oxaloacetic transaminase (S.G.O.T.).

Serum Bilirubin.

The serum bilirubin level was found to be elevated in ten patients and in four patients exceeded 10 mgm. per 100 ml. If the patient with the homotransplanted liver was excluded, the biochemical findings in the other cases suggested an obstructive type of jaundice. In the patients who had marked jaundice clinically and who subsequently died, no obvious obstruction to the larger bile ducts was found. Inspissated bile causing biliary stasis in the

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smaller bile canaliculi appeared to be the cause of the obstructive jaundice. Similar cholestatic type of jaundice has been described by ELEZ ET AL. (1965) in the course of severe bacterial infections.

Serum Amylase.

The serum amylase was occasionally raised. In only two cases, however, was it considered that pancreatitis was sufficiently well established to contribute to the shock. In most cases the poor renal function, preventing the excretion of amylase could be reflected in the above-normal serum amylase levels.

Gastro-intestinal Findings.

In most of the cases in the group, gastro-intestinal symptoms were common. Several patients had blood-stained vomiting which frequently progressed some hours later to massive gastro-intestinal bleeding. Abdominal pain was associated with abdominal distension. Diarrhoea occurred and the stools were sometimes blood-stained.

One patient (Case 7) had an infarction of the small bowel due to occlusion of the superior mesenteric artery. For some weeks prior to admission to hospital he had symptoms suggestive of "abdominal angina". At laparotomy endarterectomy was carried out and the resultant blood flow in the superior mesenteric artery appeared to be adequate.

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A large part of the small bowel was already necrotic and had to be resected. Hypotension and renal failure were irreversible and at post-mortem examination further ischaemic changes in the remainder of the small bowel were found associated with general peritonitis.

MARSTON (1964) has reviewed the literature of cases of acute occlusion of the superior mesenteric artery and found that the condition was usually irreversible when discovered. In Case 5 (Appendix 4) the patient had a mitral valve replacement and in the post-operative period was hypotensive. Operation did not involve the abdominal cavity. The patient developed abdominal pain. The abdomen became silent and distended and in the later stages there was a dusky discoloration in the flanks. At post-mortem examination a patchy necrosis involved the whole of the gastro-intestinal tract. The ischaemia appeared to be due to the failure to perfuse the peripheral vascular bed in the bowel wall. The major arteries of supply were all patent. The appearances in this case were similar to the gastro-intestinal findings in the dog subjected to irreversible haemorrhagic shock (FINE, 1958; LILLEHEI and MacLEAN, 1958).

In three patients who had mild gastro-intestinal haemorrhage, complicating bacteraemic shock, and who subsequently died, post-mortem examination revealed

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congestion and mucosal haemorrhages of the oesophagus, stomach and duodenum. In a further five cases (including three patients with major burns) necropsy demonstrated multiple ulcers of the oesophagus, stomach and duodenum. Four patients had acute fulminating enterocolitis. At post-mortem examination the mucosa of the small and large intestines was dark red with patchy or confluent areas of haemorrhage and necrosis. Thrombi were present in the vessels of the intestinal wall.

Burns.

In the clinical management of the eight burned patients the immediate initial problems were concerned with hypotension, blood volume stabilisation and the associated problems of oliguria and kidney damage. In only two cases were early respiratory difficulties important. The burns were usually sterile in the early stages.

All the burned patients were nursed in separate isolation rooms and strict "barrier" precautions were followed by all the patients' attendants. Frequent bacteriological sampling from the patient, blankets, furniture surfaces and the room air demonstrated that the burned surfaces soon became colonised with bacteria. At first, in most of the cases studied, gram-positive spore-formers, (B. cereus) colonised the burned surfaces. This

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organism was found to be present in the environment. When B. cereus was widespread on the burned surfaces, it appeared to inhibit early colonisation of the burned areas by pathogenic bacteria especially by staphylococcus aureus.

If early skin cover was achieved by excision and grafting this proved to be the best way of reducing or abolishing superficial skin sepsis.

Gradually the burned areas became colonised with pathogenic organisms and as the bacteriological flora changed Staphylococcus aureus (coagulase positive) and Pseudomonas aeruginosa became the dominant organisms. Other gram-negative organisms often present were Escherichia coli, Klebsiella-Aerobacter species and Proteus organisms. Figure 23 tabulates the details of the bacteriological data in one of the seriously burned patients (Case 16).

Operative intervention for excision and grafting was followed in four cases by shivering, spiking temperature and hypotension. In three cases post-operative blood cultures were positive and three out of the four patients with post-operative complications died within 48 hours of the onset of symptoms.

<u>Carbohydrate Upsets in Burns</u>.

In two of the eight seriously burned patients, upsets in carbohydrate metabolism were encountered. Both patients had episodes of hyperglycaemia and hypo-

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hypoglycaemia. The hyperglycaemia occurred when both patients were suffering from pyrexia and toxaemia and in both cases operative excision and grafting of the burned areas had been a preceding event. In both cases positive blood cultures of gram-negative organisms were present at the time of the carbohydrate upset.

Immunosuppression (In Homotransplantation).

The occurrence of sepsis in the cases of immunosuppression following homotransplantation of organs presented special problems. Once established, infection proved to be very difficult to eradicate. With immunosuppression with chemotherapeutic substances and cortisone sepsis often appears quiescent. It was frequently difficult to decide whether the symptoms and signs observed were due to sepsis or from acute rejection of immunological tolerance.

In the cases studied, however, pyrexia was not prevented. In two patients marked elevation of temperature persisted relentlessly for 2-3 weeks. Only one patient had a leucopenia which could be attributable to drug therapy. Two had marked coagulation defects with profound thrombocytopenia.

Gastro-intestinal ulceration, haemorrhagic necrosis and adynamic ileus were salient features and in three cases marked bacterial proliferation occurred in the liver. At necropsy widespread foci of infection were found.

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Staphylococcus aureus and several gram-negative organisms were the pathogenic bacteria producing the overwhelming toxaemia.

General Post-mortem Findings in the Patients who died in Bacteraemic Shock.

At post-mortem examination of those patients who died in shock associated with severe sepsis, the dominant pathological findings were in the gastro-intestinal tract, in the kidneys, and in the lungs. Thirteen patients had acute generalised peritonitis or extensive intra-abdominal abscess formation. Acute congestion of the spleen, or acute splenitis and congestion of the liver, were common. Associated with congestive hepatomegaly, biliary stasis in the small biliary canaliculi was found. In some cases histological examination of liver tissue showed centri-lobular necrosis due to congestive hypoxia. In the case of the liver homotransplantation, complete hepatic necrosis with bacterial overgrowth was found and in two cases of renal homotransplantation clumps of gram-negative bacteria were easily demonstrated in liver sections. There was intense vascular congestion of the gastro-intestinal mucosa. The mucosa was dark red with patchy or confluent areas of haemorrhage or necrosis.

Mucosal haemorrhages or erosions were frequent in the stomach and duodenum. Similar changes occurred less

frequently in the small and large intestine. Four patients had died with acute enterocolitis. Microscopy revealed that superficial erosions did not usually spread deep to the submucosa. There appeared to have been spasm in the arteries with multiple scattered small thrombi in the dilated venules of the bowel wall.

Renal Changes. The kidneys were frequently pale and swollen and on section pooling of blood in the cortico-medullary junction of the kidney resulted in a visible red zone and congestion of the vasa recta. Eight patients had well established acute tubular necrosis. A further three cases had bilateral suppurative pyelonephritis and there was one case of pyoureter.

There were no cases of adrenal insufficiency. Two patients were found to have diffuse hypertrophy of the adrenal glands.

Respiratory Findings. Pulmonary changes were extensive and it was usually difficult to assess the initial changes which would have occurred.

There were nineteen cases of severe bronchopneumonia with patchy atelectasis, associated in eleven patients with extensive tracheobronchitis. Multiple small peripheral emboli were frequently found, large emboli being present in five patients.

Intrapulmonary abscesses, haemorrhages and pleural effusions were found. Pulmonary oedema was frequent.

D) Management and Therapy.

The main purpose of the present work was to assess the importance of the bacteriological factors in shock in critically-ill surgical patients, and to study the pathological and haemodynamic changes associated with bacteraemic shock.

No attempt was made to study the relative efficacy of different therapeutic regimes or drug combinations. Each patient was treated according to individual needs without reference to any strict regime or drug trial. In such a small group and with the wide variety of drugs employed it was not possible to make an accurate assessment of the relative importance of the different therapeutic measures.

Detailed records of systemic arterial blood pressure, central venous pressure, blood volume and serum electrolytes were used to correct hypotension and fluid imbalance. In some patients the blood volume was expanded until an effective circulating volume was achieved. Blood, plasma, low molecular-weight dextran, and crystalloid solutions were used. In one patient (Main Table 41) the effective blood volume was shown to be considerably in excess of the predicted volume.

/ Where the central venous pressure became dangerously high, digitalis, isoproterenol or diuretic therapy were employed and in very acute rises of central venous pressure phlebotomy of 300-500 ml. blood was sometimes carried out. Vasopressor drugs were frequently used, mainly for short periods. Noradrenaline (Levophed) was the main vasoconstrictor used. Angiotensin II and metaraminol were sometimes employed.

Vasodilator therapy was not used on any trial basis. Phenoxybenzamine was used only where fluid replacement appeared adequate. The peripheral flow as judged by the disappearance of the peripheral cyanosis and coldness, appeared to improve dramatically after phenoxybenzamine was given. Intravenous isoproterenol also seemed to produce improvement in respiratory symptoms, systemic arterial blood pressure and in peripheral perfusion, although care had to be taken to prevent excessive tachycardia.

The blood gas status was frequently re-assessed and where necessary oxygen therapy with controlled mechanical ventilation was instituted. Sodium bicarbonate and THAM (Tris-buffer) were used to correct severe acidosis.

Antibiotic and steroid therapy were chosen according to the needs of the individual patient.

Hypothermia, using a cooling blanket was used in several cases to control pyrexia.

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E) Discussion.

Shock has been recognised as a complication of gram-negative infection only in the last fifteen years. (WAISBREN, 1951).

The principal sign is the acute onset of hypotension in a patient with overwhelming sepsis. The syndrome is observed mainly in elderly patients and in pregnant women, after the invasion of the blood-stream by gram-negative bacteria.

In the cases reported by WEIL ET AL. (1964) the median age of the patients was 60 years. McHENRY ET AL. (1962) noted that except for septic abortion bacteraemic shock was unusual in the young. The present series however shows that where the natural immunological mechanisms are suppressed, as in cases of organ transplantation, bacteraemic shock can occur in young persons.

Precipitating Events.

The majority of the cases of bacteraemic shock occur during the patient's hospital stay (WEIL ET AL., 1964). EBERT and ABERNETHY (1961) found that trauma or manipulation of the genito-urinary tract was responsible for most of the cases of bacteraemic shock. Abdominal operations, infection at the site of a "cut down" infusion, dressing or manipulating the skin, and septic abortions were also precipitating events in cases of bacteraemic

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shock.

Time Sequence.

Septic shock occurred usually within 16 hours of the manipulative event and the duration of shock until the time of death was less than two days.

"Portals of Entry" in Bacteraemic Shock.

MAIZTEGUI ET AL. (1965) showed that in 65 per cent of cases the urinary tract was the site from which the bacteria invaded the blood stream. In 10 per cent of cases the gastro-intestinal tract was involved (especially in cases of peritonitis or biliary infections). The skin (14%) and the respiratory tract (3%) were sometimes involved. A similar distribution in the portals of entry of bacteria was given by WAISBREN (1951) in his original paper.

BRAUDE ET AL. (1953) described an infected blood transfusion as the source of septic shock and similarly GILAT ET AL. (1958) reported infected, improperly sterilised, crystalloid solutions as the source of infection.

Mortality.

In all reported series the mortality has been high (up to 91%) e.g. HALL and GOLD, 1955; EZZO and KNIGHT, 1957; WEIL and SPINK, 1958 and HARRIS and WILSON, 1965. WEIL ET AL. (1964) reported that with gram-negative bacteraemia alone, the mortality was 28 per cent. In

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cases where there was associated hypotension the mortality rose to 91 per cent.

McCABE (1963) noted that gram-negative bacteraemia was associated with a lower mortality rate in patients with long-standing urinary infections than in patients with gram-negative sepsis arising from extra-urinary tract foci. In addition it was noted that patients with chronic bacteraemia had less fever following a challenging dose of endotoxin than in patients with sterile urine.

Reduced Resistance to Infection.

Patients with diabetes mellitus, hepato-biliary disease, leukaemia and other blood dyscrasias, and malignant disease have been shown to be prone to bacteraemic disease. Therapeutic regimes, e.g. the use of steroids, antibiotics or cytotoxic drugs, can also reduce the patient's resistance to infection (HALL and GOLD, 1955; SPITTELL ET AL., 1956; McHENRY ET AL., 1962).

Clinical Features.

The onset of bacteraemic shock is usually heralded by a chill or rigor and then fever (temperature 99°F - 106°F). In the early stages the skin is dry and warm. Later the skin becomes cold and moist and the pallor is replaced by a violaceous mottling (WAISBREN, 1951; ALTEMEIER and COLE, 1956; WEIL and SPINK, 1958).

Vomiting and abdominal pain and distension occur and

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if diarrhoea is present the fluid stools may be green or blood stained. Jaundice is an ominous sign. Oliguria is frequent. There is respiratory distress. Mental confusion may be noted early by the patient's nurses.

Bacteriological Findings.

WAISBREN (1951) found that Escherichia coli was the commonest organism isolated from the blood in bacteraemic shock. Klebsiella/Aerobacter, Pseudomonas, Proteus and Bacteroides species were the other common gram-negative organisms isolated from patients with septic shock.

The Cardio-vascular System in Bacteraemic Shock.

There is still doubt whether or not the heart is primarily affected in bacteraemic shock. FROLICH ET AL. (1962) in animal experiments, perfused the coronary vessels with endotoxin and found no direct cardiac action. GUYTON and CROWELL (1964) postulate that the importance of the heart in shock has been neglected as cardiac deterioration is not discovered early because of the considerable cardiac reserve. E.C.G. recordings in patients in bacteraemic shock show ST and T wave abnormalities due to ischaemic myocardial changes from decreased coronary flow.

In septic shock there is a metabolic acidosis. WEIL ET AL. (1957) showed that myocardial contractility is affected by acidosis. At acid pH, blood vessels and the

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heart are refractory to endogenous catecholamines (LANCING, 1963).

UDHOJI ET AL. (1963) made a detailed haemodynamic study of patients in bacteraemic shock and concluded that hypotension was associated with a marked reduction in cardiac output. Peripheral venous pooling with a decreased venous return appeared to be the primary defect producing the shock. WILSON ET AL. (1965) made similar haemodynamic observations.

LILLEHEI ET AL. (1962) believed that early in shock associated with infection there is vasospasm which affects both the arterioles and venules with ischaemia of the capillary bed. With prolongation of the shock the continued ischaemia produces relaxation of the pre-capillary sphincters. The post-capillary sphincters which are more resistant to anoxia and acidosis maintain their tone. (LEWIS and MELLANDER, 1962). Consequently with increased inflow and a relative block to outflow there is stasis of blood in the capillary bed with a loss of fluid into the tissues. SCHAYER (1962) made the same observations but suggested that with ischaemia, endogenous histamine is produced in the capillary bed, and he demonstrated that early in shock there is a high blood level of catecholamines and later as the catecholamine level falls the histamine concentration rises. Previous

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experiments (page 38) show that the typical effect of histamine on the hamster cheek pouch microvasculature was to cause arteriolar vasodilatation and post-capillary venous constriction.

Blood Volume.

GILBERT ET AL. (1954) found that in patients with bacteraemic shock both the blood volume and the cardiac index were normal.

HOPKINS ET AL. (1965) found a marked depletion of the blood volume in patients with haemorrhagic shock. In contrast their patients in septic shock had a normal or increased blood volume. The cardiac output was normal and the mean blood lactate level was high. In the present series blood volume studies showed no defect in blood volume during bacteraemic shock.

Blood Coagulation Defects in Bacteraemic Shock.

Severe upsets in the blood coagulation mechanism have been described in shock in man and in experimental animals. HARDAWAY (1962) has shown a diphasic response in shock. At first there is hypercoagulability followed by a phase of hypocoagulability and fibrinolysis.

Intravascular clotting has been demonstrated in the microcirculation in shock (McKAY and SHAPIRO, 1958; SPINK and VICK, 1961). In vitro and in vivo experiments have demonstrated platelet aggregation in endotoxin shock

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(REAM ET AL., 1965; ROBB, 1965). In earlier experiments in the present work (page 74) white emboli were seen in the hamster cheek pouch vessels after Escherichia coli endotoxin had been administered intravenously, and there was a marked fall in the platelet counts.

In several patients in the present review, where hypotension was associated with severe infections, thrombocytopenia was observed. In three cases where bone marrow studies were made to investigate the thrombocytopenia, megakaryocytes were plentiful and in the case where an isologous isotope-tagged platelet infusion was given (Appendix 4, case 8) sequestration or destruction of platelets appeared to be the main cause of the platelet depletion.

In shock there is a fall in the blood levels of fibrinogen, prothrombin and platelets (WEST ET AL., 1966). In addition there is activation of endogenous heparin and fibrinolysin. HARDAWAY and JOHNSON (1963), believed that the endogenous release of heparin and fibrinolysin may be an attempt to halt and reverse the intravascular clotting processes. SHERRY (1961) reviewed the increased proteolytic mechanisms which are activated in shock, and THAL and SARDESAI (1965) demonstrated increased bradykinin activity in shock.

Several patients in the present study demonstrated a divergence of the platelet and leucocyte counts. /

Thrombocytopenia associated with leucocytosis may be a good index of continuing gram-negative sepsis.

Respiratory System in Septic Shock.

SIMMONS ET AL. (1960) found respiratory alkalosis in patients with septic shock. Early in the course of the hypotension patients had hyperpnoea which appeared to compensate the metabolic acidosis. The oxygen consumption in shock decreased (BOURNOUS ET AL., 1963; RUSH ET AL., 1965).

ROBB (1965) examined the mesenteric vessels of animals given endotoxin and photographed multiple micro-emboli. He concluded that the micro-emboli would be carried to the lungs and could account for the pulmonary arterial hypertension, the right heart failure and the systemic arterial hypotension. Multiple micro-emboli in the portal system would also account for portal hypertension and pooling of blood in the splanchnic circulation. The hypo-coagulability of blood corresponded to platelet depletion.

HALMAGYI ET AL. (1961, 1963) demonstrated that pulmonary hypertension was the most marked finding in endotoxin shock in sheep and that intravenous isoproterenol improved the respiratory function in shock. Similar cor pulmonale findings have been demonstrated in calves (TIKOFF ET AL., 1966) and in primates (BROCKMAN and VASKO, 1965). In the pulmonary capillary bed local aggregation

of platelets, in addition to the mechanical effect and perhaps reflex neural mechanism, would also cause local release of serotonin, which would increase the pulmonary hypertension.

The onset of septic shock in man has often been difficult to differentiate from massive pulmonary embolism or myocardial infarction (McGOWANS and WALTERS, 1963).

All the patients in the present study had serious pulmonary problems and at post-mortem examination complex pathological findings were present in the lungs.

At present there have been few pulmonary haemodynamic studies carried out in patients in bacteraemic shock and it is not yet possible to say whether or not man exhibits the same pulmonary hypertension which has been noted in sheep, calves and primates.

Gastro-intestinal Failure in Septic Shock.

The association of gastro-intestinal ulceration and haemorrhage with various types of stress has been recorded. The occurrence of acute erosions and ulceration of the stomach and duodenum was noted following severe cutaneous burns (CURLING, 1841-42) and more recently CUSHING (1932) observed alimentary ulceration after intracranial injuries.

The gastro-intestinal tract differs from other organs and tissues as it is populated in the normal state by bacteria. When gram-negative bacteria disintegrate endo-

/endotoxins are liberated and the vasoactivity of those toxins have been considered by some to be the main factor in shock in man (FINE, 1954).

Haemorrhage and gastro-intestinal mucosal ulceration progressing to necrosis are frequent post-mortem findings in severe shock (PENNER and BERNHEIM, 1939). The mesenteric circulation has a large blood volume. The splanchnic vessels have a rich sympathetic vasoconstrictor supply (FOLKOW, 1955) and the mesenteric circulation is highly sensitive to the action of circulating catecholamines (AKERS and ZWEIFACH, 1955). Intense vasoconstriction of the mesenteric bed causes hypoxia and damage to the intestinal mucosa with increased capillary permeability. The release of serotonin and histamine, vasoactive substances formed in the gastro-intestinal tract may also be important contributing factors producing gastro-intestinal changes in shock.

In irreversible shock in the dog, LILLEHEI and MacLEAN (1958) have stressed the dominant role of the intestine. Haemoconcentration and hypovolaemia are marked terminal phenomena in the dog, the duodenum and upper jejunum being blue, congested and necrotic. FINE (1964) demonstrated in experimental studies that when the intestinal splanchnic vasoconstriction was overcome by coeliac blockade, (by infiltration with a local anaesthetic)

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survival rates were increased. In addition FINE and his colleagues (JACOB ET AL., 1954) had previously shown that in germ-free animals the survival rates were higher than in control animals under similar conditions of shock.

ZWEIFACH ET AL. (1958) however were unable to confirm FINE's results in germ-free animals, subjected to haemorrhagic shock.

Intestinal necrosis associated with profound hypotension has been described several times (e.g. KAY ET AL., 1958; MARSTON, 1962; DRUKER ET AL., 1964; McGOVERN and GOULSTON, 1965).

Necrotising jejunitis, acute haemorrhagic necrosis and pseudomembranous enterocolitis, all appear to be manifestations of intestinal ischaemia and necrosis. The patients are usually elderly men and the syndrome usually follows an episode of hypotension and peripheral vasoconstriction. Coincidental cardiac and respiratory diseases have been prominent features in many cases (BOURGEOIS ET AL., 1964; MING, 1965). The mortality is high. The ischaemic intestinal necrosis is very similar to the endotoxin shock described by FINE (1964) in dogs. FINE believed that shock from any cause will activate bacterial toxins in the gut and become septic shock if it lasts long enough. The intense vasoconstriction of the splanchnic vessels produces anoxic damage to the

intestinal wall allowing absorption of the endotoxin from the bowel.

PENNER and BERNHEIM (1939) in a post-mortem survey of 47 cases at the New York Mount Sinai Hospital demonstrated distension of small vessels in the submucosa and mucosa with focal haemorrhages and necrosis of mucosa with ulceration. Hyaline thrombi were present in the small vessels. The changes were in the mucosa of the stomach but in the submucosa of the intestine.

In dogs the intestinal mucosa is characteristically involved in shock (LILLEHEI and MacLEAN, 1958) but in contrast, in man the submucosa is the main site of the ischaemic change. SPANNER (1934) showed numerous arterio-venous shunts in the intestine of the dog. With low arterial perfusion pressure, blood passed through the arterio-venous anastomosis leaving the mucosa relatively ischaemic and accounting for the numerous mucosal lesions. Arterio-venous communications have also been observed in the human intestine (BOULTER and PARKS, 1960), but in the human intestine during ischaemia it is the submucosa which is affected. The formation of a pseudomembrane in the human intestine corresponds to the mucosal changes observed in the dog's intestine.

The metabolic activity of the gastro-intestinal mucosal cells is greater than almost any other tissue.

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CREAMER ET AL. (1961) have shown by radio-active tagging in histological studies that the mucosa of the stomach, duodenum and intestines can be replaced in 24-48 hours. This normally intense metabolic activity would be acutely depressed by the hypoxia and ischaemia associated with the poor splanchnic blood flow which is observed in shock.

Antibiotic therapy and bacterial infections have been suggested as the aetiological agents at the onset of the intestinal symptoms. The association of enterocolitis with profound hypotension has frequently been interpreted as shock resulting from bowel disease. However it would seem more probable that the hypotension occurred first (as in the case of the mitral valve replacement — Case 5). Cardiac output is inadequate and the peripheral vaso-constriction causes intestinal ischaemia initiating the gastro-intestinal symptoms. Endogenous intestinal bacteria — especially the anaerobic bacteroides and clostridia — are stimulated to proliferate and are absorbed causing bacteraemia and septic shock.

Burns.

The most outstanding achievements in recent years in the treatment of burns include the prompt administration of intravenous fluids in the early stages to correct hypo-tension and hypovolaemia, and the prevention or treatment of the associated renal failure. The prevention of toxaemia

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and sepsis has improved but the problems of bacterial infection in the later stages of the management of the severely burned patient still presents the major challenge in combating the mortality from extensive burns.

Staphylococcus aureus and Pseudomonas aeruginosa are the bacteria most commonly responsible for severe infection complicating the later stages of the management of the patient with burns. FELLER and HENDRIX (1964) in a clinical-pathological study of sixty fatally-burned patients showed that the majority died from severe staphylococcal or pseudomonas infection and that the average survival time was three weeks.

Pseudomonas aeruginosa bacteraemia causes a distinctive necrotising bluish skin lesion (FORKNER ET AL., 1958; McCABE and JACKSON, 1962). Recently MULL and CALLAHAN (1965) have suggested that elastase, produced by the pseudomonas destroyed the elastic lamina of vessels producing the characteristic bluish skin lesions. The green pigment in the urine of patients with widespread pseudomonas infection is due to verdoglobin, an intermediate product in haemoglobin metabolism (STONE, 1966).

FELLER and KAMEI (1964) used pseudomonas vaccine and hyperimmune plasma in the treatment of burned patients and reduced the mortality in their severely burned patients from 44 per cent to 30 per cent.

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The topical use of "sulphamylon" (p-aminomethylphenyl sulphonamide) has been reported by LINDBERG ET AL. (1965) to be efficacious in eradicating pseudomonas aeruginosa from burn surfaces.

In four out of eight patients with severe burns surgical intervention — debridement and grafting — appeared to be the precipitating event in causing bacteraemic shock. Where there are extensive necrotic infected areas, manipulation of the skin exposes the patient to sudden blood stream invasion of bacteria or their toxins. The onset of bacteraemic shock should be suspected in all cases of hypotension following operative procedures for burns.

Abnormal Carbohydrate Metabolism in Severe Burns.

The syndrome of hyperglycaemia without ketosis complicating severe burns was first described by EVANS and BUTTERFIELD in 1951. The blood glucose levels were in the range 800-1, 600 mgm. per 100 ml. The syndrome has been called pseudodiabetes. It usually is noted after the second or third week following extensive burns and is serious and can be fatal. Dehydration and uraemia can be marked and are usually the cause of mental symptoms and coma. The osmolarity of the blood is considerably increased. In one of the present patients (Appendix 4, Case 21) the blood sugar rose to 1,660 mgm. per 100 ml. and the serum

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osmolarity was 459 milliosmoles per litre.

BUTTERFIELD (1955) believed that a high calorie, high carbohydrate diet was the precipitating cause. As most of the carbohydrate appeared to be metabolised without ketosis, BUTTERFIELD considered that there was defective insulin production due to partial failure of the pancreas from excessive carbohydrate intake. BAILEY (1960) suggested that a main cause of the glycosuria was hyperadrenalinaemia from increased adrenal medulla action following the stress after burning. BAILEY also considered important the increased corticosteroid production.

In the cases in the present series showing abnormal carbohydrate metabolism and also in the patients studied by EVANS and BUTTERFIELD (1951), and by BAILEY (1960), severe sepsis and pyrexia were present at the time of the hyperglycaemia. Most of the patients did have a high carbohydrate intake, with partial failure of the pancreas as a possible contributing cause. Toxic absorption however would produce "burns stress" with a high blood catecholamine concentration. Glycogen would be mobilised from the liver and hyperglycaemia result. Later when carbohydrate intake was restricted and the liver glycogen was depleted hypoglycaemia was noted. In experimental animals WOODS ET AL. (1961) showed that endotoxin caused severe upsets in carbohydrate metabolism. SANFORD ET AL. (1960) observed that

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hyperglycaemia and depletion of liver glycogen were the most constant biochemical changes associated with endotoxaemia. The hyperglycaemia was not due to the direct action of endotoxin but was an indirect response mediated by catecholamines. In severely burned patients a similar mechanism could be the main factor in producing the "pseudodiabetes" observed.

In a bioassay of the plasma of three out of four patients with burns a pronounced vasoconstrictor activity was observed in the microvasculature of the hamster cheek pouch (page 86). PAGE (1943) found a similar vasoconstrictor effect in the plasma of experimentally burned dogs and concluded that the vasoconstrictor substance was adrenaline. A high blood catecholamine level would also stimulate ACTH production with increased adrenal cortical activity. A raised blood corticosteroid level would also play a role in the glucose metabolic upset. In case 21 (Appendix 4) urinary corticosteroid levels were highest at the time of the hyperglycaemia.

The carbohydrate upset and the "Curling's" ulcers observed in severe burns may be complications resultant to the high concentrations of circulating catecholamines.

Management and Therapy.

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Management and Therapy.

Antibiotics.

Successful treatment of bacteraemic shock depends on prompt diagnosis and early treatment with the appropriate antibiotic. In their early investigation of the use of aureomycin in brucellosis, SPINK ET AL. (1948) found that where there was overwhelming bacteraemia the use of antibiotics increased the mortality. This apparently detrimental finding appeared to be due to the rapid release of endotoxin during bacterial destruction and lysis.

The choice of antibiotic used in bacteraemic shock will usually be empirical. Blood cultures must be taken to confirm the diagnosis subsequently. Bacteriological cultures of urine, sputum, wound discharges and from other sites will allow a later appraisal of antibiotic therapy. SHUBIN and WEIL (1963) in their paper suggested that streptomycin and chloramphenicol should be used. Today, where gram-negative bacteraemia is suspected cephaloridine — with its broad-spectrum action against most gram-negative organisms except pseudomonas — appears to be the drug of choice (MURDOCH ET AL., 1964). Kanamycin has also been advocated by MURDOCH ET AL. (1962) and TALBOT (1962).

Colistin or polymixin B are the drugs of choice if the infection is caused by Pseudomonas aeruginosa. In the treatment of severe burns where extensive pseudomonas

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infection may be anticipated, the use of pseudomonas vaccine may prove beneficial (FELLER and KAMEI, 1964).

In addition to the use of antibiotic drugs, early surgical drainage of abscesses, debridement of sloughs or removal of infected cannulae, catheters and foreign bodies, will reduce the infection at localised foci.

Use of Corticosteroids.

MELBY and SPINK (1958) demonstrated that corticosteroids act as drugs rather than replacement hormones, since neither in the experimental animal nor in man has adrenal cortical insufficiency been found. Survival is significantly higher in persons receiving more than 300 mgm. hydrocortisone or its equivalent in 24 hours. SPINK (1962) has shown that corticosteroids suppress the systemic effects of endotoxin and control the pyrexia. SPINK and VICK (1961b), LILLEHEI ET AL. (1962) and WEIL ET AL. (1964) all advocate massive doses of hydrocortisone (up to 3 G. in 24 hours) as the most effective therapy in combatting septic shock. This dose of steroid is considerably in excess of the dose advocated as physiological replacement in cases of possible adrenal-cortical insufficiency.

BEIN and JAQUES (1960) noted the beneficial effects of aldosterone in the treatment of endotoxin shock in cats. Although similar protective action of aldosterone in endotoxin shock in animals has been reported by HAYASAKA

and HOWARD (1963), there have been no reports of the action of aldosterone in clinical use in the treatment of bacteraemic shock in man.

Fluid Replacement.

By recording the serial measurements of haemodynamic data, the central venous pressure should be maintained at levels not exceeding 15 cm. water. Blood volume studies are helpful and deficits in blood volume should be corrected or the blood volume expanded to compensate the increased vascular capacity. Plasma, electrolyte solutions and whole blood should be used. In bacteraemic shock if blood transfusion is necessary fresh unhaemolysed blood should be used. LITWIN ET AL. (1963) have demonstrated the synergistic toxicity of gram-negative bacteria and free colloidal haemoglobin. The indications and efficacy of low molecular weight dextran in bacteraemic shock are still being evaluated (GELIN, 1962; COUCH, 1965).

Vasoactive Substances.

Vasopressor agents have been in widespread use in the treatment of hypotension. Von EULER (1955) indicated the value of noradrenaline in shock. Although the clinical state of the patient appears to improve temporarily with vasopressor drugs no improvement in the mortality has been demonstrated in control trials. WALTERS and McGOWAN (1964) were unable to demonstrate any improvement in mortality

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when noradrenaline was used in hypotensive states complicating bacterial infection. Nevertheless, catecholamines have a direct stimulant action on the myocardium. They have both an inotropic and chronotropic effect. Although the peripheral vasoconstrictor effect of the catecholamines play an important part in raising the central arterial blood pressure the direct stimulant effect on the heart is also valuable. As shown earlier (page 116) the apparent increasing refractoriness to noradrenaline in a continuous infusion in the treatment of shock may be due to the increasing metabolic acidosis. If the acidosis is corrected the action of the catecholamines is enhanced (LANCING, 1963). Angiotensin II in the shocked patient raises the blood pressure but markedly reduces the cardiac output. Angiotensin constricts the coronary vessels and unlike the catecholamines has no direct stimulant effect on the heart (NICKERSON and SUTTER, 1964). It does not appear to have any advantages over the catecholamines in the treatment of shock.

Vasodilator Drugs.

Recently the normal vasoconstriction produced in response to the hypotension associated with shock has been considered to be detrimental to peripheral tissue perfusion and adrenergic-blocking agents have been suggested in the treatment of shock. The alpha receptor-

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blocking agents, phenoxybenzamine and phentolamine have been the drugs most widely used in overcoming deleterious vasoconstriction and improving vital organ perfusion. NICKERSON (1963), one of the earliest advocates of the use of pharmacological adrenolytic drugs reviewed the use of dibenzyline (phenoxybenzamine) in the treatment of shock. He was careful to indicate that alpha-receptor-blocking agents should not be employed if oligaemia is present. By lowering the peripheral resistance and increasing the vascular capacity, vasodilator therapy should usually be accompanied by an expansion of the blood volume, haemodynamic changes in systemic arterial and central venous pressures being monitored closely during therapy.

LILLEHEI ET AL. (1963) have also reported the value of vasodilator therapy in bacteraemic shock. MacLEAN ET AL. (1965) have used a different approach to vasodilator therapy. Rather than using an alpha-blocking agent they have used "Isuprel" (isoproterenol) a synthetic catecholamine with marked beta-receptor activity. This drug in addition to improving peripheral flow especially through muscle tissue is the catecholamines with the greatest inotropic and chronotropic action on the heart. It also produces dilatation of the bronchi and lowers pulmonary arterial pressure, which in animal experiments at least, can be dangerously high in bacteraemic shock

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(HAMAGYI ET AL., 1963). KARDOS (1966) used isoproterenol in the treatment of patients in shock due to bacteraemia with gram-negative pathogens. There was a profound change in the peripheral vascular resistance, venous tone, renal blood flow, cardiac output and redistribution of circulating blood flow. In a recent therapeutic trial of different pharmacological regimes to overcome endotoxin shock in dogs, VICK ET AL. (1965) found that the most satisfactory therapy was combination of isoproterenol and phenoxybenzamine. Phenoxybenzamine decreased the peripheral vasoconstriction while isoproterenol, with its beta-adrenergic action increased the cardiac output and augmented the perfusion of the tissues.

Oxygen Administration.

In bacteraemic shock hypoxia is common and oxygen therapy is frequently required.

Tracheostomy, often in association with mechanical respiration, can allow control of the patient's breathing and ease of access for tracheal aspiration. Tracheostomy also diminishes the energy requirements for breathing.

The use of hyperbaric oxygen in the treatment of septic shock has been reported by EVANS ET AL. (1964) and in a later paper, EVANS and DARIN (1965) reported the additive effects of low molecular weight dextran and

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hyperbaric oxygen.

Hypothermia.

BANNISTER (1960) and ATWOOD and KASS (1964) have demonstrated that elevation of temperature increased the morbidity of septic shock. Prolonged moderate hypothermia has been suggested as an important adjuvant to therapy (BLAIR ET AL., 1964). In the present clinical group of patients, a cooling blanket was employed frequently to overcome persistent elevation of temperature.

Correction of Acidosis.

Regulation of the acid-base status is often required in bacteraemic shock to overcome the metabolic acidosis resultant to poor tissue perfusion. The acidosis is usually treated with intravenous sodium bicarbonate or THAM (Tris-buffer). Peritoneal dialysis or haemodialysis may be required to correct renal failure and electrolyte imbalance.

Alteration of the Blood Coagulation Mechanism.

In man in shock associated with infection, upsets in the blood coagulation mechanism have been observed. To date however, clinical indications for the therapeutic use of heparin, fibrinolysins or epsilon-aminocaproic acid in patients have not been reported. In animal experiments however SPINK and VICK (1961a) reported that EACA, a potent inhibitor of plasminogen activators, administered prior

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to and up to 30 minutes before the injection of a lethal dose of endotoxin in dogs resulted in 70-100 per cent survival.

HARDAWAY and associates (1961) have emphasised the value of heparin administration in counteracting intravascular coagulation in septic shock. Where a generalised Shwartzman phenomenon is suspected, as in certain bacterial complications during pregnancy heparin should inhibit the deposition of fibrin. Alteration of intravascular clotting has also been achieved by the administration of fibrinolysins with a reduction in the mortality in the experimental animal (HARDAWAY and DRAKE, 1963).

The liberation of various vasoactive substances in septic shock increases capillary permeability. The proteolytic processes which are activated can be influenced by the use of trypsin-kallikrein inhibitors (e.g. Trasylol, a high molecular weight polypeptide extracted from the parotid glands and lungs of cattle is a polyvalent inhibitor of proteases as well as inhibiting the Kallikrein-trypsin enzyme (THAL and SARDESAI, 1965).

Hypercoagulability and hypocoagulability both occur in bacteraemic shock and if potent drugs are used in clinical practice to influence the blood coagulation mechanism, careful and frequent monitoring of the blood factors involved will be required.

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F) General Conclusions from the Surgical Cases Studied.

(1) Bacterial colonisation of the critically ill surgical patients was the rule rather than the exception.

(2) Gram-negative organisms accounted for the majority of cases of bacteraemia with refractory hypotension.

(3) Sputum, tracheal aspirate, skin, wound and urine cultures often grew the same organism.

(4) After 24-48 hours of colonisation, one type of organism became dominant, often with blood stream spread.

(5) Trauma, instrumentation or surgical treatment usually preceded the bacteraemia and hypotension.

(6) Oliguria, from acute tubular necrosis, coagulation defects, alimentary tract ulceration and haemorrhages, bronchopneumonia, hypoxia and metabolic acidosis were usually associated complications.

(7) Mortality was high 65-70 per cent.

SECTION VIII

BACTERAEMIC SHOCK AND THE MICROCIRCULATION

GENERAL CONCLUSIONS AND SUMMARY

PART I. Experimental Studies.

In a specialised tissue, (the hamster cheek pouch), a quantitative assessment was made of the blood volume distribution in the microvasculature. Three quarters of the blood in the microcirculation was in the venules and only 2.2 per cent of the microvascular blood volume was in the capillary vessels.

A pharmacological approach was employed in an attempt to understand the role of the microcirculation in shock. A method for directly assessing the response of arterial and venous vessels to vasoactive drugs, and indirectly of capillary filtration was developed for the hamster cheek pouch. The responses to histamine, acetylcholine, lactic acid, serotonin, angiotensin II, and the catecholamines were observed.

The action of a purified lipopolysaccharide extract of Escherichia coli endotoxin was studied in the hamster cheek pouch preparation and a preliminary survey was made of the vasoactivity of plasma from patients in bacteraemic shock.

PART II. Clinical Observations.

With the introduction of the antibiotics into general clinical practice, many gram-positive infections have become less common and gram-negative organisms which previously did not show such invasiveness have become major bacteriological hazards in surgical patients.

In man, hypotension associated with severe infections has not been adequately studied. In order to determine the mechanism by which bacterial toxins initiate the shock state, studies must be made in the early stages of shock before secondary reactions occur. In all types of shock nearing the stage of irreversibility there is a common pathological state produced by tissue hypoxia, resultant to poor tissue perfusion. The initiating "trigger" mechanisms may be dissimilar and difficult to assess.

In animal experiments during the production of endotoxin shock there is marked peripheral pooling especially in the hepatic, splanchnic and pulmonary beds. Early in the course of the shock there is increased peripheral resistance and later there is a marked fall in the vascular resistance. In septic shock both in man and in animals there does not appear to be primary cardiac failure and in man blood volume deficit is not a major factor.

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The haemodynamic changes found in man during bacteraemic shock produce pathological effects mainly in the microvasculature of the kidneys, the gastro-intestinal tract, and the lungs, and upsets in the blood coagulation mechanism occur.

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BACTERAEMIC SHOCK

AND

THE MICROCIRCULATION.

Experimental studies and

clinical observations.

by

ADRIAN LITTON.

VOLUME 2.

(Appendices)

BACTERAEMIC SHOCK AND THE MICROCIRCULATION

VOLUME 2.

APPENDIX 1. FIGURES 1-25.

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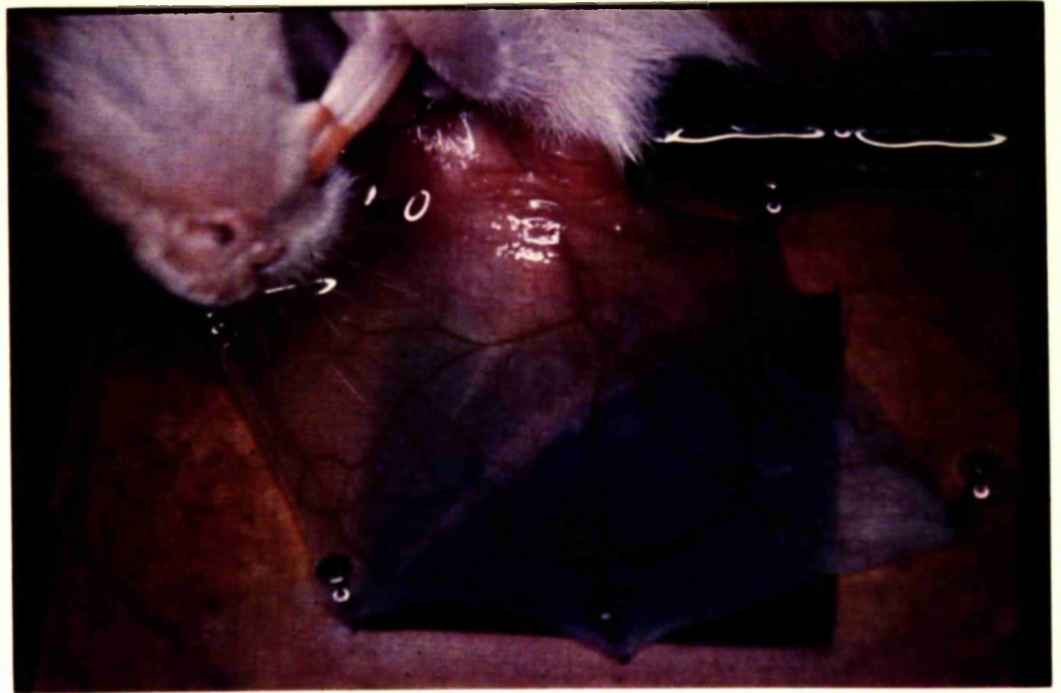
APPENDIX 1.

FIGURES 1-25.



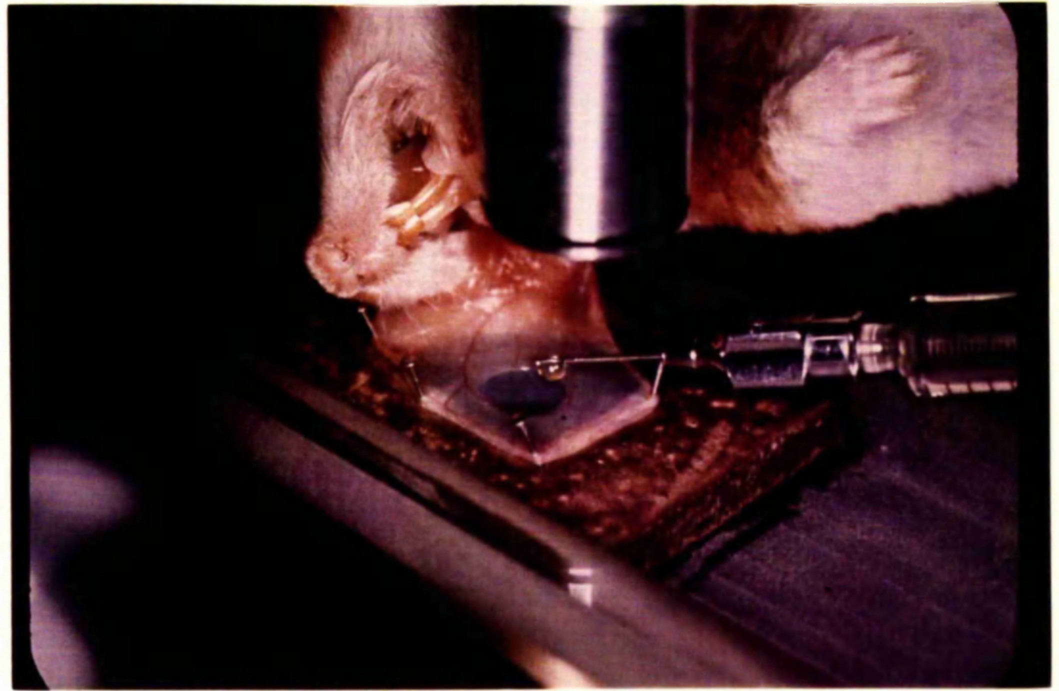
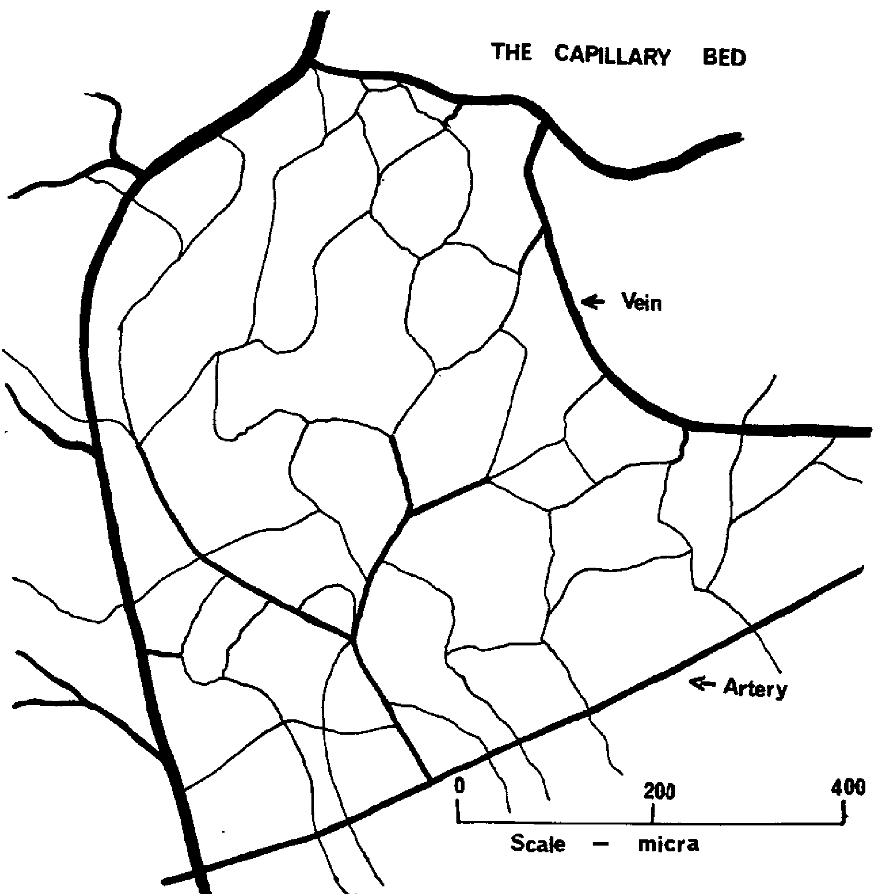


FIGURE I. THE HAMSTER CHEEK POUCH.

A: The pouch has been everted, cleaned, and pinned out for observation of the vessel

B: A single membrane preparation. A 'windo has been removed from the upper epiderma layer.



<u>FIGURE 2</u>. Camera Lucida Drawing of the Capillary Bed of the Hamster Cheek Pouch.

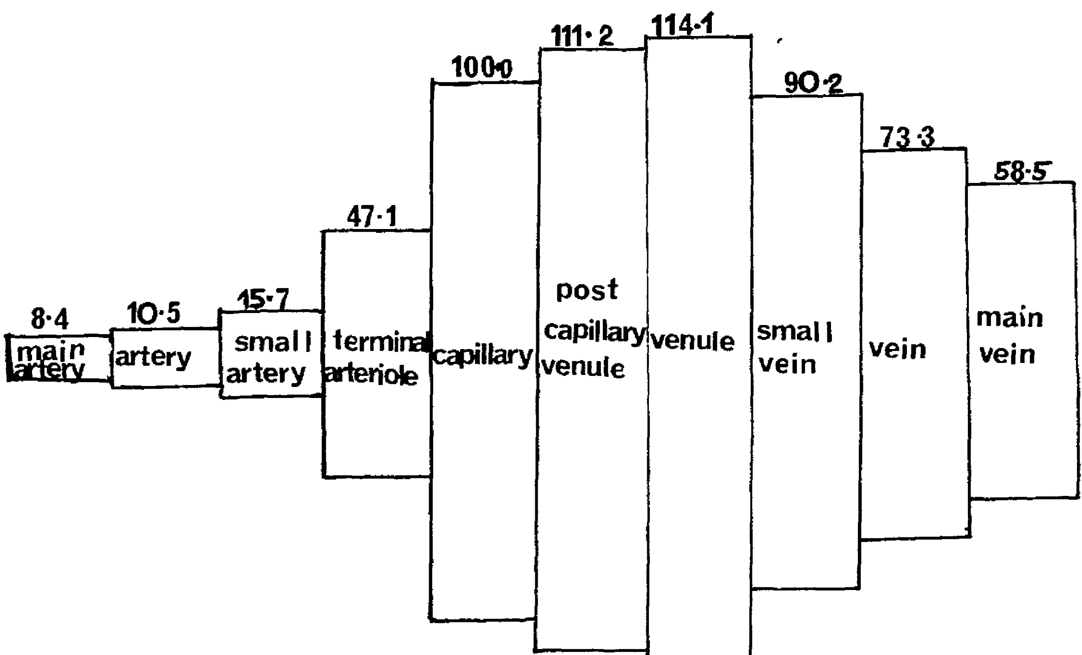
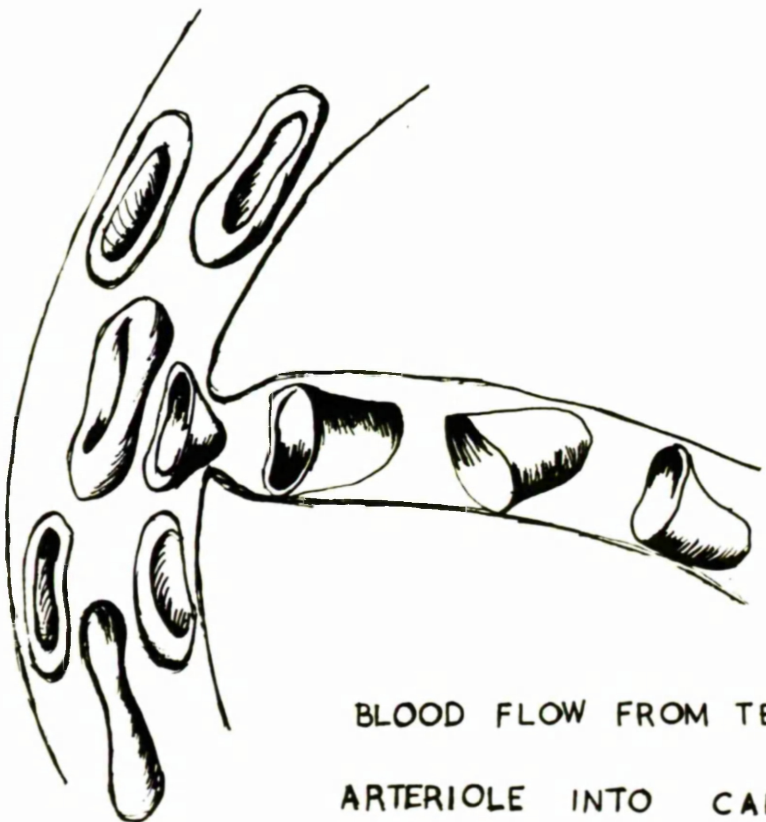


FIGURE 3. Comparison of the Relative Total Cross-sectional Areas of Arteries, Capillaries and Veins in the Hamster Cheek Pouch.



<u>FIGURE 4</u>. Diagram of Deformation of the Erythrocytes in a Capillary Vessel.

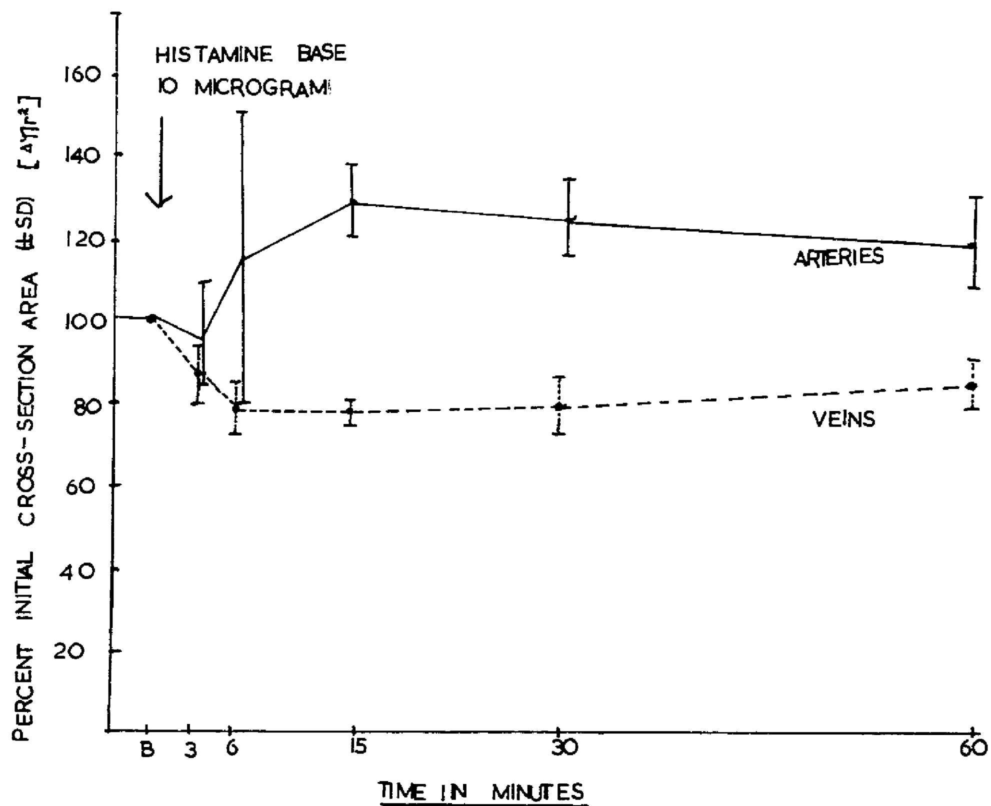


FIGURE 5. The Action of Histamine on the Microvasculature of the Hamster Cheek Pouch.
A) The Local Injection of 10 Micrograms of Histamine Base into the Cheek Pouch.
(Mean Values and Standard Deviations of Six Experiments).

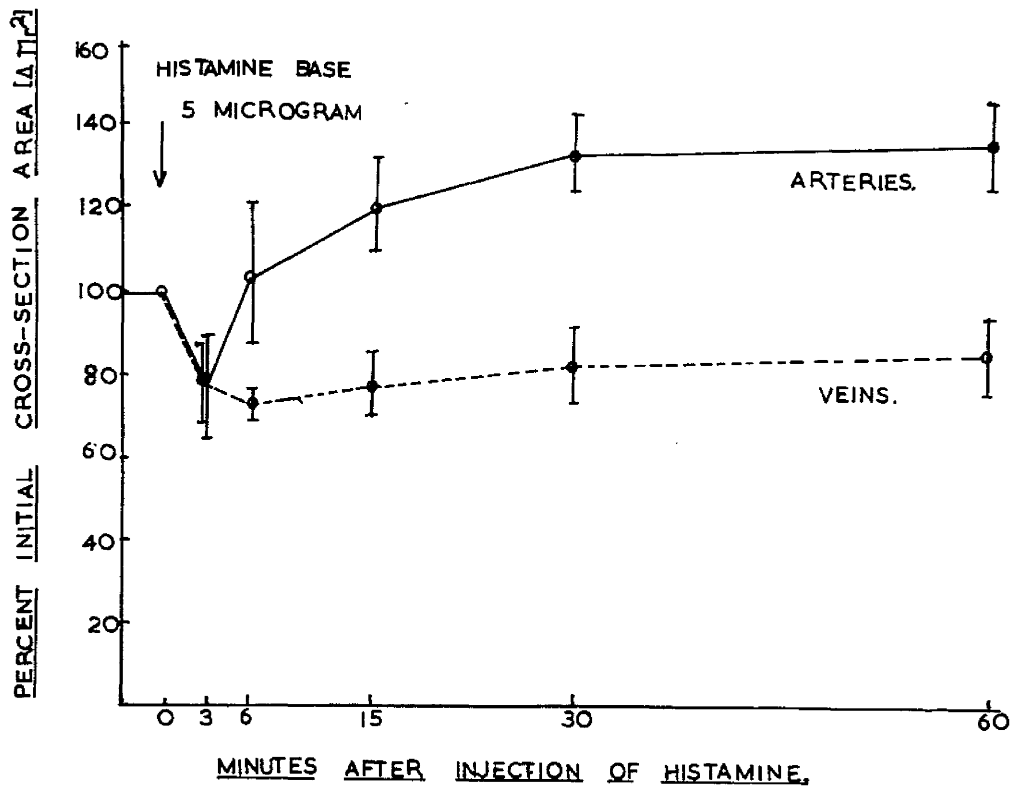


FIGURE 6. The Action of Histamine on the Microvasculature of the Hamster Cheek Pouch. B) The Local Injection of 5 Micrograms Histamine Base into the Cheek Pouch. (Mean Values and Standard Deviations of Six Experiments).

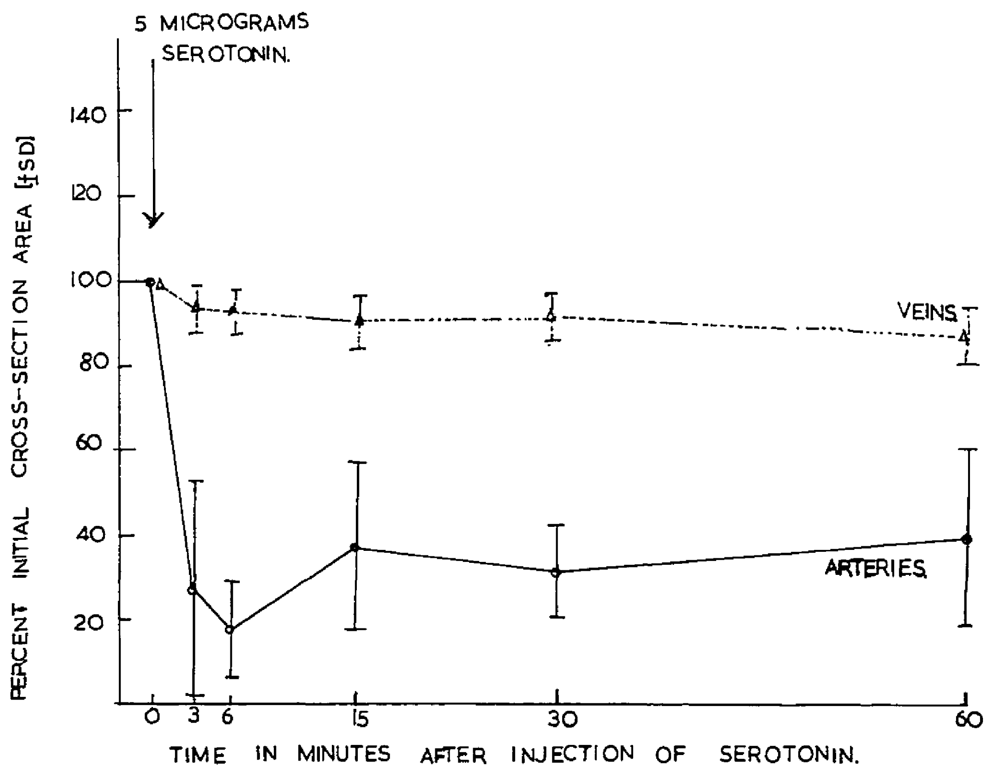
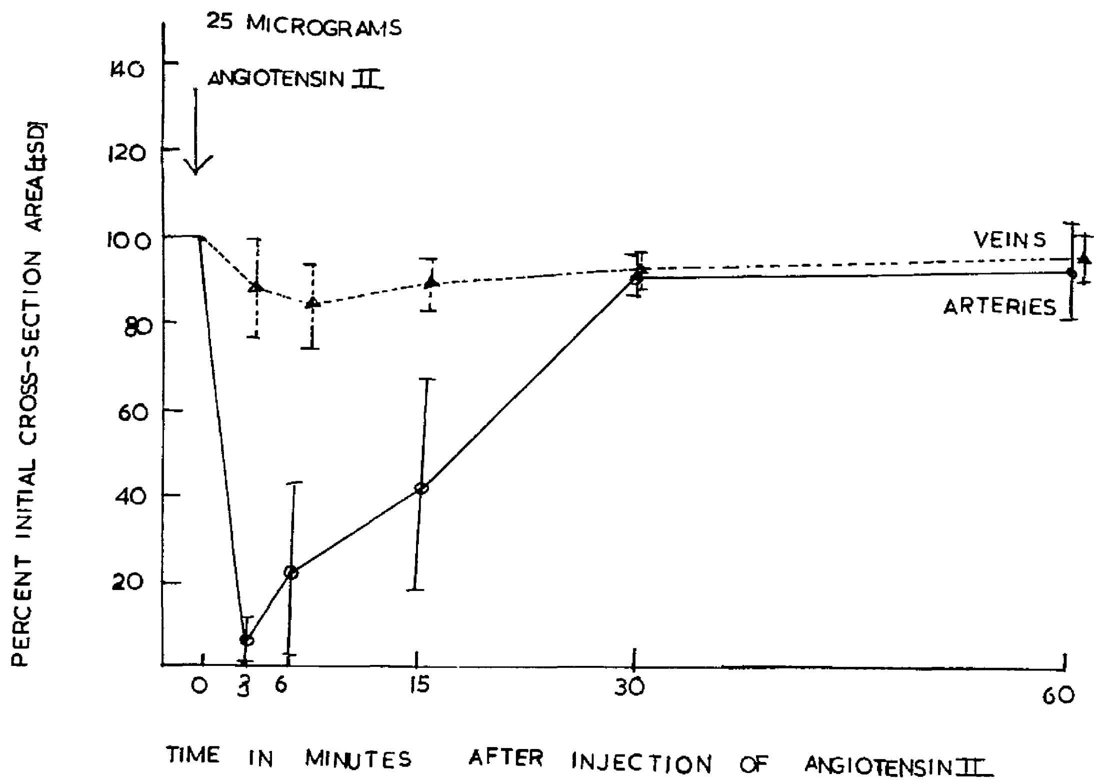
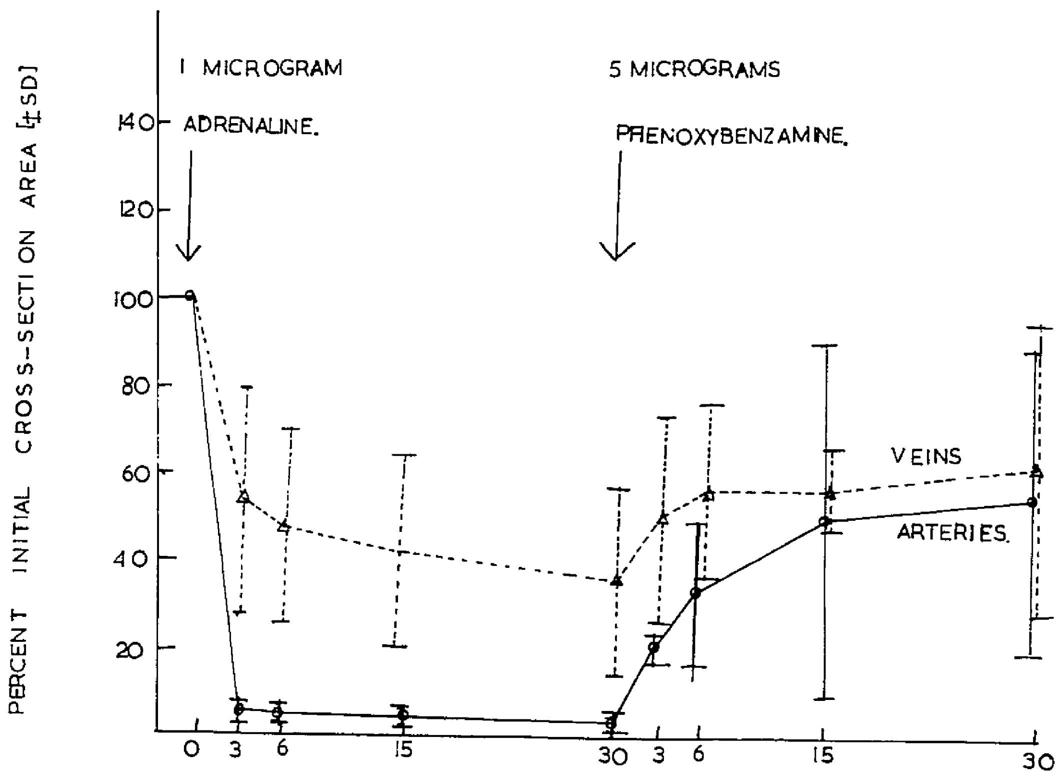


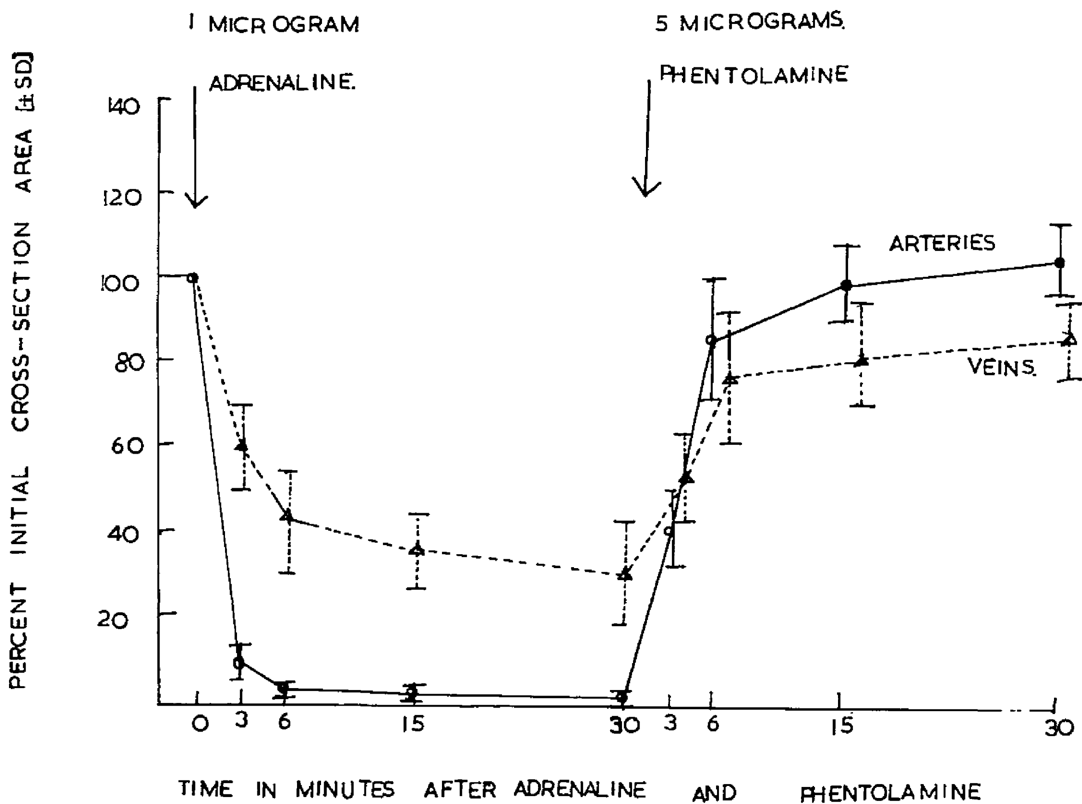
FIGURE 7. The Action of Serotonin (5-Hydroxytryptamine) on the Microvasculature of the Hamster Cheek Pouch. The Local Injection of 5 Micrograms Serotonin into the Cheek Pouch. (Mean Values and Standard Deviations of Six Experiments).



<u>FIGURE 8</u>. The Action of Angiotensin on the Microvasculature of the Hamster Cheek Pouch. The Local Injection of 25 Micrograms Angiotensin II into the Cheek Pouch. (Mean Values and Standard Deviations of 4 Experiments).



<u>FIGURE 9</u>. The Action of Adrenaline, followed by Phenoxybenzamine on the Microvasculature of the Hamster Cheek Pouch. (Mean Values and Standard Deviations of 3 Experiments).



<u>FIGURE 10</u>. The Action of Adrenaline followed by Phentolamine on the Microvasculature of the Hamster Cheek Pouch. (Mean Values and Standard Deviations of 3 Experiments).

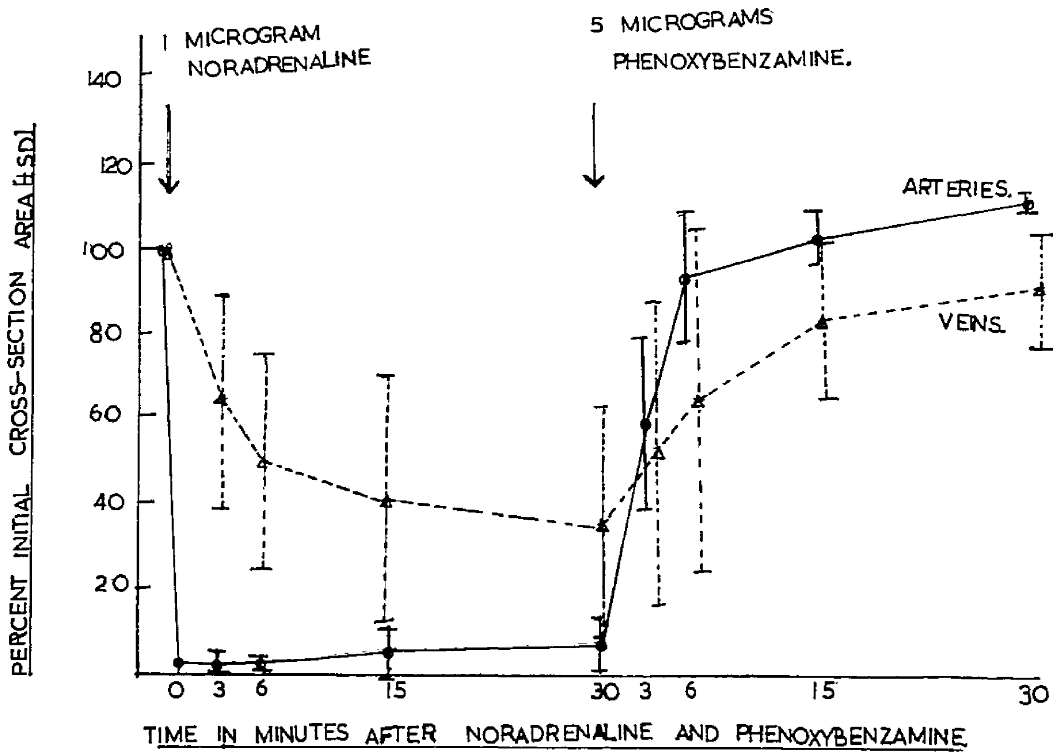


FIGURE 11. The Action of Noradrenaline followed by Phenoxybenzamine on the Microvasculature of the Hamster Cheek Pouch. (Mean Values and Standard Deviations of 3 Experiments).

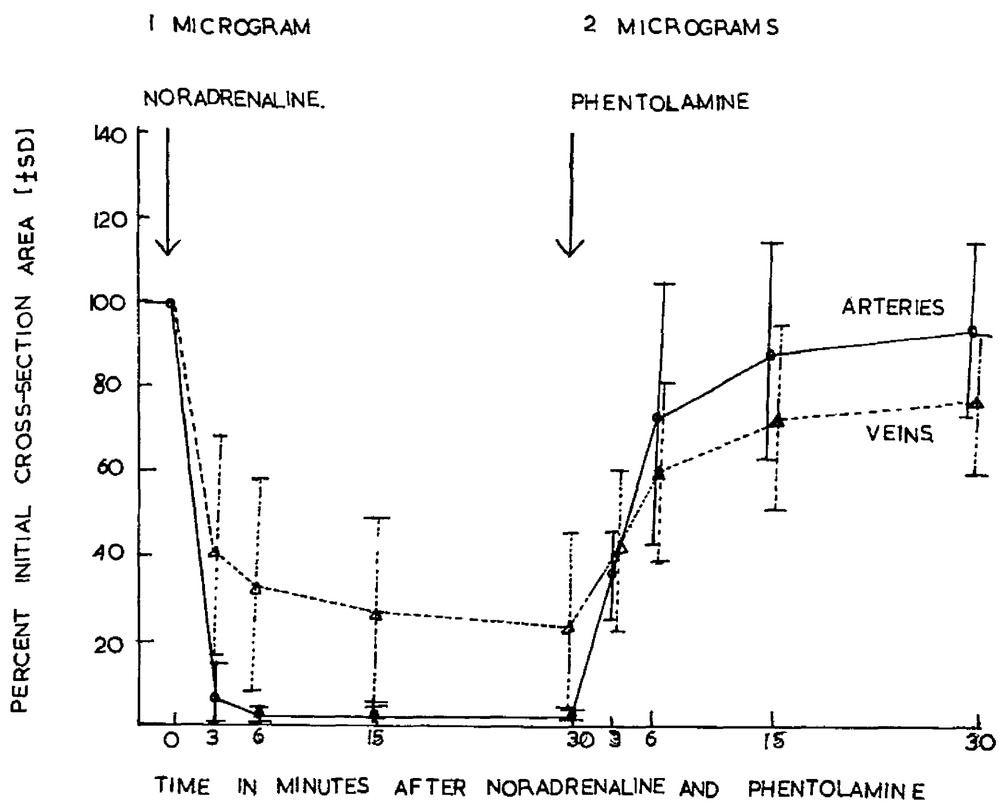


FIGURE 12. The Action of Noradrenaline followed by Phentolamine on the Microvasculature of the Hamster Cheek Pouch. (Mean Values and Standard Deviations of 3 Experiments).

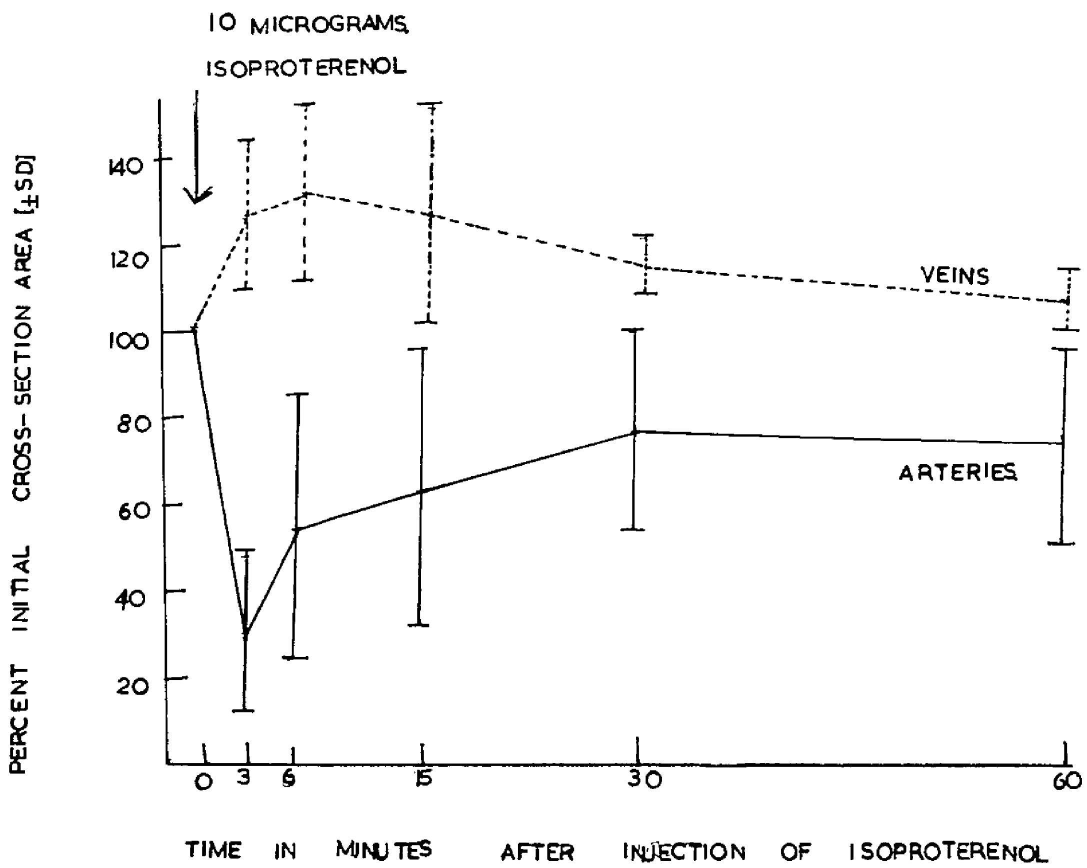


FIGURE 13. The Action of Isoproterenol on the Microvasculature of the Hamster Cheek Pouch. The Local Injection of 10 Micrograms Isoproterenol into the Cheek Pouch. (Mean Values and Standard Deviations of 6 Experiments).

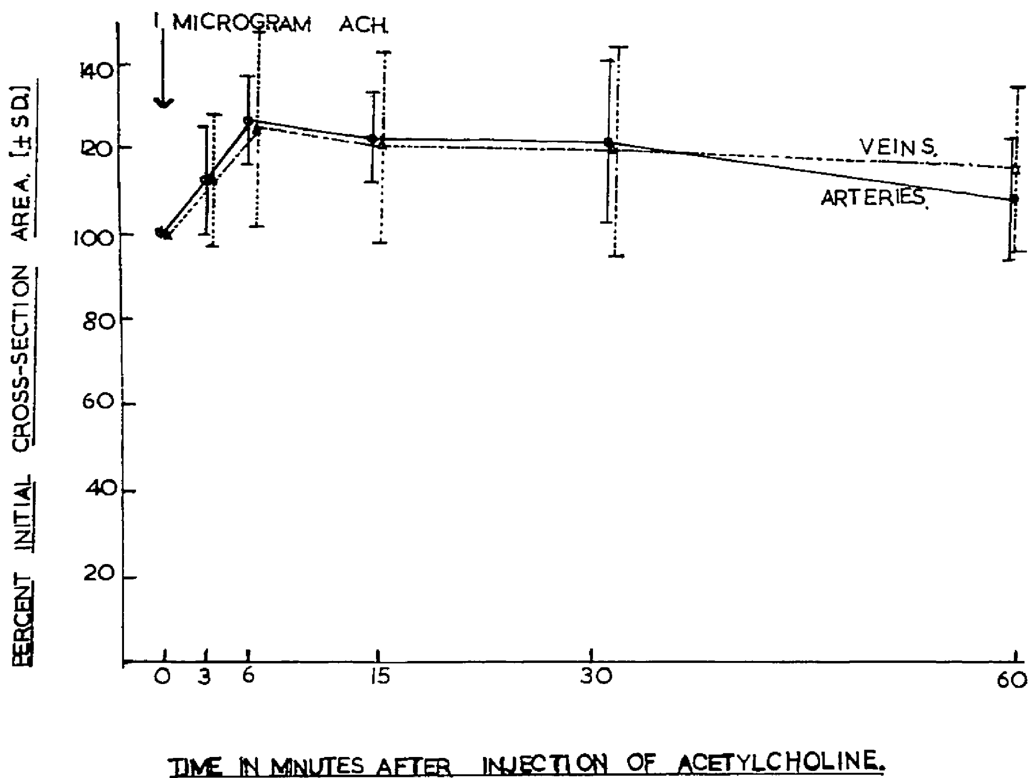


FIGURE 14. The Action of Acetylcholine on the Microvasculature of the Hamster Cheek Pouch. The Local Injection of One Microgram Acetylcholine into the Cheek Pouch. (Mean Values and Standard Deviations of 6 Experiments).

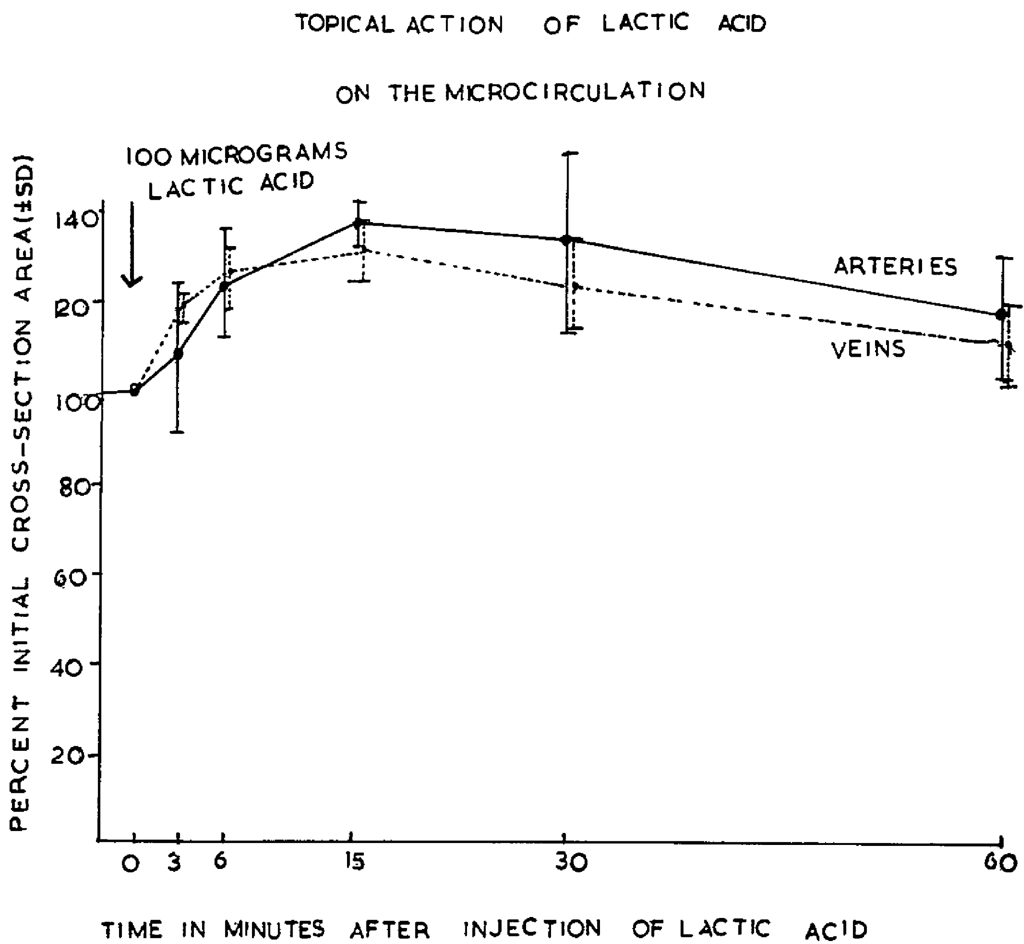


FIGURE 15. The Action of Lactic Acid on the Microvasculature of the Hamster Cheek Pouch. The Local Injection of 100 Micrograms Lactic Acid into the Cheek Pouch. (Mean Values and Standard Deviations of 3 Experiments).

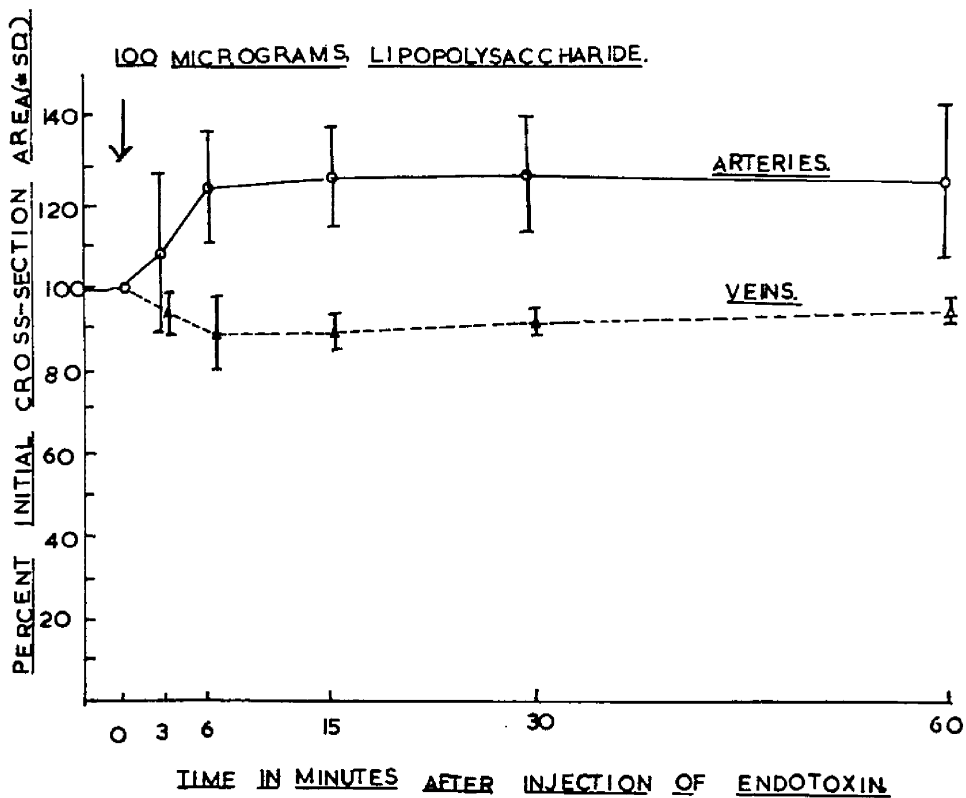


FIGURE 16. The Action on the Microvasculature of the Hamster Cheek Pouch of Locally Injected Endotoxin. The Local Injection into the Cheek Pouch of 100 Micrograms E. coli 026:B6 Lipopolysaccharide. (Mean Values and Standard Deviations of 6 Experiments

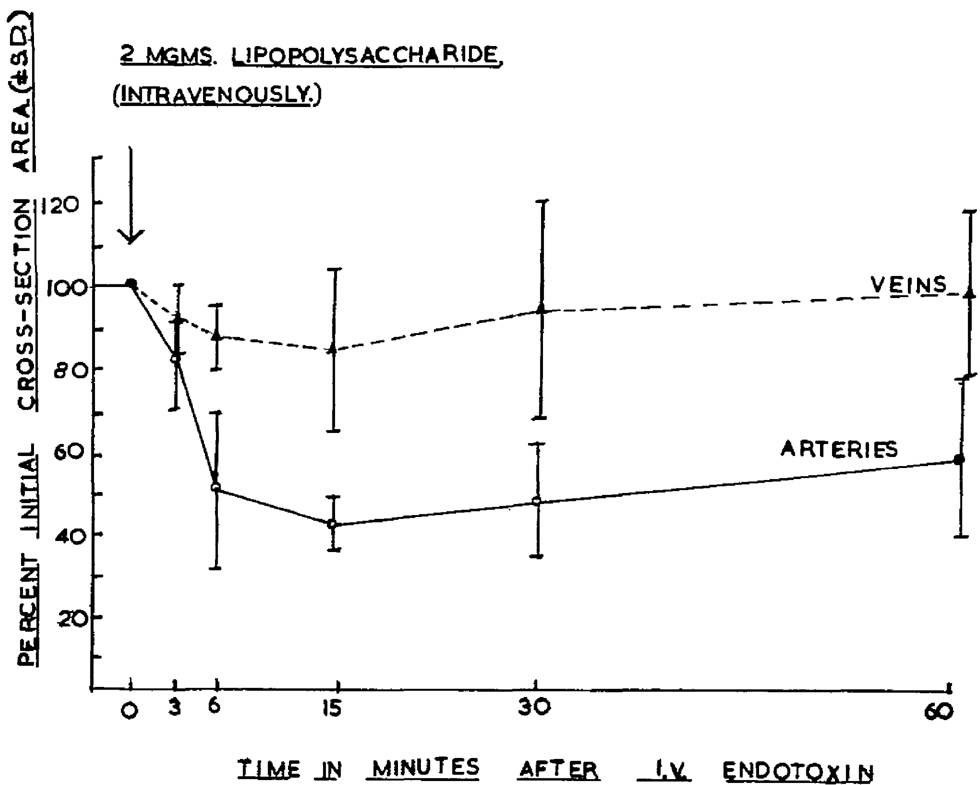


FIGURE 17. The Action on the Microvasculature of the Hamster Cheek Pouch of an Intravenous Injection of Endotoxin. 2 mgms. E. coli 026:B6 Lipopolysaccharide injected Intravenously. (Mean Values and Standard Deviations of 4 Experiments).

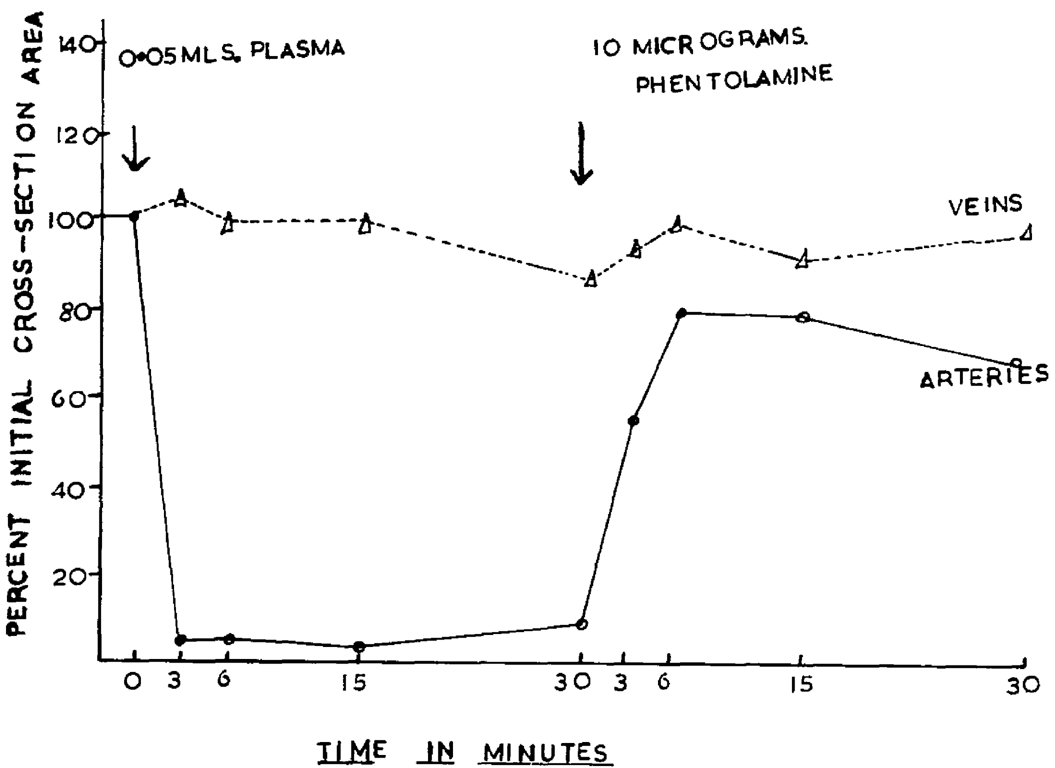


FIGURE 18. The Vasoconstriction of the Plasma of a Patient with Bacteraemic Shock, receiving an Intravenous Infusion of Noradrenaline.

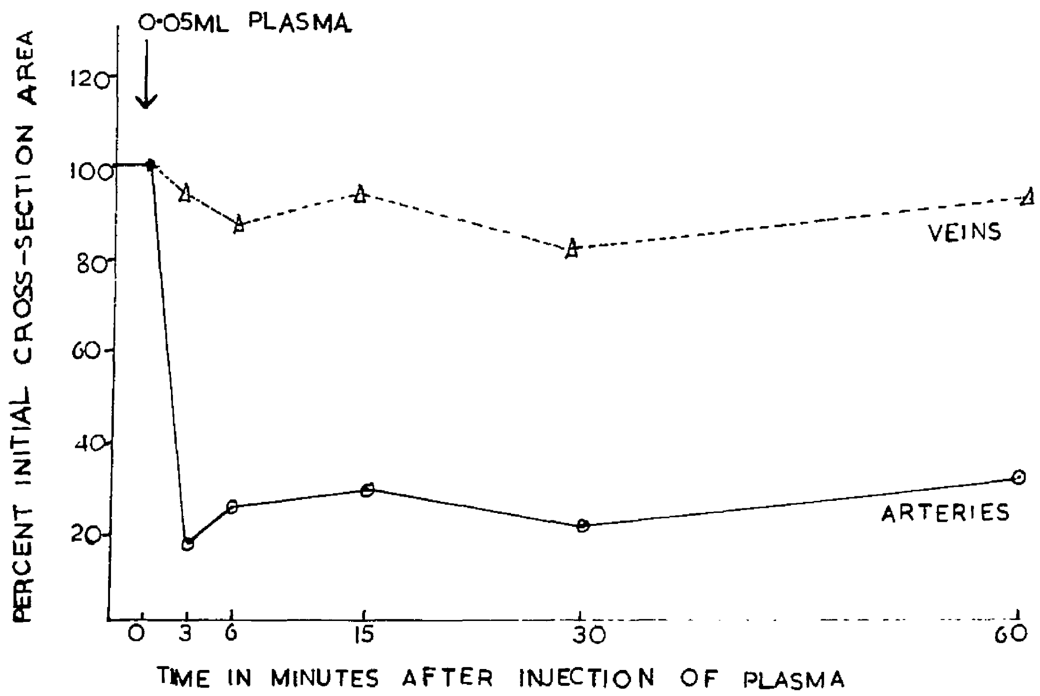


FIGURE 19. The Vasoactivity of Plasma from a Burned Patient.

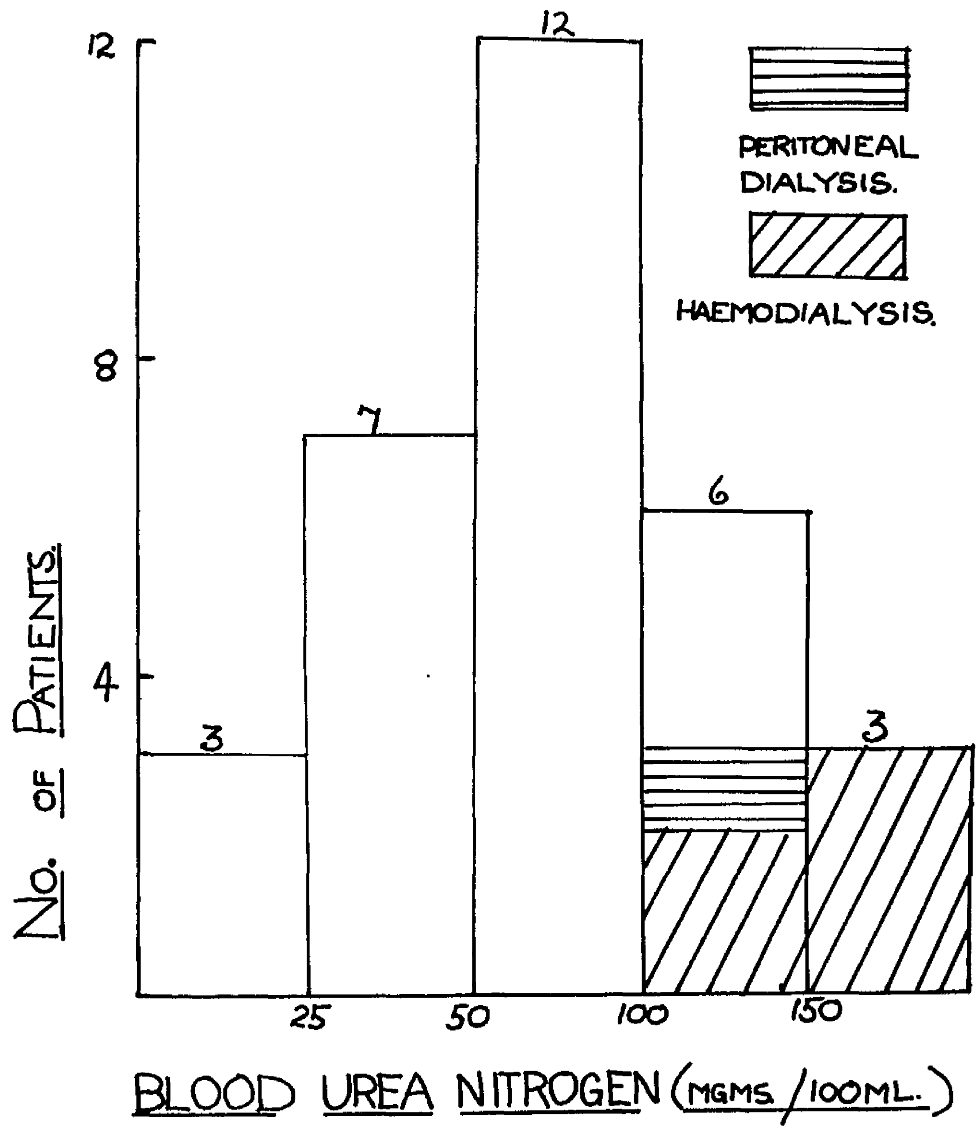


FIGURE 20 Blood urea nitrogen concentrations in patients in bacteraemic shock.

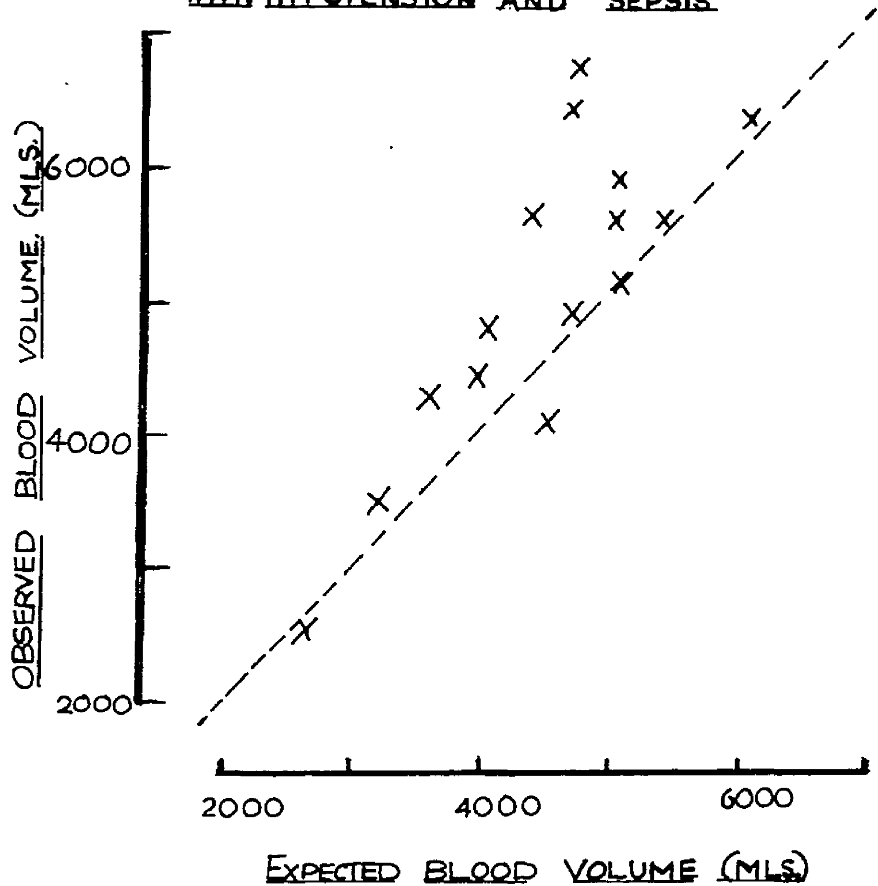


FIGURE 21 Blood Volumes in 15 Patients with Hypotension associated with sepsis. Comparison of the expected blood volume with the observed blood volume of patients with bacteraemic shock. The line of coincidence indicates that hypovolaemia is not a major factor in "Septic Shock".

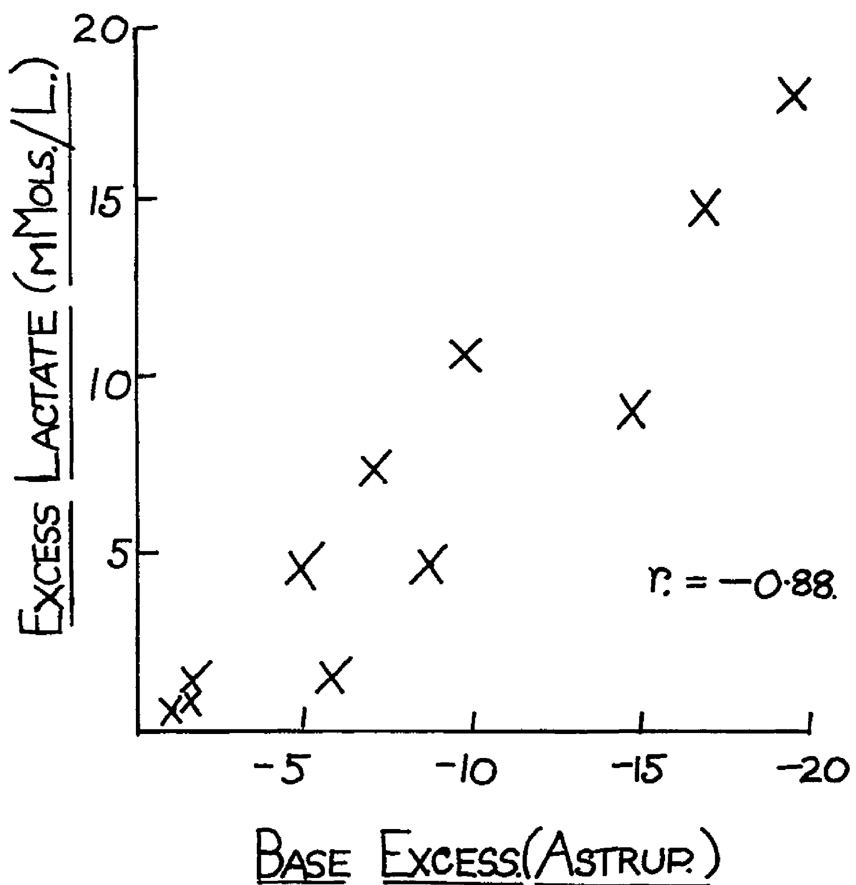
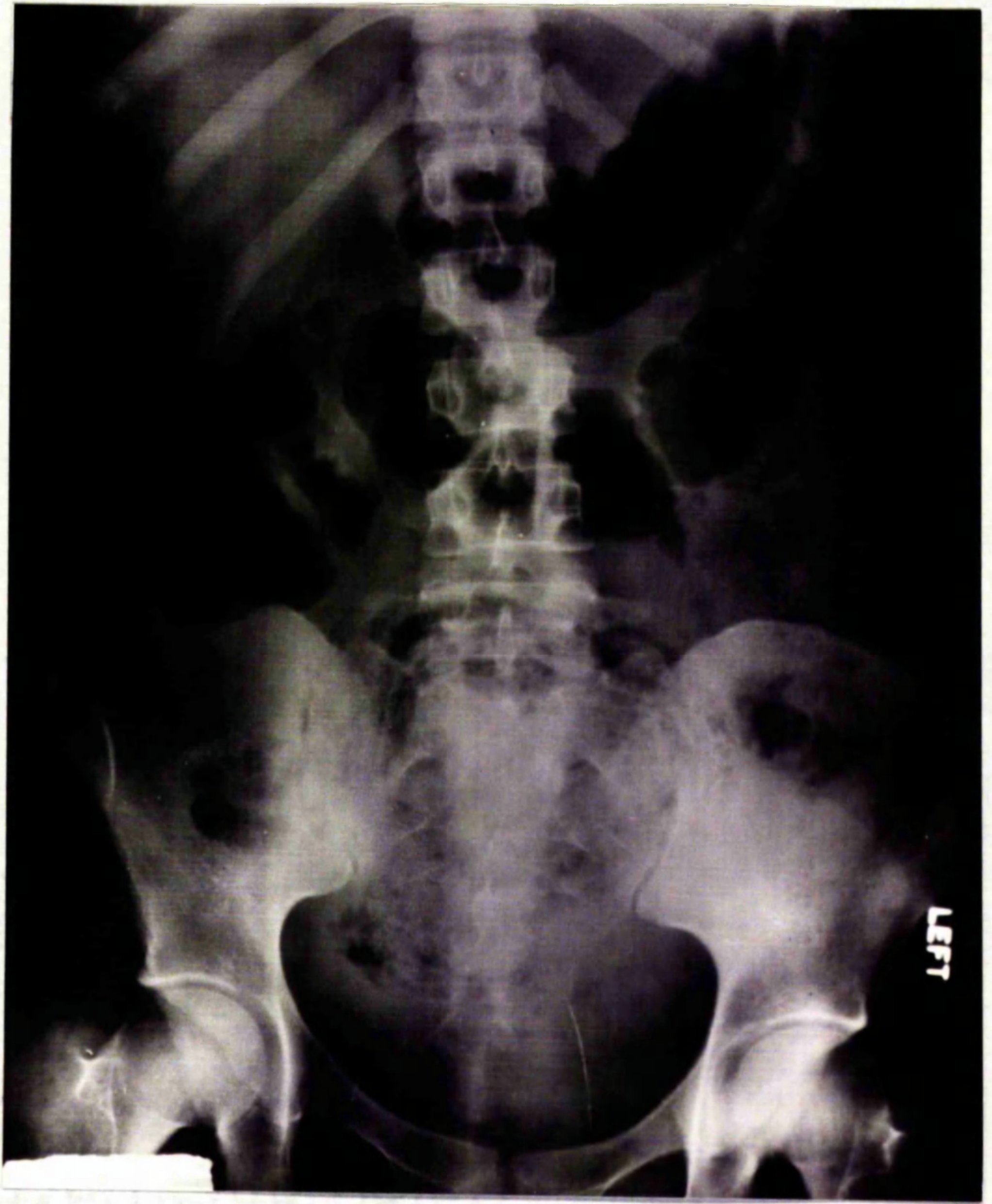


FIGURE 22 Correlation of excess lactate and base excess in patients with hypotension associated with sepsis.

M. C. (Female 66 yrs. #4-76-27) 70% Burns

	January 64 24	1	February 8	15	22	March 1
Room settling plates	S. aureus (6-7-47-77)		S. aureus (UC-18) →			→
Bedding		Sporeformers (B. cereus) S. epidermidis		S. aureus (UC-18) →		→
Nose		S. epidermidis gm. neg. rods		S. aureus (UC-18) → Aerobacter →	Ps. aeruginosa →	→
Sputum				S. aureus (UC-18) → Aerobacter →	Ps. aeruginosa →	→
Hands		Sporeformers (B. cereus) gm. neg. rods			S. aureus (UC-18) →	→
Burns		Sporeformers (B. cereus) gm. neg. rods		S. aureus (UC-18) → E. coli →	Proteus → Aerobacter → Ps. aeruginosa →	→
Blood cultures		Sterile		Sterile		Ps. aeruginosa

FIGURE 23 Bacterial colonisation of burns - Bacteriological data of a patient with extensive deep burns.



<u>FIGURE 24</u>. Patient B.W. (F. 26 yrs) - Septic Abortion. X-ray of Abdomen shows concentric gas shadows in the uterus.

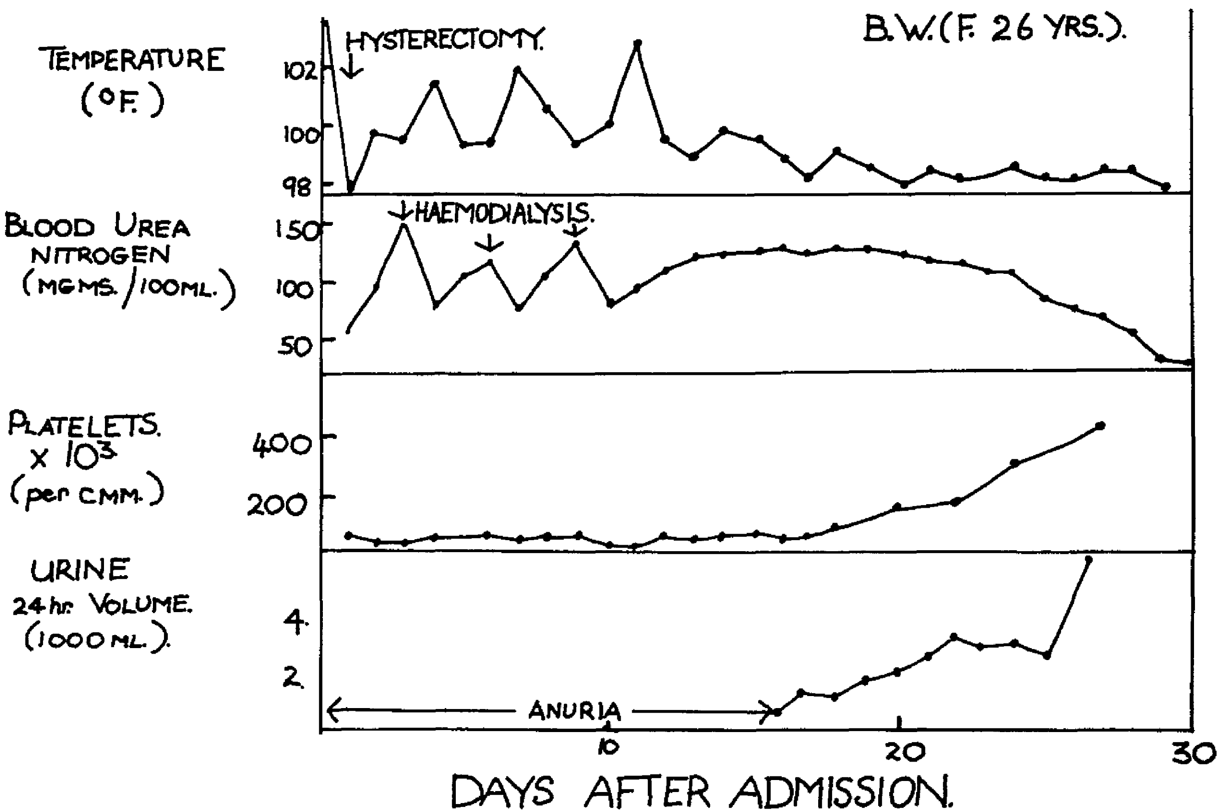


FIGURE 25 Clinical Course in a Case of Septic Abortion. (Case 24 in Appendix 4).

APPENDIX 2.

MAIN TABLES 1–41.

MAIN TABLE 1

MAJOR VESSELS AT ORIGIN OF HAMSTER CKEEK POUCH

	ARTERIES	VEINS
Mean No. of vessels	3.4	3.8
Mean square root diameter (Microns)	72.3	184.5
Total Cross-section area ($x10^{-3} mm^2$)	1.40	10.15
Ratio area vein/artery	7.27	

MAIN TABLE 2

LENGTHS AND DIAMETERS OF MINUTE VESSELS OF THE HAMSTER CHEEK POUCH

(Mean Values ± Standard Error)

Vessel	Length (mm) ± S.E.	Diameter (Microns) ± S.E.
Main Artery	9.1 ± 1.2	74.6 ± 3.6
Artery	4.6 ± 0.33	28.6 ± 1.2
Small Artery	5.1 ± 0.31	19.0 ± 1.3
Terminal Arteriole	1.55 ± 0.14	11.72 ± 0.47
Capillary	0.29 ± 0.009	4.84 ± 0.12
Post Capillary Venule	0.309 ± 0.04	9.13 ± 0.49
Venule	1.64 ± 0.22	24.3 ± 1.5
Small Vein	2.5 ± 0.31	35.5 ± 1.9
Vein	4.17 ± 0.71	75.7 ± 5.3
Main Vein	11.94 ± 1.5	184.0 ± 5.0

MAIN TABLE 3

MEAN DIMENSIONS OF MINUTE VESSELS OF HAMSTER CHEEK POUCH

Vessel	Mean Length (mm)	Mean Diameter (Microns)	Mean No. of Branches	No. of Vessels	Total Cross Sect. Area Microns^2.	Total Volume mm^3.	% Total Volume
Main Artery	9.1	74.6	8.5	3.4*	14,861	0.1347	5.8
Artery	4.6	28.6	3.4	28.9	18,566	0.0852	3.8
Small Artery	5.1	19.0	7.9	98.3	27,871	0.1421	6.3
Terminal Arteriole	1.5	11.7	12.4	776.6	83,485	0.1292	5.6
Capillary	0.29	4.8	-	9,629.8	177,188	0.0514	2.2
Post Cap. Venule	0.31	9.1	3.2	3,009.3	197,019	0.0609	2.7
Venule	1.6	24.3	6.9	436.1	202,250	0.3321	14.6
Small Vein	2.5	35.5	2.7	161.5	159,852	0.3996	17.5
Vein	4.2	75.7	5.6	28.8	129,620	0.5405	23.5
Main Vein	11.9	184.0	7.3	3.9	103,701	0.4127+	17.9

* Mean number of main arteries at origin of Cheek Pouch.

\+ Volume of main veins - assuming these veins to be cones and not cylinders.

MAIN TABLE 4

DISTRIBUTION OF VASCULAR ENDOTHELIUM AND BLOOD VOLUME IN MICROVASCULATURE OF HAMSTER CHEEK POUCH

	% Endothelium (1)	% Volume (2)	Ratio 1/2
Main Artery	2.4	5.8	0.4
Artery	3.9	3.8	1.0
Small Artery	9.8	6.3	1.6
Terminal Arteriole	14.5	5.6	2.6
Capillary	14.0	2.2	6.4
Post Cap. Venule	8.8	2.7	3.3
Venule	18.0	14.6	1.2
Small Vein	14.8	17.5	0.8
Vein	9.4	23.5	0.4
Main Vein	4.4	17.9	0.2

MAIN TABLE 5

THE MICROVASCULATURE IN THE HAMSTER CHEEK POUCH

	Volume	Endothelium
Arteries	21.5%	30.6%
Capillaries	2.2%	14.0%
Veins	76.3%	55.4%

MAIN TABLE 6

PRE-CAPILLARY BOTTLENECKS IN MESENTERIC ARTERIOLES

- IN VIVO MEASUREMENTS - SAUNDERS AND KNISELY (1954).

Animal	Internal Diameter (Microns)
Frog	16.2
Hamster	6.2
Mouse	5.7
Rat	5.95
Rabbit	5.5
Cat	7.99
Dog	6.64

MAIN TABLE 7

CAPILLARY DIAMETERS IN VARIOUS MAMMALS

(in vivo measurements)

Author	Animal	Site	Capillary Diameter (Microns)
Wiedeman (1962)	Bat	Wing	3.7
Zweifach, et al., (1937)	Mouse	Mesentery	3 - 10
Landau, et al., (1957)	Man	Nail bed	5 - 12
Reynolds, et al., (1958)	Dog	Heart	4.0
Irwin, et al., (1954)	Rabbit	Lung	5.0
Beeler, et al., (1964)	Mouse	Muscle and mesentery	4.6
Beeler, et al., (1964)	Pup	Muscle and mesentery	7.4
Present Study	Hamster	Cheek Pouch	4.8

MAIN TABLE 8

BLOOD VOLUME DISTRIBUTION IN THE MICROVASCULATURE

Author	Animal and Tissue	Arteries	Capillaries	Veins
Lutz and Fulton (1958)	Hamster Cheek Pouch	a) 22%	4%	74%
		b) 21%	18%	61%
Wiedeman (1963)	Bat Wing	15.1%	0.4%	84.4%
Present Study	Hamster Cheek Pouch	21.5%	2.2%	76.3%

MAIN TABLE 9

CONTROL EXPERIMENTS. (A)

OBSERVATION OF THE CHEEK POUCH AND NO INJECTION.

% Control Cross-section Area.		TIME IN MINUTES AFTER CONTROL OBSERVATIONS.				
		3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp. 1	Arteries	98.5	107.1	102.0	101.6	91.5
	Veins	97.1	100.3	101.1	91.8	97.6
Exp. 2	Arteries	99.2	97.9	104.2	105.2	108.1
	Veins	100.7	100.8	95.9	95.8	104.2
Exp. 3	Arteries	101.6	96.4	101.2	99.8	97.7
	Veins	98.7	96.3	93.9	93.9	98.7
Mean	Arteries	99.8	100.5	102.5	102.2	99.1
	± S.D.	± 1.6	± 5.8	± 1.6	± 2.7	± 8.4
Mean	Veins	98.8	99.1	97.0	93.8	100.2
	± S.D.	± 1.8	± 2.5	± 3.7	± 2.0	± 3.5

MAIN TABLE 10

CONTROL EXPERIMENTS (B)

Injection of 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	82.3	88.3	100.4	84.0	84.0
		Veins	87.5	93.3	95.9	97.6	100.6
Exp.	2	Arteries	104.3	103.5	94.8	98.9	94.4
		Veins	98.7	97.1	98.0	100.9	97.3
Exp.	3	Arteries	90.3	96.3	97.8	94.8	-
		Veins	95.7	101.1	107.5	97.2	-
Exp.	4	Arteries	98.0	97.8	104.2	105.2	108.1
		Veins	100.7	100.8	95.9	95.8	104.2
Exp.	5	Arteries	98.0	95.4	87.7	95.4	93.1
		Veins	98.9	96.7	94.8	96.7	100.6
Mean		Arteries	94.6	96.3	97.0	95.7	95.0
		± S.D.	± 8.5	± 5.4	± 5.2	± 7.7	± 9.9
Mean		Veins	96.3	97.8	98.4	97.6	100.7
		± S.D.	± 5.2	± 3.2	± 6.4	± 1.9	± 2.8

MAIN TABLE 11

ACTION OF HISTAMINE ON MICROCIRCULATION

(1) Local injection of 10 micrograms histamine base in 0.05 ml. Ringer's Solution into Hamster Cheek Pouch

% Control Cross-section Area.		TIME IN MINUTES AFTER INJECTION OF HISTAMINE. 3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp. 1	Arteries	80.0	114.2	125.9	138.6	129.5
	Veins	87.3	74.2	78.2	74.4	75.4
Exp. 2	Arteries	90.3	49.0	119.2	134.3	140.2
	Veins	86.3	73.8	75.4	70.7	76.3
Exp. 3	Arteries	83.4	130.0	138.3	132.6	108.9
	Veins	74.2	70.7	82.1	70.7	86.6
Exp. 4	Arteries	80.1	122.1	129.0	125.6	126.9
	Veins	96.5	79.5	78.5	85.4	92.3
Exp. 5	Arteries	79.9	123.5	121.1	117.7	112.7
	Veins	90.8	82.2	77.6	84.1	87.7
Exp. 6	Arteries	143.2	153.1	136.9	110.3	104.9
	Veins	91.4	86.0	79.2	87.1	82.5
Mean	Arteries	92.8	115.3	128.4	126.5	120.1
	± S.D.	±20.6	±34.6	± 7.9	±10.8	±13.9
Mean	Veins	87.8	77.7	78.5	78.4	83.5
	± S.D.	± 7.5	± 5.8	± 4.9	± 7.6	± 6.7

MAIN TABLE 12

ACTION OF HISTAMINE ON MICROCIRCULATION

(2) Local injection of 5 micrograms histamine base in 0.05 ml. Ringer's Solution into Hamster Cheek Pouch

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF HISTAMINE.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	87.4	121.2	121.2	136.5	147.2
		Veins	89.8	79.1	82.9	85.0	89.0
Exp.	2	Arteries	80.4	107.5	117.6	120.3	125.3
		Veins	82.9	74.7	67.1	75.3	74.6
Exp.	3	Arteries	80.0	120.0	131.4	146.8	138.1
		Veins	84.8	73.9	73.1	67.2	76.4
Exp.	4	Arteries	86.6	-	96.4	126.8	123.7
		Veins	62.4	-	74.3	88.5	91.8
Exp.	5	Arteries	80.1	88.6	123.6	133.7	147.7
		Veins	69.1	67.2	90.3	93.4	97.3
Exp.	6	Arteries	51.1	80.2	145.4	145.0	-
		Veins	79.4	74.2	82.0	86.0	-
Mean		Arteries	77.6	103.5	122.6	134.9	136.4
		± S.D.	±13.3	±18.5	±16.2	±10.3	±11.4
Mean		Veins	78.1	73.8	78.3	82.6	85.8
		± S.D.	±10.3	± 4.3	± 8.3	±10.3	±11.5

MAIN TABLE 13

ACTION OF SEROTONIN ON MICROCIRCULATION

Local injection of 5 micrograms of serotonin in 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF SEROTONIN.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	10.8	14.1	15.7	19.1	15.1
		Veins	88.2	88.2	87.9	95.9	99.7
Exp.	2	Arteries	17.8	32.6	32.9	28.6	38.6
		Veins	97.7	100.2	90.9	86.1	80.3
Exp.	3	Arteries	70.4	31.1	60.4	45.4	44.1
		Veins	96.4	99.2	100.5	99.8	79.5
Exp.	4	Arteries	4.6	8.5	22.3	21.8	21.7
		Veins	95.9	90.1	87.0	89.4	85.7
Exp.	5	Arteries	48.1	19.7	64.6	45.5	49.4
		Veins	99.7	100.7	96.0	98.7	93.8
Exp.	6	Arteries	19.3	9.1	32.1	29.2	73.7
		Veins	86.1	84.4	95.3	87.7	89.4
Mean		Arteries	28.5	19.2	38.0	31.6	40.4
		± S.D.	±25.4	±10.6	±19.9	±11.4	±21.0
Mean		Veins	94.0	93.8	92.9	92.9	88.1
		± S.D.	± 5.5	± 7.1	± 5.2	± 5.2	± 7.8

MAIN TABLE 14

ACTION OF ACETYLCHOLINE ON THE MICROCIRCULATION

Local injection of 1 microgram Acetylcholine in 0.05 ml. Ringer's Solution into Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF ACETYLCHOLINE.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	118.8	128.0	107.7	109.7	108.5
		Veins	98.2	92.3	91.6	93.0	96.5
Exp.	2	Arteries	112.7	127.1	132.7	142.8	114.8
		Veins	135.6	159.2	148.2	156.3	134.6
Exp.	3	Arteries	110.7	118.1	123.8	97.5	94.9
		Veins	102.6	147.6	153.2	147.6	146.4
Exp.	4	Arteries	93.5	115.5	111.8	105.8	91.0
		Veins	103.8	105.7	114.2	109.8	98.2
Exp.	5	Arteries	112.0	140.3	128.8	142.4	129.1
		Veins	108.3	117.7	110.9	126.1	117.7
Exp.	6	Arteries	132.7	138.9	128.4	128.1	116.9
		Veins	129.6	131.0	114.8	109.8	111.6
Mean		Arteries	113.4	128.0	122.2	121.1	109.2
		± S.D.	±12.7	±10.2	±10.1	±19.5	±14.3
Mean		Veins	113.0	125.6	122.2	123.8	117.3
		± S.D.	±15.6	±25.3	±23.7	±24.3	±19.9

MAIN TABLE 15

ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION

(A) Local action of 25 micrograms Angiotensin II in 0.05 ml. Ringer's Solution in the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN II.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	4.8	3.3	11.3	93.7	93.6
		Veins	68.6	69.4	90.3	91.6	90.2
Exp.	2	Arteries	4.2	16.9	20.7	92.9	105.4
		Veins	96.0	86.6	82.5	87.8	92.7
Exp.	3	Arteries	12.8	62.3	74.0	88.1	80.1
		Veins	96.0	94.2	95.3	95.5	99.5
Exp.	4	Arteries	4.6	11.8	61.6	86.4	91.7
		Veins	90.0	89.5	90.5	95.4	97.1
Mean		Arteries	6.6	23.6	41.9	90.3	92.7
		± S.D.	± 4.1	±19.1	±24.5	± 3.6	±10.3
Mean		Veins	87.7	84.9	89.7	92.6	94.9
		± S.D.	±13.0	±10.8	± 5.3	± 3.7	± 4.2

MAIN TABLE 16

ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION

(B) Local action of 5 micrograms Angiotensin II in 0.05 ml. Ringer's Solution in the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN II. 3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	5.4	16.1	31.3	27.7	37.9
		Veins	79.1	73.3	80.0	74.5	84.7
Exp.	2	Arteries	84.7	83.4	74.5	56.1	52.5
		Veins	93.1	93.7	91.0	93.2	86.7
Exp.	3	Arteries	26.6	30.9	55.4	79.0	90.3
		Veins	94.4	96.0	90.9	96.9	100.9
Exp.	4	Arteries	13.7	19.9	54.3	81.2	108.2
		Veins	96.2	95.5	90.1	93.0	104.2
Mean		Arteries	32.6	37.6	53.9	61.0	72.2
		± S.D.	±35.8	±31.2	±17.7	±24.9	±32.6
Mean		Veins	90.7	89.6	88.0	89.4	94.1
		± S.D.	± 7.8	±10.9	± 5.3	±10.2	± 9.8

MAIN TABLE 17

ACTION OF CATECHOLAMINES ON MICROCIRCULATION

(A) Injection of 1 microgram Adrenaline followed in 30 mins. by injection of 5 micrograms Phenoxybenzamine (Dibenzyline).

% Control Cross-section Area.		TIME IN MINUTES AFTER INJECTION							
		3 mins.	6 mins.	15 mins.	30 mins.	3 mins.	6 mins.	15 mins.	30 mins.
Exp. 1	Arteries	6.4	5.4	2.7	2.7	22.3	31.6	34.2	36.0
	Veins	61.0	52.7	41.9	33.0	40.9	45.8	49.3	47.9
Exp. 2	Arteries	4.9	4.7	5.4	6.2	17.6	21.4	21.1	34.6
	Veins	75.9	69.2	65.2	62.7	79.1	81.5	66.3	63.9
Exp. 3	Arteries	9.1	8.0	5.9	5.1	24.5	54.0	95.3	95.4
	Veins	25.0	25.0	21.4	17.3	30.4	45.3	58.2	82.0
Mean	Arteries	6.8	6.0	4.7	4.7	21.5	35.7	50.2	55.3
	± S.D.	± 2.1	± 1.7	± 2.2	± 2.2	± 3.5	±16.7	±39.6	±34.7
Mean	Arteries	54.0	49.0	42.8	37.7	50.1	57.6	57.9	64.6
	± S.D.	±26.2	±22.3	±21.9	±23.1	±25.6	±20.7	± 8.1	±34.7

MAIN TABLE 18

ACTION OF CATECHOLAMINES ON MICROCIRCULATION

(A) Injection of 1 microgram Adrenaline followed in 30 mins. by injection of 5 micrograms Phentolamine (Regitine).

% Control Cross-section Area.		TIME IN MINUTES AFTER INJECTIONS.							
		3 mins.	6 mins.	15 mins.	30 mins.	3 mins.	6 mins.	15 mins.	30 mins.
Exp. 1	Arteries	12.8	5.1	4.7	5.1	42.2	102.9	106.2	114.5
	Veins	52.4	33.9	29.4	23.2	48.1	85.8	85.6	96.2
Exp. 2	Arteries	15.4	5.9	4.6	4.6	50.6	77.1	102.0	99.9
	Veins	73.8	57.3	45.9	46.2	65.1	89.1	92.7	91.0
Exp. 3	Arteries	6.7	3.7	2.9	1.5	34.4	78.4	88.9	100.4
	Veins	60.4	43.5	36.1	26.5	46.8	61.1	68.4	79.6
Mean	Arteries	11.6	4.9	4.1	3.7	42.4	86.1	99.0	104.9
	± S.D.	± 4.5	± 1.6	± 1.4	± 2.6	± 8.1	±14.5	± 9.0	± 8.3
Mean	Veins	62.2	44.9	37.1	32.0	53.3	78.7	82.2	88.9
	± S.D.	±10.8	±11.8	± 8.3	±12.4	±10.2	±15.3	±12.5	± 8.5

MAIN TABLE 19

ACTION OF CATECHOLAMINES ON MICROCIRCULATION

(C) Injection of 1 microgram Noradrenaline followed in 30 mins. by injection of 5 micrograms Phenoxybenzamine.

% Control Cross-section Area.		TIME IN MINUTES AFTER INJECTIONS.							
		3 mins.	6 mins.	15 mins.	30 mins.	3 mins.	6 mins.	15 mins.	30 mins.
Exp. 1	Arteries	5.5	4.2	15.7	15.7	82.1	109.1	109.4	102.1
	Veins	72.2	49.4	64.0	57.8	80.1	92.6	92.8	99.4
Exp. 2	Arteries	1.3	1.6	2.6	2.9	42.0	94.1	103.1	101.8
	Veins	83.6	77.4	53.3	47.7	69.6	86.4	95.5	97.0
Exp. 3	Arteries	2.4	1.3	1.5	5.0	54.6	79.1	96.0	101.6
	Veins	34.6	24.7	8.9	6.5	12.9	20.5	61.9	74.2
Mean	Arteries	3.1	2.4	6.6	7.9	59.6	94.1	102.8	101.8
	± S.D.	± 2.2	± 1.6	± 7.9	± 6.9	±20.5	±15.0	± 6.7	± 0.4
Mean	Veins	63.5	50.5	42.1	37.3	54.2	66.5	83.4	90.2
	± S.D.	±25.6	±25.4	±29.2	±27.2	±36.1	±39.9	±18.2	±13.9

MAIN TABLE 20

ACTION OF CATECHOLAMINES ON MICROCIRCULATION

(D) Injection of 1 microgram Noradrenaline followed in 30 mins. by injection of 2 micrograms Phentolamine.

% Control Cross-section Area.		TIME IN MINUTES AFTER INJECTIONS.							
		3 mins.	6 mins.	15 mins.	30 mins.	3 mins.	6 mins.	15 mins.	30 mins.
Exp. 1	Arteries	5.5	1.6	1.5	0.6	31.6	45.9	59.6	71.5
	Veins	10.8	6.3	4.1	2.3	21.3	38.6	50.9	58.7
Exp. 2	Arteries	17.5	4.8	2.5	1.7	30.1	69.3	96.2	98.8
	Veins	51.8	40.6	28.6	24.0	51.9	78.7	86.8	83.9
Exp. 3	Arteries	3.2	1.2	1.9	1.2	48.4	106.6	111.4	111.1
	Veins	60.9	56.2	49.6	46.0	54.6	62.5	83.0	86.8
Mean	Arteries	8.7	2.5	2.0	1.2	36.7	73.9	89.1	93.9
	± S.D.	± 7.6	± 1.9	± 0.5	± 0.2	±10.2	±30.6	±26.6	±20.4
Mean	Veins	41.2	34.4	27.4	24.1	42.6	59.9	73.6	76.5
	± S.D.	±26.7	±25.5	±22.8	±21.8	±18.5	±20.2	±19.7	±15.4

MAIN TABLE 21

ACTION OF PHENOXYBENZAMINE ON THE MICROCIRCULATION

Injection of 20 micrograms Phenoxybenzamine (Dibenzyline) in 0.05 ml. Ringer's Solution in the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	96.2	101.0	98.6	88.0	-
		Veins	97.0	95.0	90.6	93.9	-
Exp.	2	Arteries	92.5	101.7	113.9	113.9	105.8
		Veins	99.0	101.0	93.1	96.6	94.9
Exp.	3	Arteries	97.4	105.7	105.5	107.7	105.7
		Veins	100.2	98.8	99.3	97.3	100.1
Mean		Arteries	95.4	102.8	106.0	103.2	105.8
		± S.D.	± 2.6	± 2.5	± 7.6	±11.5	± 0
Mean		Veins	98.7	98.3	94.3	96.6	97.0
		± S.D.	± 1.1	± 3.0	± 4.5	± 1.5	± 3.7

MAIN TABLE 22

ACTION OF PHENTOLAMINE ON THE MICROCIRCULATION

Injection of 10 micrograms Phentolamine (Regitine) in 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

% Control Cross-section Area.		TIME IN MINUTES AFTER INJECTION. 3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp. 1	Arteries	86.3	98.5	101.9	100.2	99.0
	Veins	91.6	100.6	98.2	106.6	101.1
Exp. 2	Arteries	95.0	95.7	92.3	97.7	102.8
	Veins	100.4	99.9	100.1	102.9	98.7
Exp. 3	Arteries	95.7	98.0	101.6	99.5	99.0
	Veins	98.8	98.0	96.8	102.0	102.5
Mean	Arteries	92.3	97.4	101.9	99.1	100.3
	± S.D.	± 5.1	± 1.5	± 5.5	± 1.3	± 3.1
Mean	Veins	96.9	99.5	98.4	104.1	100.8
	± S.D.	± 4.7	± 1.6	± 1.7	± 2.4	± 2.7

MAIN TABLE 23

ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION

(1) Injection of 10 micrograms Isoproterenol in 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

% Control Cross-section Area.		TIME IN MINUTES AFTER INJECTION. 3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp. 1	Arteries	20.5	12.4	8.2	37.1	46.9
	Veins	108.9	124.8	102.6	109.6	99.0
Exp. 2	Arteries	25.0	82.7	96.2	104.2	-
	Veins	150.0	127.7	123.4	112.1	-
Exp. 3	Arteries	19.0	59.7	70.4	65.1	56.8
	Veins	140.2	124.5	108.1	116.5	117.6
Exp. 4	Arteries	62.3	77.9	83.4	91.4	96.1
	Veins	120.0	171.7	174.2	124.0	104.7
Exp. 5	Arteries	44.1	73.5	82.2	88.6	87.0
	Veins	137.8	131.5	126.3	123.6	115.5
Exp. 6	Arteries	17.6	19.7	44.1	84.7	95.8
	Veins	109.1	112.5	115.2	112.7	107.4
Mean	Arteries	31.4	54.3	64.1	78.5	76.5
	± S.D.	±18.0	±30.7	±32.6	±23.9	±23.0
Mean	Veins	127.7	132.1	124.9	116.4	108.8
	± S.D.	±17.4	±20.4	±25.1	± 6.1	± 7.7

MAIN TABLE 24

ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION

(2) Injection of 5 micrograms Isoproterenol in 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	71.2	87.7	78.7	55.3	35.8
		Veins	117.7	124.8	114.9	115.7	124.1
Exp.	2	Arteries	21.2	42.0	37.9	49.6	84.4
		Veins	136.3	120.9	112.2	98.8	95.8
Exp.	3	Arteries	54.4	61.2	77.4	88.8	85.7
		Veins	125.3	144.4	130.5	113.7	114.7
Mean		Arteries	48.9	63.6	64.7	64.6	68.6
		± S.D.	±25.4	±23.0	±23.2	±21.2	±28.4
Mean		Veins	123.3	130.0	119.2	109.4	114.6
		± S.D.	±12.3	±12.9	±13.9	±12.9	±14.4

MAIN TABLE 25

ACTION OF LACTIC ACID ON THE MICROCIRCULATION

Injection of 100 micrograms Lactic Acid in 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	113.0	127.9	140.0	127.9	106.9
		Veins	121.2	129.8	127.4	130.1	119.3
Exp.	2	Arteries	89.5	111.4	131.5	119.0	115.3
		Veins	118.5	118.1	127.2	111.7	100.8
Exp.	3	Arteries	122.3	134.9	140.9	156.1	133.3
		Veins	115.2	129.8	138.7	128.2	114.4
Mean		Arteries	108.3	124.7	137.5	134.3	118.5
		± S.D.	±16.9	±12.1	± 5.2	±19.4	±13.5
Mean		Veins	118.3	125.9	131.1	123.3	111.5
		± S.D.	± 2.7	± 6.8	± 6.6	±10.1	± 9.8

MAIN TABLE 26

ACTION OF CORTISONE ON THE MICROCIRCULATION

Injection of 50 micrograms cortisone acetate in 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	104.5	100.7	90.2	79.5	80.0
		Veins	94.6	89.4	90.1	88.4	94.7
Exp.	2	Arteries	98.4	101.6	94.4	92.8	98.3
		Veins	92.9	90.1	92.9	95.9	99.7
Exp.	3	Arteries	103.3	94.5	103.3	99.8	105.3
		Veins	99.9	104.1	104.1	110.9	98.1
Mean		Arteries	102.1	98.9	96.0	90.7	94.5
		± S.D.	± 3.2	± 3.9	± 6.7	±10.3	±13.2
Mean		Veins	95.8	94.5	95.7	98.4	97.5
		± S.D.	± 3.7	± 8.3	± 7.4	±11.4	± 2.6

MAIN TABLE 27

ACTION OF ENDOTOXIN ON THE MICROCIRCULATION

(A) Injection of 100 micrograms E. coli 026:B6 Lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	106.2	115.0	118.3	122.3	120.8
		Veins	97.8	99.4	92.3	93.8	92.6
Exp.	2	Arteries	113.5	123.0	124.6	127.4	117.5
		Veins	98.2	92.4	96.6	96.7	96.2
Exp.	3	Arteries	139.4	143.5	146.6	149.4	154.7
		Veins	94.4	84.8	91.6	94.2	97.0
Exp.	4	Arteries	89.4	112.0	129.2	135.9	141.8
		Veins	95.5	95.8	86.6	87.5	91.8
Exp.	5	Arteries	109.5	138.9	118.9	110.7	104.1
		Veins	83.6	72.7	89.3	89.0	94.7
Exp.	6	Arteries	79.1	107.8	107.8	115.6	107.8
		Veins	97.5	91.7	84.0	91.9	97.5
Mean		Arteries	106.2	123.4	124.2	126.9	124.4
		± S.D.	±20.9	±14.7	±13.1	±14.2	±19.8
Mean		Veins	94.5	89.5	90.1	92.2	95.0
		± S.D.	± 5.5	± 9.5	± 4.1	± 3.4	± 2.4

MAIN TABLE 28

ACTION OF ENDOTOXIN ON THE MICROCIRCULATION

(B) Injection of 500 micrograms E. coli 026:B6 Lipopolysaccharide in 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	162.5	187.5	175.3	133.9	107.5
		Veins	95.5	95.7	89.4	95.2	92.4
Exp.	2	Arteries	104.0	147.2	177.3	163.8	146.5
		Veins	91.8	86.9	77.0	83.7	90.0
Exp.	3	Arteries	136.9	165.6	175.7	159.9	145.2
		Veins	67.7	70.0	57.4	61.3	70.6
Mean		Arteries	134.5	166.8	176.1	152.5	133.1
		± S.D.	±29.7	±20.2	± 1.5	±16.3	±22.2
Mean		Veins	85.0	84.2	74.6	80.1	84.3
		± S.D.	±15.1	±13.1	±16.1	±17.2	±11.9

MAIN TABLE 29

ACTION OF ENDOTOXIN ON THE MICROCIRCULATION

(C) Injection 0.05 ml. E. coli antigen (crude extract) into Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	121.3	132.9	126.2	131.9	109.9
		Veins	81.5	80.7	74.4	81.5	81.5
Exp.	2	Arteries	56.8	65.8	112.0	150.7	124.9
		Veins	82.0	84.5	81.4	87.8	90.5
Exp.	3	Arteries	100.9	113.5	120.0	117.6	109.9
		Veins	94.0	81.3	75.0	74.9	83.2
Mean		Arteries	93.0	104.1	119.4	133.4	114.9
		± S.D.	±32.9	±26.3	± 7.1	±16.6	± 8.7
Mean		Veins	85.8	82.2	76.9	81.4	85.1
		± S.D.	± 7.1	± 2.0	± 3.9	± 6.4	± 4.8

MAIN TABLE 30

ACTION OF ENDOTOXIN ON THE MICROCIRCULATION

(D) Injection 0.05 ml. E. coli Filtrate into Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION.				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	153.5	159.6	186.2	175.0	-
		Veins	84.0	76.6	82.7	65.7	-
Exp.	2	Arteries	95.3	82.1	168.1	147.1	191.3
		Veins	74.1	69.4	88.0	58.2	61.0
Exp.	3	Arteries	100.0	158.2	174.0	142.8	155.2
		Veins	92.6	80.4	79.5	77.3	88.4
Mean		Arteries	116.3	133.3	176.1	155.2	173.3
		± S.D.	±32.3	±44.4	± 9.2	±19.3	±25.5
Mean		Veins	83.6	75.5	83.4	67.1	74.7
		± S.D.	± 9.3	± 5.6	± 4.3	±11.9	±19.4

MAIN TABLE 31

SYSTEMIC ACTION OF ENDOTOXIN ON THE MICROCIRCULATION

Injection into femoral vein of 2 milligrams E. coli 026:B.6 Lipopolysaccharide in 0.5 ml. Ringer's Solution. Microcirculatory changes observed in Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INTRAVENOUS INJECTION OF ENDOTOXIN				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	88.7	53.6	44.3	57.4	60.9
		Veins	98.1	90.1	106.4	131.4	117.1
Exp.	2	Arteries	92.5	20.0	28.9	26.0	32.0
		Veins	96.0	97.3	91.3	96.1	104.7
Exp.	3	Arteries	74.6	72.9	38.9	56.7	76.6
		Veins	76.2	74.9	52.1	62.6	69.4
Exp.	4	Arteries	65.3	48.1	45.2	37.0	-
		Veins	95.8	88.0	79.9	77.0	-
Mean		Arteries	80.3	48.7	39.3	44.3	56.5
		± S.D.	±12.6	±21.8	± 7.5	±15.4	±22.6
Mean		Veins	91.5	87.6	82.4	91.8	97.1
		± S.D.	±10.3	± 9.3	±22.9	±29.8	±24.8

MAIN TABLE 32

SEQUESTRATION OF PLATELETS AFTER INTRAVENOUS ENDOTOXIN.

2 milligrams E. coli 026: B.6 Lipopolysaccharide injected intravenously.

Platelet Counts in Hamsters (per c.mm.)

		A Control (Before Endotoxin)	B 30 mins. after Endotoxin
Exp. 1	a.	744,000	17,000
	b.	767,000	14,000
Exp. 2	a.	742,000	116,000
	b.	766,000	134,000
Exp. 3	a.	782,000	196,000
	b.	753,000	184,000

MAIN TABLE 33

CONTROL EXPERIMENTS (A)

ACTION OF NORMAL SERUM ON MICROCIRCULATION

Local injection of 0.05 ml. normal human serum into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF SERUM				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	61.3	96.5	101.3	79.9	72.2
		Veins	85.5	98.5	94.7	90.8	95.4
Exp.	2	Arteries	11.8	22.9	66.1	80.5	89.7
		Veins	76.1	85.2	84.3	91.3	88.7
Exp.	3	Arteries	54.4	70.2	101.6	97.3	107.1
		Veins	101.1	109.9	110.9	101.9	100.2

MAIN TABLE 34

CONTROL EXPERIMENTS (B)

ACTION OF NORMAL PLASMA ON MICROCIRCULATION

Local injection of 0.05 ml. normal human plasma into the Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF PLASMA				
			3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Exp.	1	Arteries	100.9	99.7	102.9	105.3	-
		Veins	104.7	103.0	90.4	86.6	-
Exp.	2	Arteries	97.2	96.0	104.0	99.2	102.9
		Veins	99.6	99.2	100.8	103.6	103.0
Exp.	3	Arteries	98.1	93.7	89.5	86.3	85.4
		Veins	97.9	96.1	100.8	102.7	103.8

MAIN TABLE 35

ACTION OF PLASMA FROM PATIENTS IN BACTERAEMIC SHOCK

Local injection of 0.05 ml. plasma into Hamster Cheek Pouch.

% Control Cross-section area.			3 mins.	6 mins.	15 mins.	30 mins.	60 mi
1.	Male (54 years) perineal prostactomy Blood culture - E. coli.	Arteries	45.6	56.1	38.9	47.6	-
		Veins	99.8	101.8	102.6	106.0	-
2.	Male (66 years) Peritonitis, leak from ileal bladder anastomosis Blood culture - Ps. aeruginosa.	Arteries	87.3	69.3	50.7	53.2	84.8
		Veins	95.2	94.6	88.2	92.1	94.4
3.	Male (58 years) Peritonitis. Perforation of carcinoma of stomach Blood culture - Serratia species.	Arteries	25.1	13.7	11.7	8.0	-
		Veins	97.7	64.3	58.5	42.8	-
3B.	Injection of 10 micrograms Phenoxybenzamine at 30 mins. after injection of plasma of patient 3 above.	Arteries	36.7	53.6	45.7	70.1	
		Veins	67.6	73.4	85.3	63.2	

MAIN TABLE 36

ACTION OF PLASMA FROM PATIENTS WITH BURNS

Local injection of 0.05 ml. plasma into Hamster Cheek Pouch.

% Control Cross-section Area.			TIME IN MINUTES AFTER INJECTION OF PLASMA.			
		3 mins.	6 mins.	15 mins.	30 mins.	60 mins.
Patient 1	Arteries	19.3	25.8	29.7	21.7	32.1
	Veins	92.8	87.4	93.0	80.5	92.5
Patient 2	Arteries	22.2	32.2	24.8	28.5	33.2
	Veins	71.6	76.4	73.3	68.5	86.1
Patient 3	Arteries	51.1	43.4	41.5	50.8	66.7
	Veins	95.1	108.8	106.0	97.5	106.9
Patient 4	Arteries	95.4	96.2	97.0	96.3	92.0
	Veins	99.0	97.6	101.6	98.1	99.4

MAIN TABLE 37

MAJOR SITE OF DISEASE IN PATIENTS WITH BACTERAEMIC SHOCK.

MAJOR SITE OF DISEASE	TOTAL	DEAD
ALIMENTARY TRACT (including traumatic and post-operative)	12	11
BILIARY TRACT	3	2
URINARY TRACT	2	1
FEMALE REPRODUCTIVE TRACT	2	1
BURNS. (30-80% body surface)	8	4
IMMUNOSUPPRESSION (Homotransplantation)	4	4
TOTAL	31	23 (74%)

MAIN TABLE 38

POSITIVE BLOOD CULTURES

	TOTAL NUMBER	DEAD	BACTERIUM
GRAM-POSITIVE BACTERIA	1	0	Staphylococcus aureus (U.C. 18) *
GRAM-NEGATIVE BACTERIA	7	4	Escherichia coli
	4	3	Aerobacter/Klebsiella species
	3	3	Pseudomonas aeruginosa
	1	1	Pseudomonas and Aerobacter
	1	1	Proteus species
	1	1	Bacteroides
	1	0	Alcaligenes faecalis
	1	1	Serratia species
TOTAL	20	14 (70%)	

* Staphylococcus found to be untypeable by usual phages but lysed by Group III phages at 1000 times routine test dose. U.C. 18. (A phage first isolated at the University of Cincinnati and found to lyse many untypeable pathogenic staphylococci found in hospital.

MAIN TABLE 39

BACTERIOLOGICAL DATA FOR PATIENTS IN BACTERAEMIC SHOCK

Patient	Respiratory Tract	Urine	Wound	Peritoneum	Blood	Other Sites	POST MORTEM Heart Blood	POST MORTEM Lung	POST MORTEM Other Sites
E.C. (F. 38 yrs) Abdominal injuries	-	E.coli Yeasts	E.coli Proteus Entero-coccus	E. coli	E. coli	-	No autopsy		
J.D. (M. 35 yrs) Abdominal injuries	Ps. S.aureus	Ps.	Ps.	Ps.	Ps.	-	Ps.	Ps. Ae./Kl.	Peritoneum Ps., Ae./Kl Enterococci
R.M. (M. 29 yrs) Abdominal injuries	Candida	-	E.coli	E. coli	E. coli	C.S.F. - E. coli	Ae./Kl.	Ae./Kl.	Peritoneum E. coli Wound Ps., Ae./Kl
C.M. (M. 58 yrs) Carcinoma of stomach Peritonitis	Ae./Kl.	-	E.coli Ps. Ae./Kl.	E. coli Ps. Ae./Kl.	Serratia sp.	-	S.aureus entero-coccus	-	-
B.G. (M. 57 yrs) Mitral valve Replacement. Enterocolitis.	-	Ae./Kl.	-	-	-	-	-	Ae./Kl.	-

MAIN TABLE 39 (CONTINUED)

BACTERIOLOGICAL DATA FOR PATIENTS IN BACTERAEMIC SHOCK

Patient	Respiratory Tract	Urine	Wound	Peritoneum	Blood	Other Sites	POST MORTEM		
							Heart Blood	Lung	Other Sites
T.T. (M. 66 yrs) Ileal conduit Peritonitis	Proteus	-	Proteus E. coli S.aureus	Proteus E. coli	Ps.	-	Ps.	Ps. Proteus	-
F.R./A/(M. 75 yrs) Superior mesenteric artery. Thrombosis	-	Proteus	-	E. coli	-	-	E.coli	E.coli	Peritoneum E. coli
F.R./B/(M. 57 yrs) Ileal conduit. Peritonitis.	E. coli S.aureus Ae./Kl.	-	E. coli	E. coli	E. coli	-	Recovered.		
K.W. (M. 64 yrs) Aortic aneurysm. Abdominal abscess.	E. coli	E.coli	S.aureus Diph-theroids	-	-	-	Ae./Kl.	Ae./Kl. E.coli S.aureus	-
E.F. (M. 75 yrs) Carcinoma of Pancreas. Pancreatectomy. Peritonitis.	S.aureus	Candida	E. coli Ae./Kl. S.aureus	E. coli Ae./Kl. S.aureus	-	-	Ae./Kl. Proteus	-	Peritoneum Proteus Liver Proteus Kidney Proteus Ae./Kl.

MAIN TABLE 39 (CONTINUED)

BACTERIOLOGICAL DATA FOR PATIENTS IN BACTERAEMIC SHOCK

Patient	Respiratory Tract	Urine	Wound	Peritoneum	Blood	Other Sites	POST MORTEM		
							Heart Blood	Lung	Other Sites
B.B. (M. 42 yrs) Haematemesis.	Ae./Kl. E. coli Candida	-	Ae./Kl.	Ae./Kl.	Ae./Kl.	-	Ae./Kl.	Ae./Kl.	-
E.K. (F. 63 yrs) Carcinoma of Rectum Post-op. obstruction	Ae./Kl.	Ae./Kl.	Ae./Kl.	S.aureus	Ae./Kl.	Gastrostomy. Ae./Kl.	Ae./Kl.	Ae./Kl.	Peritoneum Ae./Kl.
C.T. (M. 50 yrs) Common Bile Duct Stenosis	-	-	E.coli	E. coli Proteus	E.coli	Bile. E. coli Ps. Proteus	Recovered.		
A.A. (M. 70 yrs) Cholecystectomy Liver Abscess	S.aureus	Candida	Ae./Kl. E.coli	-	Bacter-oides	Gall Bladder Ae./Kl., E. coli a-haem. strep.	Ae./Kl.	-	Hepatic abscess and Peritoneum Ae./Kl.
G.S. (F. 79 yrs) Cholecystitis Pancreatitis	-	Ae./Kl.	-	Ae./Kl.	Ae./Kl.	Gall Bladder Ae./Kl. E. coli	Ae./Kl. Ps.	Ae./Kl. Ps.	Bile. Ae./Kl. Ps.

MAIN TABLE 39 (CONTINUED)

BACTERIOLOGICAL DATA FOR PATIENTS IN BACTERAEMIC SHOCK

Patient	Respiratory Tract	Urine	Wound	Peritoneum	Blood	Other Sites	POST MORTEM		
							Heart Blood	Lung	Other Sites
M.C. (F. 66 yrs) Burns.	S. aureus Ae./Kl. Ps.	-	-	-	Ps.	Burn. Ps. S. aureus E. coli Ae./Kl.	Ps. E.coli	Ae./Kl. Candida a-haem. strep.	Brain. Ps
L.R. (F. 60 yrs) Burns.	Ae./Kl.	Candida Ae./Kl.	-	-	-	Burn. S.aureus Ae./Kl., Ps. E. coli.		Recovered.	
S.W. (F. 66 yrs) Burns.	S. aureus	E. coli	-	-	-	Burn. S. aureus Ae./Kl., Ps. E. coli.		Recovered.	
F.J. (M. 65 yrs) Burns.	S. aureus Ae./Kl.	-	-	-	S.aureus	Burn. S. aureus Ae./Kl. Ps.		Recovered.	
R.W. (M. 52 yrs) Burns.	-	-	-	-	Ps. Ae./Kl.	Burn. Ps. Ae./Kl. E. coli.	Ps. E.coli	-	Burn. Ps. Ae./Kl. E. coli

MAIN TABLE 39 (CONTINUED)

BACTERIOLOGICAL DATA FOR PATIENTS IN BACTERAEMIC SHOCK

Patient	Respiratory Tract	Urine	Wound	Peritoneum	Blood	Other Sites	POST MORTEM Heart Blood	POST MORTEM Lung	POST MORTEM Other Sites
C.A. (M. 36 yrs) Burns	E. coli Ae./Kl. Alc.faecalis	S. aureus Ae./Kl. Proteus	-	-	Alc. faecalis	Burn. Ae./Kl. Alc. faecalis E. coli S. aureus		Recovered.	
M.N. (F. 54 yrs) Burns	Ae./Kl.	-	-	-	Proteus	Burn. Proteus Ps. Ae./Kl. S.aureus	S.epi-derm. a-haem. strep.	S. epi-derm. a-haem. strep.	Burn. Proteus Kidney Proteus
F.G. (M. 78 yrs) Burns	Ae./Kl.	Ae./Kl.	-	-	-	Burn. Ae./Kl. S.aureus	-	Ae./Kl.	
B.W. (F. 26 yrs) Septic abortion	S.aureus E. coli Candida	E. coli Candida	E.coli Ae./Kl.	E. coli Ae./Kl. Cl.per-fringens	Ae/Kl.	Uterus. E. coli Ae./Kl. Cl.perfringens		Recovered.	
G.L. (F. 35 yrs) Hysterectomy Peritonitis	Ps.	-	E.coli	E. coli	-	-	Ps.	Ps.	Peritoneu[illegible] Ps. Enter[illegible] coccus.

MAIN TABLE 39 (CONTINUED)

BACTERIOLOGICAL DATA FOR PATIENTS IN BACTERAEMIC SHOCK

Patient	Respiratory Tract	Urine	Wound	Peritoneum	Blood	Other Sites	POST MORTEM		
							Heart Blood	Lung	Other Sites
H.F. (M. 83 yrs) Urethral stricture	-	E. coli Ae./Kl. entero-coccus	-	-	-	-	No autopsy.		
F.L. (M. 54 yrs) Prostatectomy	-	E. coli	-	-	E. coli	-	Recovered.		
W.K. (M. 24 yrs) Renal Homotransplantation	S. aureus	Proteus	S. aureus	S. aureus	-	-	S.aureus E. coli Ae./Kl.	S.aureus	Wound. S. aureu Liver. E. coli Peritoneu E. coli Kidney S. aureu
M.D. (M. 24 yrs) Renal Homotransplantation	Ps. S.epiderm.	Ps. Ae./Kl.	Ps. Ae./Kl. E. coli S.aureus	-	E. coli	Throat. Ps.	Ps. Ae./Kl.	Ae./Kl.	Leg. Ae./Kl. Liver. gm-ve Ro

MAIN TABLE 39 (CONTINUED)

BACTERIOLOGICAL DATA FOR PATIENTS IN BACTERAEMIC SHOCK

Patient	Respiratory Tract	Urine	Wound	Peritoneum	Blood	Other Sites	POST MORTEM Heart Blood	POST MORTEM Lung	POST MORTEM Other Sites
G.J. (M. 46 yrs) Renal Homotransplantation	Ae./Kl. Candida E. coli	E. coli Ae./Kl.	E. coli	-	E. coli	-	-	E. coli Ae./Kl.	Pleura. E. coli Kidney. E. coli
J.B. (M. 58 yrs) Liver Homotransplantation	S.aureus	S.aureus	S.aureus	S. aureus	-	T-Tube S. aureus	Ae./Kl.	-	Liver. S. aureus Peritoneum Ae./Kl.

E. coli = Escherichia coli

Ae./Kl. = Aerobacter/Klebsiella species

S. aureus = Staphylococcus aureus, coagulase positive

Ps. = Pseudomonas aeruginosa

Serratia = Serratia species

Proteus = Proteus species

Cl. perfringens = Clostridium perfringens

Alc. faecalis = Alcaligenes faecalis

S. epiderm. = Staphylococcus epidermidis, coagulase negative

a-haem. strep. = Alpha-haemolytic streptococcus

MAIN TABLE 40.

ACID-BASE UPSET IN BACTERAEMIC SHOCK

(Biochemical data of patients in bacteraemic shock).

	PATIENT	LACTATE m.Mols. per Litre	PYRUVATE m. Mols. per Litre	L/P (Lactate Pyruvate Ratio)	Excess Lactate *	pH.	pCO_2 (mm.Hg)	Base Excess +
1	C.T. (March 31)	1.02	0.16	6.4	0.31	7.42	35.0	-1
2	C.M. (Aug.8)	2.4	0.22	11.0	0.75	7.41	35.04	-1.5
3	L.R. (April 29)	1.223	0.182	6.7	1.05	7.375	39.5	-1.5
4	J.D. (Sept. 11)	2.25	0.23	9.8	1.32	7.33	37.0	-6
5	B.B. (Nov. 14)	6.33	0.477	13.2	4.48	7.39	30.0	-5
6	F.R. (Nov. 4)	7.45	0.57	13.0	4.96	7.43	20.1	-9
7	G.L. (1) (April 5)	9.8	0.56	17.5	7.35	7.28	40.0	-7
8	T.T. (July 20)	10.3	0.38	27.0	8.87	7.26	23.0	-15
9	G.S. (July 19)	13.1	0.63	21.0	10.57	7.28	32.2	-10
10	G.L. (2) (April 8)	17.1	0.56	30.6	14.60	6.92	78	-17
11	M.C. (1) (March 2-2 pm)	19.9	0.49	41	17.76	7.26	14.6	-20
12	M.C. (2) (March 2-10 pm)	25.1	0.66	38	22.22	7.18	28.0	-17

* Excess Lactate (calculated from Huckabee's formula (1958).

\+ Base Excess (calculated from Nomogram - Astrup).

MAIN TABLE 41

Course of a 58 year old Male (F.R.) in shock from E. coli peritonitis

	POST OPERATIVE DAYS			
	1	2	3	4
HAEMATOCRIT (per cent)	35	37	43	42
BLOOD VOLUME* (mls.)	4,330	6,720	5,900	4,700
BLOOD PRESSURE (mm. Hg.)	84/50	132/80	150/80	145/80
URINARY OUTPUT (24 hr. volume in mls.)	300	2,020	2,660	3,040
BLOOD UREA NITROGEN (mgms. per 100 mls.)	23	52	29	35
TEMPERATURE (°F)	101.6	103.0	101.4	100.4
WHITE BLOOD CELLS (per c.mm.)	10,500	14,800	6,400	7,000
PLATELETS (per c.mm.)	Normal Films	21,500	40,500	81,000

* Predicted normal blood volume 4,900 ml.

APPENDIX 3.

SUPPORTING TABLES 1–106.

SUPPORTING TABLE 1

A) CONTROL EXPERIMENT 1

Observation of the Hamster Cheek Pouch without injections.

	TIME IN MINUTES OF OBSERVATION OF CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	38	1,134.1	38	1,134.1	40	1,256.6	40	1,256.6	38	1,134.1	36	1,017.9
2	34	907.9	34	907.9	36	1,017.9	34	907.9	36	1,017.9	34	907.9
3	36	1,017.9	36	1,017.9	36	1,017.9	34	907.9	34	907.9	32	804.2
4	16	201.1	14	153.9	16	201.1	18	254.5	18	254.5	18	254.5
TOTAL AREA		3,261.0		3,213.8		3,493.5		3,326.9		3,314.4		2,984.5
% Control Area		100		98.5		107.1		102.0		101.6		91.5
VEINS												
1	38	1,134.1	34	907.9	32	804.2	34	907.9	34	907.9	34	907.9
2	48	1,809.6	50	1,963.5	50	1,963.5	54	2,290.2	48	1,809.6	48	1,809.6
3	60	2,827.4	58	2,642.1	62	3,019.1	58	2,642.1	56	2,463.0	60	2,827.4
4	24	452.4	26	530.9	24	452.4	24	452.4	26	530.9	26	530.9
TOTAL AREA		6,223.5		6,044.4		6,239.2		6,292.6		5,711.4		6,075.8
% Control Area		100		97.1		100.3		101.1		91.8		97.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 2

A) CONTROL EXPERIMENT 2

Observation of the Hamster Cheek Pouch without injections.

	TIME IN MINUTES OF OBSERVATION OF CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	62	3,019.1	60	2,827.4	60	2,827.4	62	3,019.1	62	3,019.1	64	3,217.0
2	30	706.9	30	706.9	30	706.9	30	706.9	32	804.2	32	804.2
3	58	2,642.1	60	2,827.4	58	2,642.1	60	2,827.4	60	2,827.4	60	2,827.4
4	30	706.9	32	804.2	32	804.2	34	907.9	34	907.9	32	804.2
5	52	2,123.7	50	1,963.5	52	2,123.7	52	2,123.7	52	2,123.7	54	2,290.2
TOTAL AREA		9,198.7		9,129.4		9,104.3		9,585.0		9,682.3		9,943.0
% Control Area		100		99.2		97.9		104.2		105.2		108.1
VEINS												
1	30	706.9	28	615.8	30	706.9	30	706.9	30	706.9	32	804.2
2	40	1,256.6	40	1,256.6	42	1,385.4	38	1,134.1	40	1,256.6	40	1,256.6
3	36	1,017.9	36	1,017.9	32	804.2	34	907.9	34	907.9	36	1,017.9
4	40	1,256.6	42	1,385.4	42	1,385.4	42	1,385.4	40	1,256.6	40	1,256.6
5	44	1,520.5	44	1,520.5	44	1,520.5	42	1,385.4	42	1,385.4	46	1,661.9
TOTAL AREA		5,758.5		5,796.2		5,802.4		5,519.7		5,513.4		5,997.2
% Control Area		100		100.7		100.8		95.9		95.8		104.2

D = Diameter in microns   Area = Area in microns^2

SUPPORTING TABLE 3

A) CONTROL EXPERIMENT 3

Observation of the Hamster Cheek Pouch without injections.

	TIME IN MINUTES OF OBSERVATION OF CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	38	1,134.1	38	1,134.1	36	1,017.9	36	1,017.9	38	1,134.1	36	1,017.9
2	34	907.9	32	804.2	32	804.2	34	907.9	32	804.2	32	804.2
3	30	706.9	32	804.2	30	706.9	32	804.2	32	804.2	32	804.2
4	16	201.1	18	254.5	20	314.2	18	254.5	16	201.1	18	254.5
TOTAL AREA		2,950.0		2,997.0		2,843.5		2,984.5		2,943.6		2,880.8
% Control Area		100		101.6		96.4		101.2		99.8		97.7
VEINS												
1	40	1,256.6	40	1,256.6	42	1,385.4	40	1,256.6	40	1,256.6	40	1,256.6
2	35	962.1	36	1,017.9	34	907.9	34	907.9	34	907.9	36	1,017.9
3	42	1,385.4	40	1,256.6	40	1,256.6	40	1,256.6	40	1,256.6	40	1,256.6
4	48	1,809.6	48	1,809.6	46	1,661.9	46	1,661.9	46	1,661.9	48	1,809.6
TOTAL AREA		5,413.7		5,340.7		5,211.8		5,083.0		5,083.0		5,340.7
% Control Area		100		98.7		96.3		93.9		93.9		98.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 4

B) CONTROL OBSERVATIONS ON THE MICROCIRCULATION

Local injection of 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

EXPERIMENT 1

	Control		TIME IN MINUTES AFTER INJECTION OF RINGER'S SOLUTION									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	36	1,017.9	32	804.2	34	907.9	38	1,134.1	32	804.2	30	706.9
2	34	907.9	30	706.9	30	706.9	32	804.2	30	706.9	28	615.8
3	32	804.2	32	804.2	30	706.9	32	804.2	28	615.8	32	804.2
4	18	254.5	14	153.9	20	314.2	18	254.5	22	380.1	22	380.1
TOTAL AREA		2,984.5		2,469.2		2,635.9		2,997.0		2,507.0		2,507.0
% Control Area		100		82.3		88.3		100.4		84.0		84.0
VEINS												
1	34	907.9	32	804.2	30	706.9	32	804.2	30	706.9	30	706.9
2	48	1,809.6	44	1,520.5	44	1,520.5	46	1,661.9	50	1,963.5	50	1,963.5
3	60	2,827.4	56	2,463.0	60	2,827.4	60	2,827.4	58	2,642.1	60	2,827.4
4	26	530.9	26	530.9	28	615.8	26	530.9	28	615.8	28	615.8
TOTAL AREA		6,075.8		5,318.6		5,670.6		5,824.4		5,928.3		6,113.6
% Control Area		100		87.5		93.3		95.9		97.6		100.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 5

B) CONTROL OBSERVATIONS ON THE MICROCIRCULATION

Local injection of 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

EXPERIMENT 2

	TIME IN MINUTES AFTER INJECTION OF RINGER'S SOLUTION											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	52	2,123.7	54	2,290.2	54	2,290.2	54	2,290.2	52	2,123.7	52	2,123.7
2	36	1,017.9	38	1,134.1	38	1,134.1	34	907.9	36	1,017.9	36	1,017.9
3	44	1,520.5	42	1,385.4	44	1,520.5	42	1,385.4	44	1,520.5	42	1,385.4
4	38	1,134.1	40	1,256.6	38	1,134.1	36	1,017.9	38	1,134.1	36	1,017.9
5	22	380.1	22	380.1	20	314.2	18	254.5	20	314.2	20	314.2
TOTAL AREA		6,176.3		6,446.4		6,393.1		5,855.9		6,110.4		5,859.1
% Control Area		100		104.3		103.5		94.8		98.9		94.9
VEINS												
1	64	3,217.0	62	3,019.1	62	3,019.1	60	2,827.4	62	3,019.1	58	2,642.1
2	52	2,123.7	56	2,463.0	54	2,290.2	56	2,463.0	54	2,290.2	54	2,290.2
3	76	4,536.5	72	4,071.5	72	4,071.5	74	4,300.8	76	4,536.5	76	4,536.5
4	82	5,281.0	84	5,541.8	84	5,541.8	86	5,808.8	84	5,541.8	82	5,281.0
5	82	5,281.0	80	5,026.5	80	5,026.5	78	4,778.4	82	5,281.0	80	5,026.5
6	76	4,536.5	76	4,536.5	74	4,300.8	74	4,300.8	76	4,536.5	76	4,536.5
TOTAL AREA		24 ,975.7		24,658.4		24,249.9		24,479.2		25,205.1		24,312.8
% Control Area		100		98.7		97.1		98.0		100.9		97.3

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 6

B) CONTROL OBSERVATIONS ON THE MICROCIRCULATION

Local injection of 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

EXPERIMENT 3

	TIME IN MINUTES AFTER INJECTION OF RINGER'S SOLUTION											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	66	3,421.2	60	2,827.4	64	3,217.0	64	3,217.0	64	3,217.0		-
2	54	2,290.2	58	2,642.1	58	2,642.1	60	2,827.4	58	2,642.1		-
3	12	113.1	12	113.1	18	254.5	16	201.1	16	201.1		-
4	20	314.2	12	113.1	6	28.3	0	0	0	0		-
5	18	254.5	10	78.5	4	12.6	0	0	0	0		-
TOTAL AREA		6,393.2		5,774.2		6,154.5		6,245.5		6,060.2		-
% Control Area		100		90.3		96.3		97.8		94.8		-
VEINS												
1	54	2,290.2	50	1,963.5	54	2,290.2	54	2,290.2	56	2,463.0		-
2	42	1,385.4	44	1,520.5	44	1,520.5	44	1,520.5	40	1,256.6		-
3	18	254.5	20	314.2	24	452.4	24	452.4	18	254.5		-
4	32	804.2	34	907.9	28	615.8	32	804.2	32	804.2		-
5	26	530.9	22	380.1	24	452.4	28	615.8	26	530.9		-
6	20	314.2	18	254.5	20	314.2	20	314.2	12	113.1		-
TOTAL AREA		5,579.4		5,340.7		5,645.5		5,997.3		5,422.3		-
% Control Area		100		95.7		101.1		107.5		97.2		-

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 7

B) CONTROL OBSERVATIONS ON THE MICROCIRCULATION

Local injection of 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

EXPERIMENT 4

	Control		TIME IN MINUTES AFTER INJECTION OF RINGER'S SOLUTION									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	62	3,019.1	60	2,827.4	60	2,827.4	62	3,019.1	62	3,019.1	64	3,217.0
2	30	706.9	30	706.9	30	706.9	30	706.9	32	804.2	32	804.2
3	58	2,642.1	60	2,827.4	58	2,642.1	60	2,827.4	60	2,827.4	60	2,827.4
4	30	706.9	32	804.2	32	804.2	34	907.9	34	907.9	32	804.2
5	52	2,123.9	50	1,963.5	52	2,123.7	52	2,123.7	52	2,123.7	54	2,290.2
TOTAL AREA		9,198.7		9,129.4		9,104.3		9,585.0		9,682.3		9,943.0
% Control Area		100		98.0		97.8		104.2		105.2		108.1
VEINS												
1	30	706.9	28	615.8	30	706.9	30	706.9	30	706.9	32	804.2
2	40	1,256.6	40	1,256.6	42	1,385.4	38	1,134.1	40	1,256.6	40	1,256.6
3	36	1,017.9	36	1,017.9	32	804.2	34	907.9	34	907.9	36	1,017.9
4	40	1,256.6	42	1,385.4	42	1,385.4	42	1,385.4	40	1,256.6	40	1,256.6
5	44	1,520.5	44	1,520.5	44	1,520.5	42	1,385.4	42	1,385.4	46	1,661.9
TOTAL AREA		5,758.5		5,796.2		5,802.4		5,519.7		5,513.4		5,997.2
% Control Area		100		100.7		100.8		95.9		95.8		104.2

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 8

B) CONTROL OBSERVATIONS ON THE MICROCIRCULATION

Local injection of 0.05 ml. Ringer's Solution into the Hamster Cheek Pouch.

EXPERIMENT 5

	TIME IN MINUTES AFTER INJECTION OF RINGER'S SOLUTION											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	42	1,385.4	40	1,256.6	40	1,256.6	38	1,134.1	40	1,256.6	40	1,256.6
2	38	1,134.1	38	1,134.1	38	1,134.1	38	1,134.1	38	1,134.1	36	1,017.9
3	30	706.9	30	706.9	28	615.8	26	530.9	28	615.8	30	706.9
4	18	254.5	20	314.2	20	314.2	18	254.5	20	314.2	18	254.5
TOTAL AREA		3,480.9		3,411.8		3,320.7		3,053.6		3,320.7		3,235.9
% Control Area		100		98.0		95.4		87.7		95.4		93.1
VEINS												
1	40	1,256.6	40	1,256.6	40	1,256.6	42	1,385.4	40	1,256.6	42	1,385.4
2	22	380.1	24	452.4	22	380.1	22	380.1	22	380.1	22	380.1
3	36	1,017.9	34	907.9	34	907.9	32	804.2	34	907.9	34	907.9
4	30	706.9	30	706.9	30	706.9	28	615.8	30	706.9	30	706.9
TOTAL AREA		3,361.5		3,323.8		3,251.5		3,185.5		3,251.6		3,380.3
% Control Area		100		98.9		96.7		94.8		96.7		100.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 9

A) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 1.

Local action of 10 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	32	804.2	44	1,520.5	50	1,963.5	54	2,290.2	50	1,963.5
2	45	1,590.4	44	1,520.5	50	1,963.5	50	1,963.5	52	2,123.7	50	1,963.5
3	50	1,963.5	50	1,963.5	58	2,642.1	60	2,827.4	62	3,019.1	62	3,019.1
TOTAL AREA		5,363.5		4,288.2		6,126.1		6,754.4		7,433.0		6,946.1
% Control Area		100		80.0		114.2		125.9		138.6		129.5
VEINS												
1	30	706.9	28	615.8	24	452.4	28	615.8	30	706.9	28	615.8
2	36	1,017.9	32	804.2	32	804.2	30	706.9	28	615.8	30	706.9
3	58	2,642.1	52	2,123.7	48	1,809.6	50	1,963.5	50	1,963.5	48	1,809.6
4	38	1,134.1	40	1,256.6	36	1,017.9	36	1,017.9	32	804.2	36	1,017.9
TOTAL AREA		5,501.0		4,800.3		4,084.1		4,304.1		4,090.4		4,150.2
% Control Area		100		87.3		74.2		78.2		74.4		75.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 10

A) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 2.

Local action of 10 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	54	2,290.2	50	1,963.5	36	1,017.9	56	2,463.0	60	2,827.4	60	2,827.4
2	28	615.8	24	452.4	20	314.2	30	706.9	34	907.9	32	804.2
3	52	2,123.7	52	2,123.7	38	1,134.1	60	2,827.4	62	3,019.1	66	3,421.2
TOTAL AREA		5,029.7		4,539.6		2,466.2		5,997.3		6,754.4		7,052.8
% Control Area		100		90.3		49.0		119.2		134.3		140.0
VEINS												
1	48	1,809.6	50	1,963.5	42	1,385.4	48	1,809.6	46	1,661.9	48	1,809.6
2	26	530.9	20	314.2	20	314.2	22	380.1	22	380.1	24	452.4
3	20	314.2	18	254.5	20	314.2	16	201.1	16	201.1	18	254.5
4	38	1,134.1	32	804.2	32	804.2	30	706.9	28	615.8	26	530.9
5	40	1,256.6	36	1,017.9	34	907.9	30	706.9	30	706.9	32	804.2
TOTAL AREA		5,045.4		4,354.3		3,725.9		3,804.6		3,565.8		3,851.6
% Control Area		100		86.3		73.8		75.4		70.7		76.3

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 11

A) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 3.

Local action of 10 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	36	1,017.9	32	804.2	40	1,256.6	42	1,385.4	42	1,385.4	38	1,134.1
2	14	153.9	20	314.2	22	380.1	24	452.4	20	314.2	18	254.5
3	40	1,256.6	34	907.9	44	1,520.5	44	1,520.5	44	1,520.5	14	1,256.6
TOTAL AREA		2,428.4		2,026.3		3,157.2		3,358.3		3,220.1		2,645.2
% Control Area		100		83.4		130.0		138.3		132.6		108.9
VEINS												
1	34	907.9	32	804.2	30	706.9	32	804.2	30	706.9	32	804.2
2	38	1,134.1	30	706.9	30	706.9	32	804.2	30	706.9	33	855.3
3	22	380.1	20	314.2	20	314.2	22	380.1	20	314.2	20	314.2
4	22	380.1	18	254.5	18	254.5	20	314.2	18	254.5	24	452.4
TOTAL AREA		2,802.2		2,079.8		1,982.5		2,302.7		1,982.5		2,426.1
% Control Area		100		74.2		70.7		82.1		70.7		86.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 12

A) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 4.

Local action of 10 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	50	1,963.5	60	2,827.4	62	3,019.1	62	3,019.1	62	3,019.1
2	50	1,963.5	46	1,661.9	58	2,642.1	60	2,827.4	58	2,642.1	60	2,827.4
3	32	804.2	30	706.9	38	1,134.1	38	1,134.1	38	1,134.1	36	1,017.9
TOTAL AREA		5,409.8		4,332.3		6,603.6		6,980.6		6,795.3		6,864.4
% Control Area		100		80.1		122.1		129.0		125.6		126.9
VEINS												
1	84	5,541.8	82	5,281.0	78	4,778.1	76	4,536.5	78	4,778.4	82	5,281.0
2	58	2,642.1	58	2,642.1	50	1,963.5	50	1,963.5	52	2,123.7	54	2,290.2
3	46	1,661.9	46	1,661.9	42	1,385.4	44	1,520.5	46	1,661.9	46	1,661.9
4	48	1,809.6	46	1,661.9	38	1,134.1	38	1,134.1	42	1,385.4	44	1,520.5
TOTAL AREA		11,655.4		11,246.9		9,261.1		9,154.6		9,949.4		10,753.6
% Control Area		100		96.5		79.5		78.5		85.4		92.3

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 13

A) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 5.

Local action of 10 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH.											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	44	1,520.5	52	2,123.7	52	2,123.7	50	1,963.5	50	1,963.5
2	50	1,963.5	44	1,520.5	56	2,463.0	52	2,123.7	52	2,123.7	50	1,963.5
3	24	452.4	20	314.2	28	615.8	32	804.2	30	706.9	30	706.9
4	12	113.1	12	113.1	14	153.9	16	201.1	20	314.2	18	254.5
TOTAL AREA		4,338.6		3,468.3		5,356.4		5,252.7		5,108.3		4,888.4
% Control Area		100		79.9		123.5		121.1		117.7		112.7
VEINS												
1	62	3,019.1	60	2,827.4	56	2,463.0	56	2,463.0	58	2,642.1	60	2,827.4
2	34	907.9	30	706.9	28	615.8	28	615.8	30	706.9	30	706.9
3	30	706.9	28	615.8	30	706.9	28	615.8	28	615.8	28	615.8
4	28	615.8	28	615.8	26	530.9	22	380.1	24	452.4	24	452.4
TOTAL AREA		5,249.7		4,765.9		4,316.6		4,074.7		4,417.2		4,602.5
% Control Area		100		90.8		82.2		77.6		84.1		87.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 14

A) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 6.

Local action of 10 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH.											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	70	3,848.5	72	4,071.5	68	3,631.7	60	2,827.4	58	2,642.1
2	50	1,963.5	58	2,642.1	60	2,827.4	58	2,642.1	52	2,123.7	52	2,123.7
3	32	804.2	40	1,256.6	42	1,385.4	38	1,134.1	36	1,017.9	34	907.9
TOTAL AREA		5,409.8		7,747.2		8,284.3		7,407.9		5,969.0		5,673.7
% Control Area		100		143.2		153.1		136.9		110.3		104.9
VEINS												
1	65	3,318.3	60	2,827.4	58	2,642.1	56	2,463.0	60	2,827.4	58	2,642.1
2	22	380.1	26	530.9	26	530.9	26	530.9	20	314.2	20	314.2
3	30	706.9	28	615.8	26	530.9	24	452.4	28	615.8	27	572.6
4	28	615.8	28	615.8	28	615.8	26	530.9	28	615.8	28	615.8
TOTAL AREA		5,021.1		4,589.9		4,319.7		3,977.2		4,373.2		4,144.7
% Control Area		100		91.4		86.0		79.2		87.1		82.5

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 15

B) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 1.

Local action of 5 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH.									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	40	1,256.6	38	1,134.1	42	1,385.4	44	1,522.5	48	1,809.6	50	1,963.5
2	38	1,134.1	34	907.9	44	1,520.5	42	1,385.4	44	1,520.5	46	1,661.9
3	22	380.1	22	380.1	24	452.4	24	452.4	24	452.4	24	452.4
TOTAL AREA		2,770.8		2,422.1		3,358.3		3,358.3		3,782.5		4,077.8
% Control Area		100		87.4		121.2		121.2		136.5		147.2
VEINS												
1	34	907.9	30	706.9	30	706.9	28	615.8	30	706.9	32	804.2
2	30	706.9	30	706.9	26	530.9	28	615.8	30	706.9	30	706.9
3	28	615.8	28	615.8	26	530.9	26	530.9	24	452.4	24	452.4
4	16	201.1	14	153.9	14	153.9	18	254.5	16	201.1	16	201.1
TOTAL AREA		2,431.7		2,183.5		1,922.6		2,017.0		2,067.3		2,164.6
% Control Area		100		89.8		79.1		82.9		85.0		89.0

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 16

B) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 2.

Local action of 5 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	52	2,123.7	44	1,520.5	52	2,123.7	54	2,290.2	54	2,290.2	56	2,463.0
2	58	2,642.1	52	2,123.7	62	3,019.1	66	3,421.2	66	3,421.2	66	3,421.2
3	60	2,827.4	56	2,463.0	62	3,019.1	64	3,217.0	66	3,421.2	68	3,631.7
TOTAL AREA		7,593.2		6,107.2		8,161.9		8,928.4		9,132.6		9,515.9
% Control Area		100		80.4		107.5		117.6		120.3		125.3
VEINS												
1	80	5,026.5	76	4,536.5	68	3,631.7	66	3,421.2	68	3,631.7	64	3,217.0
2	48	1,809.6	38	1,134.1	38	1,134.1	34	907.9	42	1,385.4	46	1,661.9
3	44	1,520.5	42	1,385.4	42	1,134.1	38	1,134.1	38	1,134.1	40	1,256.6
4	26	530.9	20	314.2	24	452.4	22	380.1	24	452.4	24	452.4
5	22	380.1	20	314.2	20	314.2	22	380.1	22	380.1	20	314.2
TOTAL AREA		9,267.6		7,684.4		6,917.8		6,223.4		6,983.7		6,902.1
% Control Area		100		82.9		74.7		67.1		75.3		74.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 17

B) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 3.

Local action of 5 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	40	1,256.6	50	1,963.5	54	2,290.2	56	2,463.0	52	2,123.7
2	40	1,256.6	38	1,134.1	46	1,661.9	46	1,661.9	50	1,963.5	50	1,963.5
3	32	804.2	30	706.9	36	1,017.9	38	1,134.1	40	1,256.6	40	1,256.6
TOTAL AREA		3,870.4		3,097.6		4,643.3		5,086.2		5,683.1		5,343.8
% Control Area		100		80.0		120.0		131.4		146.8		138.1
VEINS												
1	26	530.9	26	530.9	22	380.1	22	380.1	14	153.9	20	314.2
2	54	2,290.2	52	2,123.7	50	1,963.5	50	1,963.5	48	1,809.6	50	1,963.5
3	38	1,134.1	32	804.2	30	706.9	32	804.2	30	706.9	36	1,017.9
4	60	2,827.4	54	2,290.2	50	1,963.5	48	1,809.6	48	1,809.6	48	1,809.6
TOTAL AREA		6,782.6		5,749.0		5,014.0		4,957.4		4,480.0		5,105.2
% Control Area		100		84.8		73.9		73.1		67.2		76.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 18

B) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 4.

Local action of 5 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH.									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	56	2,463.0	56	2,463.0		-	60	2,827.4	68	3,631.7	60	2,827.4
2	38	1,134.1	32	804.2		-	32	804.2	42	1,385.4	44	1,520.5
3	62	3,019.1	58	2,542.1		-	60	2,827.4	66	3,421.2	68	3,631.7
4	52	2,123.7	46	1,661.9		-	50	1,963.5	58	2,642.1	60	2,827.4
TOTAL AREA		8,739.9		7,571.2		-		8,422.5		11,080.4		10,807.0
% Control Area		100		86.6		-		96.4		126.8		123.7
VEINS												
1	126	12,469.0	110	9,503.3		-	112	9,852.0	120	11,309.7	124	12,076.3
2	88	6,082.1	58	2,642.1		-	72	4,071.5	84	5,541.8	82	5,281.0
3	110	9,503.3	94	6,939.8		-	96	7,238.2	104	8,494.9	116	10,568.3
4	116	10,568.3	80	5,026.5		-	98	7,543.0	106	8,842.7	98	7,543.0
TOTAL AREA		38,622.7		24,111.7		-		28,704.7		34,171.1		35,468.6
% Control Area		100		62.4		-		74.3		88.5		91.8

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 19

B) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 5.

Local action of 5 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	20	314.2	18	254.5	18	254.5	24	452.4	24	452.4	26	530.9
2	22	380.1	20	314.2	22	380.1	24	452.4	26	530.9	26	530.9
3	10	78.5	8	50.3	8	50.3	8	50.3	8	50.3	10	78.5
TOTAL AREA		772.8		619.0		684.9		955.1		1,033.6		1,140.3
% Control Area		100		80.1		88.6		123.6		133.7		147.7
VEINS												
1	34	907.9	26	530.9	26	530.9	32	804.2	34	907.9	36	1,017.9
2	16	201.1	18	254.5	14	153.9	16	201.1	16	201.1	14	153.9
3	18	254.5	18	254.5	16	201.1	18	254.5	16	201.1	16	201.1
4	18	254.5	10	78.5	16	201.1	16	201.1	16	201.1	16	201.1
TOTAL AREA		1,618.0		1,118.4		1,087.0		1,460.9		1,511.2		1,574.0
% Control Area		100		69.1		67.2		90.3		93.4		97.3

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 20

B) ACTION OF HISTAMINE ON THE MICROCIRCULATION. EXPERIMENT 6.

Local action of 5 micrograms histamine base in 0.05 ml. Ringer's solution injected into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF HISTAMINE INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	62	3,019.1	52	2,123.7	52	2,123.7	76	4,536.5	70	3,848.5
2	30	706.9	30	706.9	52	2,123.7	60	2,827.4	62	3,019.1
3	50	1,963.5	10	78.5	20	314.2	34	907.9	42	1,385.4
TOTAL AREA		5,689.5		2,909.1		4,561.6		8,271.8		8,253.0
% Control Area		100		51.1		80.2		145.4		145.0
VEINS										
1	84	5,541.8	82	5,281.0	76	4,536.5	92	6,647.6	96	7,238.2
2	126	12,469.0	118	10,935.9	116	10,568.3	116	10,568.3	118	10,935.9
3	108	9,160.9	82	5,281.0	80	5,026.5	82	5,281.0	82	5,281.0
4	34	907.9	32	804.2	30	706.9	26	530.9	30	706.9
TOTAL AREA		28,079.6		22,302.1		20,838.2		23,027.8		24,162.0
% Control Area		100		79.4		74.2		82.0		86.0

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 21.

ACTION OF SEROTONIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 5 micrograms, serotonin in 0.05 ml. Ringer's solution into the hamster cheek pouch.

	TIME IN MINUTES AFTER INJECTION OF SEROTONIN INTO CHEEK POUCH.											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	30	706.9	18	254.5	20	314.2	22	380.1	22	380.1	20	314.2
2	38	1,134.1	10	78.5	14	153.9	14	153.9	14	153.9	14	153.9
3	54	2,290.2	12	113.1	12	113.1	12	113.1	18	254.5	14	153.9
TOTAL AREA		4,131.2		446.1		581.2		647.1		788.5		622.0
% Control Area		100		10.8		14.1		15.7		19.1		15.1
VEINS												
1	54	2,290.2	52	2,123.7	48	1,809.6	50	1,963.5	52	2,123.7	58	2,642.1
2	48	1,809.6	40	1,256.6	44	1,520.5	44	1,520.5	48	1,809.6	42	1,385.4
3	38	1,134.1	40	1,256.6	40	1,256.6	38	1,134.1	38	1,134.1	40	1,256.6
4	22	380.1	20	314.2	22	380.1	20	314.2	20	314.2	20	314.2
TOTAL AREA		5,614.0		4,951.1		4,966.8		4,932.3		5,381.6		5,598.3
% Control Area		100		88.2		88.2		87.9		95.9		99.7

D = Diameter in microns.
Area = Area in microns^2.

SUPPORTING TABLE 22.

ACTION OF SEROTONIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 5 micrograms, serotonin in 0.05 ml. Ringer's solution into the hamster cheek pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF SEROTONIN INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	20	314.2	28	615.8	36	1,017.9	34	907.9	40	1,256.6
2	38	1,134.1	18	254.5	24	452.4	18	254.5	16	201.1	18	254.5
3	50	1,963.5	24	452.4	32	804.2	28	615.8	26	530.9	30	706.9
TOTAL AREA		5,739.7		1,021.1		1,872.4		1,888.2		1,639.9		2,218.0
% Control Area		100		17.8		32.6		32.9		28.6		38.6
VEINS												
1	46	1,661.9	46	1,661.9	48	1,809.6	42	1,385.4	38	1,134.1	40	1,256.6
2	38	1,134.1	40	1,256.6	42	1,385.4	46	1,661.9	44	1,520.5	42	1,385.4
3	48	1,809.6	46	1,661.9	44	1,520.5	40	1,256.6	42	1,385.4	42	1,385.4
4	32	804.2	30	706.9	30	706.9	28	615.8	28	615.8	20	314.2
TOTAL AREA		5,409.8		5,287.3		5,422.4		4,919.7		4,655.8		4,341.6
% Control Area		100		97.7		100.2		90.9		86.1		80.3

D = Diameter in microns.

Area= Area in microns^2.

SUPPORTING TABLE 23.

ACTION OF SEROTONIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 5 micrograms, serotonin in 0.05 ml. Ringer's solution into the hamster cheek pouch.

			TIME IN MINUTES AFTER INJECTION OF SEROTONIN INTO CHEEK POUCH.									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	68	3,631.7	66	3,421.2	42	1,385.4	58	2,642.1	52	2,123.7	60	2,827.4
2	96	7,238.2	68	3,631.7	50	1,963.5	64	3,217.0	56	2,463.0	52	2,123.7
3	62	3,019.1	60	2,827.4	36	1,017.9	58	2,642.1	48	1,809.6	40	1,256.6
4	20	314.2	12	113.1	8	50.3	10	78.5	8	50.3	8	50.3
TOTAL AREA		14,203.2		9,993.4		4,417.1		8,579.7		6,446.6		6,258.0
% Control Area		100		70.4		31.1		60.4		45.4		44.1
VEINS												
1	90	6,361.7	84	5,541.8	84	5,541.8	88	6,082.1	90	6,361.7	78	4,778.4
2	42	1,385.4	38	1,134.1	34	907.9	40	1,256.6	38	1,134.1	32	804.2
3	68	3,631.7	64	3,217.0	68	3,631.7	70	3,848.5	70	3,848.5	62	3,019.1
4	88	6,082.1	94	6,939.8	96	7,238.2	90	6,361.7	88	6,082.1	82	5,281.0
TOTAL AREA		17,460.9		16,832.7		17,319.6		17,548.9		17,426.4		13,882.7
% Control Area		100		96.4		99.2		100.5		99.8		79.5

D = Diameter in microns.

Area = Area in microns^2.

SUPPORTING TABLE 24

ACTION OF SEROTONIN ON THE MICROCIRCULATION. EXPERIMENT 4.

Local injection of 5 micrograms serotonin in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF SEROTONIN INTO CHEEK POUCH. 3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	12	113.1	20	314.2	32	804.2	30	706.9	28	615.8
2	54	2,290.2	12	113.1	12	113.1	18	254.5	20	314.2	22	380.1
3	22	380.1	0	0	5	19.6	14	153.9	14	153.9	12	113.1
4	40	1,256.6	10	78.5	12	113.1	18	254.5	18	254.5	20	314.2
TOTAL AREA		6,569.0		304.7		560.0		1,467.1		1,429.5		1,423.2
% Control Area		100		4.6		8.5		22.3		21.8		21.7
VEINS												
1	30	706.9	28	615.8	30	706.9	28	615.8	30	706.9	28	615.8
2	58	2,642.1	58	2,642.1	54	2,290.2	50	1,963.5	52	2,123.7	50	1,963.5
3	74	4,300.8	72	4,071.5	70	3,848.5	72	4,071.5	72	4,071.5	68	3,631.7
4	48	1,809.6	48	1,809.6	46	1,661.9	44	1,520.5	46	1,661.9	48	1,809.6
5	44	1,520.5	42	1,385.4	42	1,385.4	42	1,385.4	40	1,256.6	42	1,385.4
TOTAL AREA		10,979.9		10,524.4		9,892.9		9,556.7		9,820.6		9,406.0
% Control Area		100		95.9		90.1		87.0		89.4		85.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 25

ACTION OF SEROTONIN ON THE MICROCIRCULATION. EXPERIMENT 5.

Local injection of 5 micrograms serotonin in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF SEROTONIN INTO CHEEK POUCH.									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	40	1,256.6	28	615.8	12	113.1	30	706.9	26	530.9	28	615.8
2	26	530.9	20	314.2	16	201.1	20	314.2	16	201.1	16	201.1
3	22	380.1	12	113.1	12	113.1	22	380.1	18	254.5	18	254.5
TOTAL AREA		2,167.6		1,043.1		427.3		1,401.2		986.5		1,071.4
% Control Area		100		48.1		19.7		64.6		45.5		49.4
VEINS												
1	38	1,134.1	36	1,017.9	38	1,134.1	40	1,256.6	38	1,134.1	36	1,017.9
2	40	1,256.6	40	1,256.6	40	1,256.6	38	1,134.1	40	1,256.6	40	1,256.6
3	26	530.9	26	530.9	24	452.4	22	380.1	22	380.1	20	314.2
4	32	804.2	34	907.9	34	907.9	32	804.2	34	907.7	34	907.9
TOTAL AREA		3,725.8		3,713.3		3,751.0		3,575.0		3,678.7		3,496.6
% Control Area		100		99.7		100.7		96.0		98.7		93.8

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 26

ACTION OF SEROTONIN ON THE MICROCIRCULATION. EXPERIMENT 6.

Local injection of 5 micrograms serotonin in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF SEROTONIN INTO CHEEK POUCH.									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	42	1,385.4	20	314.2	12	113.1	28	615.8	24	452.4	38	1,134.1
2	48	1,809.6	18	254.5	14	153.9	20	314.2	22	380.1	40	1,256.6
3	20	314.2	10	78.5	8	50.3	14	153.9	12	113.1	16	201.1
4	12	113.1	8	50.3	4	12.6	10	78.5	12	113.1	10	78.5
TOTAL AREA		3,622.3		697.5		329.9		1,162.4		1,058.7		2,670.3
% Control Area		100		19.3		9.1		32.1		29.2		73.7
VEINS												
1	54	2,290.2	52	2,123.7	50	1,963.5	54	2,290.2	50	1,963.5	50	1,963.5
2	50	1,963.5	46	1,661.9	48	1,809.6	50	1,963.5	50	1,963.5	48	1,809.6
3	55	2,375.8	50	1,963.5	50	1,963.5	52	2,123.7	48	1,809.6	50	1,963.5
4	48	1,809.6	44	1,520.5	42	1,385.4	46	1,661.9	46	1,661.9	48	1,809.6
TOTAL AREA		8,439.1		7,269.6		7,122.0		8,039.3		7,398.5		7,546.2
% Control Area		100		86.1		84.4		95.3		87.7		89.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 27

ACTION OF ACETYLCHOLINE ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of one microgram acetylcholine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ACETYLCHOLINE INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	60	2,827.4	64	3,217.0	64	3,217.0	60	2,827.0	62	3,019.1	60	2,827.0
2	48	1,809.6	52	2,123.7	56	2,463.0	50	1,963.5	48	1,809.6	50	1,963.5
3	36	1,017.9	42	1,385.4	44	1,520.5	40	1,256.6	40	1,256.6	42	1,385.4
4	24	452.4	26	530.9	28	615.8	26	530.9	28	615.8	24	452.4
TOTAL AREA		6,107.3		7,257.0		7,816.3		6,578.0		6,701.1		6,628.3
% Control Area		100		118.8		128.0		107.7		109.7		108.5
VEINS												
1	62	3,019.1	60	2,827.4	62	3,019.1	60	2,827.4	64	3,217.0	62	3,019.1
2	40	1,256.6	38	1,134.1	38	1,134.1	36	1,017.9	36	1,017.9	38	1,134.1
3	52	2,123.7	54	2,290.2	48	1,809.6	48	1,809.6	46	1,661.9	48	1,809.6
4	44	1,520.5	42	1,385.4	40	1,256.6	42	1,385.4	42	1,385.4	44	1,520.5
5	38	1,134.1	40	1,256.6	38	1,134.1	40	1,256.6	38	1,134.1	40	1,256.6
TOTAL AREA		9,054.0		8,893.7		8,353.5		8,296.9		8,416.3		8,739.9
% Control Area		100		98.2		92.3		91.6		93.0		96.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 28

ACTION OF ACETYLCHOLINE ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of one microgram acetylcholine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ACETYLCHOLINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	28	615.8	30	706.9	30	706.9	32	804.2	32	804.2	30	706.9
2	26	530.9	32	804.2	32	804.2	34	907.9	36	1,017.9	32	804.2
3	28	615.8	30	706.9	34	907.9	32	804.2	32	804.2	30	706.9
4	18	254.5	20	314.2	24	452.4	26	530.9	28	615.8	22	380.1
5	38	1,134.1	36	1,017.9	38	1,134.1	38	1,134.1	40	1,256.6	36	1,017.1
TOTAL AREA		3,151.1		3,550.1		4,005.5		4,181.3		4,498.7		3,616.0
% Control Area		100		112.7		127.1		132.7		142.8		114.8
VEINS												
1	28	615.8	30	706.9	32	804.2	30	706.9	30	706.9	28	615.8
2	20	314.2	22	380.1	24	452.4	28	615.8	28	615.8	24	452.4
3	18	254.5	24	452.4	26	530.9	22	380.1	24	452.4	24	452.4
4	14	153.9	22	380.1	27	572.6	24	452.4	26	530.9	22	380.1
5	26	530.9	28	615.8	28	615.8	28	615.8	28	615.8	28	615.8
TOTAL AREA		1,869.3		2,535.3		2,975.9		2,771.0		2,921.8		2,516.5
% Control Area		100		135.6		159.2		148.2		156.3		134.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 29

ACTION OF ACETYLCHOLINE ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of one microgram acetylcholine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ACETYLCHOLINE INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	50	1,963.5	54	2,290.2	52	2,123.7	46	1,661.9	46	1,661.9
2	58	2,642.1	60	2,827.4	62	3,019.1	64	3,217.0	60	2,827.4	58	2,642.1
3	44	1,520.5	48	1,809.6	52	2,123.7	50	1,963.5	44	1,520.5	44	1,520.5
4	36	1,017.9	36	1,017.9	36	1,017.9	38	1,134.1	34	907.9	30	706.9
5	50	1,963.5	54	2,290.2	52	2,123.7	58	2,642.1	48	1,809.6	50	1,963.5
TOTAL AREA		8,953.6		9,908.6		10,574.6		11,080.1		8,727.3		8,494.9
% Control Area		100		110.7		118.1		123.8		97.5		94.9
VEINS												
1	24	452.4	26	530.9	36	1,017.9	36	1,017.9	36	1,017.9	34	907.9
2	28	615.8	30	706.9	42	1,385.4	42	1,385.4	40	1,256.6	38	1,134.1
3	66	3,421.2	66	3,421.2	76	4,536.5	78	4,778.4	76	4,536.5	76	4,536.5
4	54	2,290.2	54	2,290.2	62	3,019.2	62	3,019.1	64	3,217.0	66	3,421.2
5	18	254.3	18	254.5	22	380.1	26	530.9	20	314.2	18	254.5
TOTAL AREA		7,034.1		7,203.7		10,339.0		10,731.7		10,342.2		10,254.2
% Control Area		100		102.6		147.6		153.2		147.6		146.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 30

ACTION OF ACETYLCHOLINE ON THE MICROCIRCULATION. EXPERIMENT 4.

Local injection of one microgram acetylcholine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ACETYLCHOLINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	50	1,963.5	48	1,809.6	52	2,123.7	50	1,963.5	50	1,963.5	48	1,809.6
2	42	1,385.4	40	1,256.6	46	1,661.9	46	1,661.9	44	1,520.5	40	1,256.6
3	36	1,017.9	36	1,017.9	40	1,256.6	40	1,256.6	38	1,134.1	34	907.9
TOTAL AREA		4,366.8		4,084.1		5,042.2		4,882.0		4,618.1		3,974.1
% Control Area		100		93.5		115.5		111.8		105.8		91.0
VEINS												
1	26	530.9	28	615.8	28	615.8	30	706.9	30	706.9	24	452.4
2	32	804.2	32	804.2	30	706.9	34	907.9	32	804.2	30	706.9
3	28	615.8	30	706.9	30	706.9	32	804.2	30	706.9	30	706.9
4	58	2,642.1	58	2,642.1	60	2,827.4	60	2,827.4	60	2,827.4	58	2,642.1
TOTAL AREA		4,593.0		4,769.0		4,857.0		5,246.4		5,045.4		4,508.3
% Control Area		100		103.8		105.7		114.2		109.8		98.2

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 31

ACTION OF ACETYLCHOLINE ON THE MICROCIRCULATION. EXPERIMENT 5.

Local injection of one microgram acetylcholine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ACETYLCHOLINE INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	28	615.8	26	530.9	32	804.2	30	706.9	32	804.2	32	804.2
2	18	254.5	20	314.2	20	314.2	22	380.1	24	452.4	22	380.1
3	26	530.9	30	706.9	34	907.9	32	804.2	30	706.9	28	615.8
4	28	615.8	30	706.9	32	804.2	30	706.9	34	907.9	32	804.2
TOTAL AREA		2,017.0		2,258.9		2,830.5		2,598.1		2,871.4		2,604.3
% Control Area		100		112.0		140.3		128.8		142.4		129.1
VEINS												
1	30	706.9	32	804.2	34	907.9	32	804.2	34	907.9	34	907.9
2	26	530.9	28	615.8	30	706.9	28	615.8	30	706.9	30	706.9
3	34	907.9	36	1,017.9	38	1,134.1	38	1,134.1	40	1,256.6	38	1,134.1
4	35	962.1	34	907.9	36	1,017.9	34	907.9	38	1,134.1	36	1,017.9
5	42	1,385.4	44	1,520.5	44	1,520.5	44	1,520.5	46	1,661.9	44	1,520.5
TOTAL AREA		4,493.2		4,866.3		5,287.3		4,982.5		5,667.4		5,287.3
% Control Area		100		108.3		117.7		110.9		126.1		117.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 32

ACTION OF ACETYLCHOLINE ON THE MICROCIRCULATION. EXPERIMENT 6.

Local injection of one microgram acetylcholine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ACETYLCHOLINE INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	62	3,019.1	72	4,071.5	74	4,300.8	72	4,071.5	70	3,848.5	64	3,217.0
2	34	907.9	40	1,256.6	46	1,661.9	42	1,385.4	42	1,385.4	40	1,256.6
3	60	2,827.4	68	3,631.7	66	3,421.2	64	3,217.0	66	3,421.2	66	3,421.2
TOTAL AREA		6,754.4		8,959.8		9,383.9		8,673.9		8,655.1		7,894.8
% Control Area		100		132.7		138.9		128.4		128.1		116.9
VEINS												
1	38	1,134.1	48	1,809.6	50	1,963.5	44	1,520.5	48	1,809.6	48	1,809.6
2	60	2,827.4	64	3,217.0	64	3,217.0	62	3,019.1	62	3,019.1	60	2,827.4
3	56	2,463.0	70	3,848.5	68	3,631.7	62	3,019.1	54	2,290.2	58	2,642.1
4	56	2,463.0	58	2,642.1	60	2,827.4	58	2,642.1	58	2,642.1	58	2,642.1
TOTAL AREA		8,887.5		11,517.2		11,639.6		10,200.8		9,761.0		9,921.2
% Control Area		100		129.6		131.0		114.8		109.8		111.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 33

A) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 25 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	12	113.1	12	113.1	18	254.5	58	2,642.1	56	2,463.0
2	60	2,827.4	14	153.9	10	78.5	12	113.1	54	2,290.2	56	2,463.0
3	38	1,134.1	8	50.3	6	28.3	22	380.1	40	1,256.6	40	1,256.6
TOTAL AREA		6,603.6		317.3		219.9		747.7		6,188.9		6,182.6
% Control Area		100		4.8		3.3		11.3		93.7		93.6
VEINS												
1	60	2,827.4	42	1,385.4	40	1,256.6	48	1,809.6	42	1,385.4	46	1,661.9
2	76	4,536.5	68	3,631.7	70	3,848.5	72	4,071.5	68	3,631.7	68	3,631.7
3	70	3,848.5	68	3,631.7	66	3,421.2	68	3,631.7	72	4,071.5	70	3,848.5
4	112	9,852.0	86	5,808.8	88	6,082.1	110	9,503.3	114	10,207.0	112	9,852.0
TOTAL AREA		21,064.4		14,457.6		14,608.4		19,016.1		19,295.6		18,994.1
% Control Area		100		68.6		69.4		90.3		91.6		90.2

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 34

A) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 25 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	45	1,590.4	12	113.1	20	314.2	24	452.4	50	1,963.5	48	1,809.6
2	28	615.8	5	19.6	10	78.5	14	153.9	20	314.2	30	706.9
3	58	2,642.1	10	78.5	24	452.4	22	380.1	54	2,290.2	58	2,642.1
4	14	153.9	0	0	0	0	8	50.3	10	78.5	12	113.1
TOTAL AREA		5,002.2		211.2		845.1		1,036.7		4,646.4		5,271.7
% Control Area		100		4.2		16.9		20.7		92.9		105.4
VEINS												
1	60	2,827.4	60	2,827.4	52	2,123.7	50	1,963.5	50	1,963.5	58	2,642.1
2	42	1,385.4	44	1,520.5	40	1,256.6	38	1,134.1	40	1,256.6	42	1,385.4
3	38	1,134.1	30	706.9	34	907.9	40	1,256.6	38	1,134.1	34	907.9
4	20	314.2	22	380.1	28	615.8	20	314.2	28	615.8	20	314.2
TOTAL AREA		5,661.1		5,434.9		4,904.0		4,668.4		4,970.0		5,249.6
% Control Area		100		96.0		86.6		82.5		87.8		92.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 35

A) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 25 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	50	1,963.5	18	254.5	40	1,256.6	40	1,256.6	44	1,520.5	42	1,385.4
2	44	1,520.5	12	113.1	32	804.2	40	1,256.6	42	1,385.4	40	1,256.6
3	28	615.8	12	113.1	24	452.4	24	452.4	28	615.8	26	530.9
4	18	254.5	10	78.5	16	201.1	18	254.5	20	314.2	20	314.2
TOTAL AREA		4,354.3		559.2		2,714.3		3,220.1		3,835.9		3,487.1
% Control Area		100		12.8		62.3		74.0		88.1		80.1
VEINS												
1	40	1,256.6	40	1,256.6	38	1,134.1	40	1,256.6	38	1,134.1	40	1,256.6
2	38	1,134.1	34	907.9	36	1,017.9	32	804.2	34	907.9	38	1,134.1
3	18	254.5	20	314.2	20	314.2	22	380.1	20	314.2	20	314.2
4	30	706.9	28	615.8	30	706.9	32	804.2	30	706.9	32	804.2
5	62	3,019.1	62	3,019.1	60	2,827.4	60	2,827.4	62	3,019.1	60	2,827.4
TOTAL AREA		6,371.2		6,113.6		6,000.5		6,072.5		6,082.2		6,336.5
% Control Area		100		96.0		94.2		95.3		95.5		99.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 36

A) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 4.

Local injection of 25 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	12	113.1	20	314.2	50	1,963.5	56	2,463.0	56	2,463.0
2	60	2,827.4	10	78.5	18	254.5	42	1,385.4	54	2,290.2	58	2,642.1
3	48	1,809.6	12	113.1	18	254.5	40	1,256.6	46	1,661.9	46	1,661.9
4	22	380.1	8	50.3	10	78.5	12	113.1	16	201.1	18	254.5
TOTAL AREA		7,659.2		355.0		901.7		4,718.6		6,616.2		7,021.5
% Control Area		100		4.6		11.8		61.6		86.4		91.7
VEINS												
1	84	5,541.8	80	5,026.5	78	4,778.4	80	5,026.5	82	5,281.0	54	5,541.8
2	52	2,123.7	46	1,661.9	50	1,936.5	50	1,963.5	52	2,123.7	50	1,963.5
3	74	4,300.8	72	4,071.5	72	4,071.5	72	4,071.5	72	4,071.5	72	4,071.5
4	42	1,385.4	40	1,256.6	38	1,134.1	36	1,017.7	40	1,256.6	42	1,385.4
TOTAL AREA		13,351.7		12,016.5		11,947.5		12,079.4		12,732.8		12,962.2
% Control Area		100		90.0		89.5		90.5		95.4		97.1

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 37

B) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 5 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	62	3,019.1	14	153.9	20	314.2	36	1,017.9	34	907.9	42	1,385.4
2	58	2,642.1	10	78.5	26	530.9	32	804.2	32	804.2	32	804.2
3	66	3,421.2	18	254.5	28	615.8	36	1,017.9	32	804.2	40	1,256.6
TOTAL AREA		9,082.4		486.9		1,460.9		2,840.0		2,516.3		3,446.2
% Control Area		100		5.4		16.1		31.3		27.7		37.9
VEINS												
1	82	5,281.0	72	4,071.5	70	3,848.5	74	4,300.8	70	3,848.5	74	4,300.8
2	22	380.1	18	254.5	20	314.2	18	254.5	12	113.1	20	314.2
3	54	2,290.2	50	1,963.5	46	1,661.9	48	1,809.6	50	1,963.5	52	2,123.7
TOTAL AREA		7,951.3		6,289.5		5,824.6		6,364.9		5,925.1		6,738.7
% Control Area		100		79.1		73.3		80.0		74.5		84.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 38

B) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 5 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	78	4,778.4	72	4,071.5	72	4,071.5	70	3,848.5	58	2,642.1	58	2,642.1
2	40	1,256.6	36	1,017.9	36	1,017.9	28	615.8	22	380.1	20	314.2
3	38	1,134.1	34	907.9	32	804.2	32	804.2	34	907.9	30	706.9
4	16	201.1	18	254.5	18	254.5	16	201.1	16	201.1	16	201.1
TOTAL AREA		7,370.2		6,251.8		6,148.7		5,469.6		4,131.2		3,864.3
% Control Area		100		84.7		83.4		74.5		56.1		52.5
VEINS												
1	40	1,256.6	40	1,256.6	44	1,520.1	40	1,256.6	42	1,385.4	40	1,256.6
2	38	1,134.1	36	1,017.9	34	907.9	34	907.9	36	1,017.9	36	1,017.9
3	26	530.9	20	314.2	22	380.1	22	380.1	24	452.4	26	530.9
4	22	380.1	20	314.2	22	380.1	22	380.1	24	452.4	20	314.2
5	34	907.9	36	1,017.9	31	754.8	34	907.9	28	615.8	26	530.9
TOTAL AREA		4,209.6		3,920.8		3,943.4		3,832.6		3,923.9		3,650.5
% Control Area		100		93.1		93.7		91.0		93.2		86.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 39

B) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 5 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	52	2,123.7	12	113.1	14	153.9	30	706.9	40	1,256.6	46	1,661.9
2	44	1,520.5	30	706.9	30	706.9	38	1,134.1	42	1,385.4	44	1,520.5
3	38	1,134.1	24	452.4	28	615.8	32	804.2	38	1,134.1	38	1,134.1
TOTAL AREA		4,778.3		1,272.4		1,476.6		2,645.2		3,776.1		4,316.5
% Control Area		100		26.6		30.9		55.4		79.0		90.3
VEINS												
1	62	3,019.1	60	2,827.4	62	3,019.1	60	2,827.4	62	3,019.1	64	3,217.0
2	22	380.1	24	452.4	22	380.1	22	380.1	24	452.4	24	452.4
3	64	3,217.0	62	3,019.1	62	3,019.1	60	2,827.4	62	3,019.1	62	3,019.1
4	34	907.9	32	804.2	32	804.2	32	804.2	32	804.2	32	804.2
TOTAL AREA		7,524.1		7,103.1		7,222.5		6,839.1		7,294.8		7,592.7
% Control Area		100		94.4		96.0		90.9		96.9		100.9

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 40

B) ACTION OF ANGIOTENSIN ON THE MICROCIRCULATION. EXPERIMENT 4.

Local injection of 5 micrograms angiotensin II in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ANGIOTENSIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	34	907.9	18	254.5	10	78.5	22	380.1	32	804.2	36	1,017.9
2	18	254.5	8	50.3	12	113.1	18	254.5	18	254.5	20	314.2
3	12	113.1	0	0	8	50.3	10	78.5	10	78.5	12	113.1
4	44	1,520.5	10	78.5	20	314.2	32	804.2	38	1,134.1	45	1,590.4
TOTAL AREA		2,796.0		383.3		556.1		1,517.3		2,271.3		3,035.6
% Control Area		100		13.7		19.9		54.3		81.2		108.2
VEINS												
1	62	3,019.1	60	2,827.4	62	3,019.1	60	2,827.4	58	2,642.1	60	2,827.4
2	44	1,520.5	46	1,661.9	44	1,520.5	42	1,385.4	46	1,661.9	50	1,963.5
3	30	706.9	26	530.9	26	530.9	26	530.9	28	615.8	30	706.9
4	32	804.2	32	804.2	30	706.9	30	706.9	30	706.9	32	804.2
TOTAL AREA		6,050.7		5,824.4		5,777.4		5,450.6		5,626.7		6,302.0
% Control Area		100		96.2		95.5		90.1		93.0		104.2

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 41

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 1.

A) Local injection of one microgram adrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phenoxybenzamine.

	TIME IN MINUTES AFTER INJECTIONS																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	78	4,778.4	26	530.9	24	452.4	16	201.1	16	201.1	32	804.2	50	1,963.5	52	2,123.7	52	2,123
2	80	5,026.5	15	176.7	16	201.1	14	153.9	14	153.9	40	1,256.6	42	1,385.4	44	1,520.5	46	1,661
3	50	1,963.5	14	153.9	10	78.5	4	12.6	4	12.6	22	380.1	22	380.1	26	530.9	30	706
4	28	615.8	4	12.6	4	12.6	2	3.1	2	3.1	18	254.5	20	314.2	22	380.1	20	314
5	42	1,385.4	2	3.1	2	3.1	0	0	0	0	22	380.1	20	314.2	14	153.9	14	153
TOTAL AREA		13,769.6		877.2		747.7		370.7		370.7		3,075.5		4,357.4		4,709.1		4,960
% Control Area		100		6.4		5.4		2.7		2.7		22.3		31.6		34.2		36
VEINS																		
1	92	6,647.6	48	1,809.6	36	1,017.9	28	615.8	24	452.4	26	530.9	30	706.9	46	1,661.9	44	1,520
2	158	19,606.7	142	15,836.8	126	12,469.0	122	11,689.9	110	9,503.3	118	10,935.9	126	12,469.0	128	12,868.0	126	12,469
3	94	6,939.8	76	4,536.5	80	5,026.5	64	3,217.0	64	3,217.0	66	3,421.2	68	3,631.7	68	3,631.7	68	3,631
4	58	2,642.1	34	907.9	34	907.9	8	50.3	6	28.3	18	254.5	22	380.1	26	530.9	24	452
5	90	6,361.7	58	2,642.1	60	2,827.4	52	2,123.7	30	706.9	52	2,123.7	52	2,123.7	52	2,123.7	52	2,123
TOTAL AREA		42,197.9		25,732.9		22,248.7		17,696.7		13,907.9		17,266.2		19,311.4		20,816.2		20,197
% Control Area		100		61.0		52.7		41.9		33.0		40.9		45.8		49.3		47

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 42

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 2.

A) Local injection of one microgram adrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phenoxybenzamine.

	Control		TIME IN MINUTES AFTER INJECTION															
			3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	8	50.3	12	113.1	14	153.9	14	153.9	24	452.4	30	706.9	30	706.9	42	1,385
2	62	3,019.1	20	314.2	14	153.9	16	201.1	18	254.5	30	706.9	32	804.2	32	804.2	38	1,134
3	50	1,963.5	8	50.3	10	78.5	12	113.1	12	113.1	22	380.1	22	380.1	20	314.2	22	380
4	54	2,290.2	8	50.3	8	50.3	10	78.5	10	78.5	18	254.5	20	314.2	20	314.2	28	615
5	38	1,134.1	10	78.5	10	78.5	8	50.3	10	78.5	14	153.9	12	113.1	12	113.1	20	314
6	14	153.9	0	0	8	50.3	4	12.6	4	12.6	6	28.3	10	78.5	12	113.1	8	50
TOTAL AREA		11,202.9		543.6		524.6		609.5		691.1		1,976.1		2,397.0		2,365.7		3,879
% Control Area		100		4.9		4.7		5.4		6.2		17.6		21.4		21.1		34
VEINS																		
1	48	1,809.6	42	1,385.4	40	1,256.6	42	1,385.4	38	1,134.1	42	1,385.4	42	1,385.4	32	804.2	34	907
2	30	706.9	32	804.2	30	706.9	28	615.8	24	452.4	30	706.9	30	706.9	28	615.8	26	530
3	40	1,256.6	32	804.2	32	804.2	26	530.9	32	804.2	36	1,017.9	36	1,017.9	32	804.2	28	615
4	22	380.1	18	254.5	14	153.9	16	201.1	18	254.5	20	314.2	22	380.1	20	314.2	22	380
5	52	2,123.7	44	1,520.5	42	1,385.4	44	1,520.5	44	1,520.5	48	1,809.6	50	1,963.5	46	1,661.9	42	1,385
6	62	3,019.1	54	2,290.2	52	2,123.7	48	1,809.6	46	1,661.9	52	2,123.7	52	2,123.7	50	1,963.5	52	2,123
TOTAL AREA		9,296.0		7,059.0		6,430.7		6,063.3		5,827.6		7,357.7		7,577.5		6,163.8		5,943
% Control Area		100		75.9		69.2		65.2		62.7		79.1		81.5		66.3		63

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 43

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 3.

A) Local injection of one microgram adrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phenoxybenzamine.

			TIME IN MINUTES AFTER INJECTIONS															
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	40	1,256.6	12	113.1	12	113.1	10	78.5	10	78.5	22	380.1	28	615.8	34	907.9	34	907.
2	22	380.1	8	50.3	8	50.3	6	28.3	6	28.3	10	78.5	18	254.5	24	452.4	22	380.
3	34	907.9	10	78.5	8	50.3	8	50.3	6	28.3	12	113.1	24	452.4	36	1,017.9	38	1,134.
4	12	113.1	0	0	0	0	0	0	0	0	10	78.5	12	113.1	14	153.9	12	113.
TOTAL AREA		2,657.7		241.9		213.7		157.1		135.1		650.2		1,435.8		2,532.1		2,535.
% Control Area		100		9.1		8.0		5.9		5.1		24.5		54.0		95.3		95.
VEINS																		
1	46	1,661.9	24	452.4	22	380.1	20	314.2	20	314.2	22	380.1	30	706.9	36	1,017.9	42	1,385.
2	28	615.8	12	113.1	12	113.1	10	78.5	8	50.3	18	254.5	18	254.5	24	452.4	30	706.
3	38	1,134.1	16	201.1	18	254.5	18	254.5	14	153.9	20	314.2	24	452.4	22	380.1	30	706.
4	16	201.1	10	78.5	6	28.3	6	28.3	6	28.3	10	78.5	14	153.9	20	314.2	22	380.
5	36	1,017.9	20	314.2	22	380.1	20	314.2	18	254.5	22	380.1	26	530.9	26	530.9	28	615.
TOTAL AREA		4,630.8		1,159.3		1,156.1		989.7		801.2		1,407.4		2,098.6		2,695.5		3,795.
% Control Area		100		25.0		25.0		21.4		17.3		30.4		45.3		58.2		82.

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 44

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 1.

B) Local injection of one microgram adrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phentolamine.

	TIME IN MINUTES AFTER INJECTIONS																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	26	530.9	10	78.5	8	50.3	8	50.3	8	50.3	18	254.5	28	615.8	26	530.9	24	452.
2	20	314.2	10	78.5	4	12.6	4	12.6	4	12.6	12	113.1	20	314.2	20	314.2	22	380.
3	14	153.9	8	50.3	5	19.6	4	12.6	5	19.6	12	113.1	16	201.1	18	254.5	20	314.
4	28	615.8	0	0	0	0	0	0	0	0	16	201.1	26	530.9	28	615.8	30	706.
TOTAL AREA		1,614.8		207.3		82.5		75.5		82.5		681.8		1,662.0		1,715.4		1,853.
% Control Area		100		12.8		5.1		4.7		5.1		42.2		102.9		106.2		114.
VEINS																		
1	44	1,520.5	38	1,134.1	28	615.8	28	615.8	24	452.4	30	706.9	42	1,385.4	42	1,385.4	44	1,520.
2	20	314.2	12	113.1	12	113.1	10	78.5	8	50.3	12	113.1	18	254.5	20	314.2	22	380.
3	44	1,520.5	26	530.9	22	380.1	18	254.5	18	254.5	32	804.2	40	1,256.6	38	1,134.1	40	1,256.
4	18	254.5	12	113.1	12	113.1	12	113.1	10	78.5	12	113.1	16	201.1	18	254.5	20	314.
TOTAL AREA		3,609.7		1,891.2		1,222.1		1,061.9		835.7		1,737.3		3,097.6		3,088.2		3,471.
% Control Area		100		52.4		33.9		29.4		23.2		48.1		85.8		85.6		96.

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 45

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 2.

B) Local injection of one microgram adrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phentolamine.

	TIME IN MINUTES AFTER INJECTIONS																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	40	1,256.6	20	314.2	12	113.1	10	78.5	10	78.5	26	530.9	32	804.2	40	1,256.6	40	1,256
2	22	380.1	0	0	0	0	0	0	0	0	18	254.5	20	314.2	20	314.2	18	254
3	38	1,134.1	12	113.1	8	50.3	8	50.3	8	50.3	28	615.8	36	1,017.9	40	1,256.6	40	1,256
TOTAL AREA		2,770.8		427.3		163.4		128.8		128.8		1,401.2		2,136.3		2,827.4		2,767
% Control Area		100		15.4		5.9		4.6		4.6		50.6		77.1		102.0		99
VEINS																		
1	54	2,290.2	50	1,963.5	42	1,385.4	38	1,134.1	36	1,017.9	45	1,590.4	54	2,290.2	52	2,123.7	52	2,123
2	48	1,809.6	40	1,256.6	36	1,017.9	34	907.9	36	1,017.9	38	1,385.4	46	1,661.9	46	1,661.9	46	1,661
3	34	907.9	28	615.8	28	615.8	22	380.1	24	452.4	28	615.8	30	706.9	32	804.2	30	706
4	30	706.9	22	380.1	18	254.5	16	201.1	14	153.9	22	380.1	30	706.9	30	706.9	30	706
TOTAL AREA		5,714.6		4,216.0		3,273.6		2,623.2		2,642.1		3,720.4		5,089.4		5,296.7		5,199
% Control Area		100		73.8		57.3		45.9		46.2		65.1		89.1		92.7		91

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 46

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 3.

B) Local injection of one microgram adrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phentolamine.

	Control		TIME IN MINUTES AFTER INJECTIONS																
			3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	14	153.9	10	78.5	8	50.3	8	50.3	22	380.1	40	1,256.6	44	1,520.5	46	1,661.
2	30	706.9	10	78.5	8	50.3	8	50.3	0	0	20	314.2	28	615.8	30	706.9	32	804.
3	28	615.8	0	0	0	0	0	0	0	0	20	314.2	24	452.4	24	452.4	28	615.
4	20	314.2	0	0	0	0	0	0	0	0	15	176.7	22	380.1	22	380.1	22	380.
TOTAL AREA		3,446.5		232.4		128.8		100.6		50.3		1,185.2		2,704.9		3,059.9		3,462.
% Control Area		100		6.7		3.7		2.9		1.5		34.4		78.4		88.8		100.
VEINS																		
1	50	1,963.5	28	615.8	26	530.9	22	380.1	20	314.2	28	615.8	25	490.9	30	706.9	38	1,134.
2	58	2,642.1	48	1,809.6	40	1,256.6	34	907.9	28	615.8	40	1,256.6	48	1,809.6	48	1,809.6	56	2,463.
3	74	4,300.8	60	2,827.4	52	2,123.7	50	1,963.5	42	1,385.4	54	2,290.2	62	3,019.1	66	3,421.2	66	3,421.
4	32	804.2	28	615.8	20	314.2	18	254.5	18	254.5	22	380.1	28	615.8	30	706.9	30	706.
TOTAL AREA		9,710.6		5,858.6		4,225.4		3,506.0		2,569.9		4,542.7		5,935.4		6,644.6		7,725.
% Control Area		100		60.4		43.5		36.1		26.5		46.8		61.1		68.4		79.

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 47

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 1.

C) Local injection of one microgram noradrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phenoxybenzamine.

	TIME IN MINUTES AFTER INJECTIONS																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	42	1,385.4	10	78.5	10	78.5	18	254.5	20	314.2	48	1,809.6	50	1,963.5	50	1,963.5	50	1,963.
2	42	1,385.4	11	95.0	9	63.7	18	254.5	18	254.5	30	706.9	38	1,134.1	40	1,256.6	36	1,017.
3	34	907.9	8	50.3	6	28.3	10	78.5	8	50.3	28	615.8	36	1,017.9	34	907.9	34	907.
4	22	380.1	0	0	0	0	8	50.3	5	19.6	16	201.1	20	314.2	20	314.2	18	254.
TOTAL AREA		4,058.8		223.8		170.5		637.8		638.6		3,333.4		4,429.7		4,442.2		4,143.
% Control Area		100		5.5		4.3		15.7		15.7		82.1		109.1		109.4		102.
VEINS																		
1	40	1,256.6	38	1,134.1	32	804.2	38	1,134.1	40	1,256.6	40	1,256.6	42	1,385.4	44	1,520.5	48	1,809.
2	32	804.2	26	530.9	22	380.1	26	530.9	22	380.9	32	804.2	34	907.9	32	804.2	32	804.
3	28	615.8	30	706.9	20	314.2	22	380.1	20	314.2	28	615.8	30	706.9	28	615.8	30	706.
4	32	804.2	26	530.9	28	615.8	28	615.8	24	452.4	30	706.9	30	706.9	28	615.8	32	804.
5	58	2,642.8	44	1,520.5	34	907.9	40	1,256.6	38	1,134.1	44	1,520.5	50	1,963.5	52	2,123.7	50	1,963.
TOTAL AREA		6,123.6		4,423.3		3,022.2		3,917.5		3,537.4		4,904.0		5,670.6		5,680.0		6,088.
% Control Area		100		72.2		49.4		64.0		57.8		80.1		92.6		92.8		99.

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 48

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 2.

C) Local injection of one microgram noradrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phenoxybenzamine.

	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
											TIME IN MINUTES AFTER INJECTIONS							
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	90	6,361.7	12	113.1	12	113.1	18	254.5	18	254.5	52	2,123.7	88	6,082.1	90	6,361.7	90	6,361.
2	82	5,281.0	0	0	8	50.3	10	78.5	12	113.1	58	2,642.1	80	5,026.5	84	5,541.8	84	5,541.
3	62	3,019.1	10	78.5	10	78.5	8	50.3	8	50.3	42	1,385.4	58	2,642.4	64	3,217.0	62	3,019.
TOTAL AREA		14,661.8		191.6		241.9		383.3		417.9		6,151.2		13,751.0		15,120.5		14.922.
% Control Area		100		1.3		1.6		2.6		2.9		42.0		94.1		103.1		101.
VEINS																		
1	128	12,868.0	114	10,207.0	108	9,160.9	92	6,647.6	72	4,071.5	98	7,543.0	112	9,852.0	122	11,689.9	126	12,469.
2	72	4,071.5	68	3,631.7	66	3,421.2	52	2,123.7	62	3,019.1	70	3,848.5	76	4,536.5	76	4,536.5	72	4,071.
3	64	3,217.0	62	3,019.1	62	3,019.1	50	1,963.5	52	2,123.7	58	2,642.1	62	3,019.1	62	3,019.1	62	3,019.
TOTAL AREA		20,156.5		16,857.8		15,601.2		10,734.8		9,214.3		14,033.6		17,407.6		19,245.5		19,559.
% Control Area		100		83.6		77.4		53.3		45.7		69.6		86.4		95.5		97.

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 49

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 3.

C) Local injection of one microgram noradrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 5 micrograms phenoxybenzamine.

			TIME IN MINUTES AFTER INJECTIONS															
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	42	1,385.4	8	50.3	6	28.3	6	28.3	10	78.5	32	804.2	40	1,256.6	42	1,385.4	42	1,385.
2	48	1,809.6	6	28.3	5	19.6	6	28.3	12	113.1	36	1,017.9	40	1,256.6	46	1,661.9	48	1,809.
3	18	254.5	4	12.6	0	0	0	0	0	0	12	113.1	20	314.2	20	314.2	22	380.
4	22	380.1	0	0	0	0	0	0	0	0	14	153.9	16	201.1	20	314.2	20	314.
TOTAL AREA		3,829.6		91.2		47.9		56.6		191.6		2,089.1		3,028.5		3,675.7		3,889.
% Control Area		100		2.4		1.3		1.5		5.0		54.6		79.1		96.0		101.
VEINS																		
1	32	804.2	22	380.1	18	254.5	12	113.1	10	78.5	12	113.1	12	113.1	28	615.8	28	615.
2	44	1,520.5	24	452.4	22	380.1	15	176.7	12	113.1	15	176.7	20	314.2	32	804.2	38	1,134.
3	30	706.9	18	254.5	12	113.1	5	19.6	5	19.6	10	78.5	16	201.1	22	380.1	24	452.
4	36	1,017.9	20	314.2	18	254.5	8	50.3	8	50.3	14	153.9	16	201.1	30	706.9	32	804.
TOTAL AREA		4,049.5		1,401.2		1,002.2		359.7		261.5		522.2		829.5		2,507.0		3,006.
% Control Area		100		34.6		24.7		8.9		6.5		12.9		20.5		61.9		74.

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 50.

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 1.

D) Local injection of one microgram noradrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 2 micrograms phentolamine.

	TIME IN MINUTES AFTER INJECTIONS																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	68	3,631.7	15	176.7	8	50.3	6	28.3	4	12.6	26	530.9	42	1,385.4	52	2,123.7	58	2,642
2	20	314.2	4	12.6	2	3.1	2	3.1	2	3.1	16	201.1	16	201.1	18	254.5	18	254
3	14	153.9	0	0	0	0	0	0	0	0	12	113.1	10	78.5	12	113.1	12	113
4	24	452.4	6	28.3	4	12.6	6	28.3	4	12.6	20	314.2	20	314.2	18	254.5	20	314
5	20	314.2	8	50.3	4	12.6	4	12.6	0	0	22	380.1	18	254.5	14	153.9	14	153
TOTAL AREA		4,866.4		267.9		78.6		72.3		28.3		1,539.4		2,233.7		2,899.7		3,477
% Control Area		100		5.5		1.6		1.5		0.6		31.6		45.9		59.6		71
VEINS																		
1	112	9,852.0	28	615.8	30	706.9	24	452.4	12	113.1	50	1,963.5	68	3,617.0	82	5,281.0	86	5,808
2	42	1,385.4	22	380.1	12	113.1	8	50.3	8	50.3	14	153.9	22	380.1	22	380.1	24	452
3	46	1,661.9	18	254.5	8	50.3	6	28.3	6	28.3	12	113.1	20	314.2	20	314.2	20	314
4	48	1,899.6	20	314.2	12	113.1	12	113.1	14	153.9	30	706.9	42	1,385.4	44	1,520.5	50	1,963
5	32	804.2	12	113.1	0	0	0	0	4	12.6	22	380.1	20	314.2	24	452.4	28	615
TOTAL AREA		15,603.1		1,677.7		983.4		644.1		358.2		3,317.5		6,025.6		7,948.2		9,154
% Control Area		100		10.8		6.3		4.1		2.3		21.3		38.6		50.9		58

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 51

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 2.

D) Local injection of one microgram noradrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 2 micrograms phentolamine.

	TIME IN MINUTES AFTER INJECTIONS																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	66	3,421.2	30	706.0	18	254.5	12	113.1	10	78.5	33	855.3	48	1,809.6	64	3,217.0	66	3,421.
2	58	2,642.1	26	530.9	12	113.1	10	78.5	8	50.3	36	1,017.9	54	2,290.2	60	2,827.4	60	2,827.
3	46	1,661.9	12	113.1	0	0	0	0	0	0	24	452.4	40	1,256.6	42	1,385.4	42	1,385.
TOTAL AREA		7,725.2		1,350.9		367.6		191.6		128.8		2,325.6		5,356.4		7,429.8		7,634.
% Control Area		100		17.5		4.8		2.5		1.7		30.1		69.3		96.2		98.
VEINS 1	51	2,042.8	46	1,661.9	38	1,134.1	24	452.4	20	314.2	34	907.9	46	1,661.9	48	1,809.6	46	1,661.
2	56	2,463.0	32	804.2	32	804.2	28	615.8	24	452.4	40	1,256.6	48	1,809.6	52	2,123.7	50	1,963.
3	72	4,071.5	48	1,809.6	44	1,520.5	42	1,385.4	40	1,256.6	52	2,123.7	64	3,217.0	66	3,421.2	68	3,631.
4	30	706.9	26	530.9	20	314.2	16	201.1	16	201.1	26	530.9	28	615.8	30	706.9	26	530.
TOTAL AREA		9,284.2		4,806.6		3,773.0		2,654.7		2,224.3		4,819.1		7,304.3		8,061.4		7,788.
% Control Area		100		51.8		40.6		28.6		24.0		51.9		78.7		86.8		83.

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 52

ACTION OF CATECHOLAMINES ON THE MICROCIRCULATION. EXPERIMENT 3.

D) Local injection of one microgram noradrenaline in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch, followed in 30 minutes by injection of 2 micrograms Phentolamine.

	Control		TIME IN MINUTES AFTER INJECTIONS 3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,385.4	10	78.5	8	50.3	10	78.5	8	50.3	32	804.2	50	1,963.5	48	1,809.6	48	1,809.
2	36	1,017.9	0	0	0	0	0	0	0	0	18	254.5	30	706.9	34	907.9	34	907.
3	46	1,661.9	8	50.3	0	0	0	0	0	0	34	907.9	46	1,661.9	48	1,809.6	48	1,809.
TOTAL AREA		4,065.2		128.8		50.3		78.5		50.3		1,966.6		4,332.3		4,527.1		4,527.
% Control Area		100		3.2		1.2		1.9		1.2		48.4		106.6		111.4		111.
VEINS																		
1	42	1,385.4	34	907.9	34	907.9	34	907.9	34	907.9	36	1,017.9	40	1,256.6	44	1,520.5	46	1,661.
2	60	2,827.4	38	1,134.1	40	1,256.6	38	1,134.1	34	907.9	38	1,134.1	40	1,256.6	48	1,809.6	52	2,123.
3	40	1,256.6	38	1,134.1	32	804.2	32	804.2	32	804.2	36	1,017.9	36	1,017.9	40	1,256.6	38	1,134.
4	34	907.9	30	706.9	28	615.8	20	314.2	20	314.2	20	314.2	24	452.4	30	706.9	28	615.
TOTAL AREA		6,377.3		3,883.0		3,584.5		3,160.4		2,934.2		3,484.1		3,983.5		5,293.6		5,535.
% Control Area		100		60.9		56.2		49.6		46.0		54.6		62.5		83.0		86.

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 53

ACTION OF PHENOXYBENZAMINE ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 20 micrograms phenoxybenzamine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PHENOXYBENZAMINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	54	2,290.2	52	2,123.7	52	2,123.7	52	2,123.7	50	1,963.5		-
2	40	1,256.6	38	1,134.1	42	1,385.4	42	1,385.4	42	1,385.4		-
3	42	1,385.4	42	1,385.4	44	1,520.5	46	1,661.9	38	1,134.1		-
4	24	452.4	28	615.8	28	615.8	28	615.8	28	615.8		-
5	58	2,642.1	56	2,463.0	56	2,463.0	52	2,123.7	50	1,963.5		-
TOTAL AREA		8,026.7		7,722.0		8,108.4		7,910.5		7,062.3		-
% Control Area		100		96.2		101.0		98.6		88.0		-
VEINS												
1	88	6,082.1	84	5,541.8	86	5,808.8	82	5,281.0	86	5,808.8		-
2	30	706.9	32	804.2	28	615.8	26	530.9	28	615.8		-
3	52	2,123.7	54	2,290.2	52	2,123.7	52	2,123.7	50	1,963.5		-
4	68	3,631.7	68	3,631.7	66	3,421.2	64	3,217.0	66	3,421.2		-
5	54	2,290.2	52	2,123.7	52	2,123.7	54	2,290.2	52	2,123.7		-
TOTAL AREA		14,834.6		14,391.6		14,093.2		13,442.8		13,933.0		-
% Control Area		100		97.0		95.0		90.6		93.9		-

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 54

ACTION OF PHENOXYBENZAMINE ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 20 micrograms phenoxybenzamine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PHENOXYBENZAMINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	20	314.2	20	314.2	22	380.1	22	380.1	22	380.1	22	380.1
2	16	201.1	16	201.1	14	153.9	16	201.1	16	201.1	16	201.1
3	28	615.8	26	530.9	28	615.8	30	706.9	30	706.9	28	615.8
TOTAL AREA		1,131.1		1,046.2		1,149.8		1,288.1		1,288.1		1,197.0
% Control Area		100		92.5		101.7		113.9		113.9		105.8
VEINS												
1	48	1,809.6	46	1,661.9	46	1,661.9	44	1,520.5	50	1,963.5	48	1,809.6
2	32	804.2	30	706.9	30	706.9	32	804.2	30	706.9	30	706.9
3	38	1,134.1	40	1,256.6	40	1,256.6	38	1,134.1	36	1,017.9	36	1,017.9
4	24	452.4	26	530.9	28	615.8	24	452.4	24	452.4	24	452.4
TOTAL AREA		4,200.3		4,156.3		4,241.2		3,911.2		4,140.7		3,986.8
% Control Area		100		99.0		107.0		93.1		98.6		94.9

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 55

ACTION OF PHENOXYBENZAMINE ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 20 micrograms phenoxybenzamine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PHENOXYBENZAMINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	60	2,827.4	58	2,642.1	62	3,019.1	60	2,827.4	62	3,019.1	62	3,019.1
2	38	1,134.1	40	1,256.6	40	1,256.6	40	1,256.6	42	1,385.4	40	1,256.6
3	18	254.5	20	314.2	20	314.2	20	314.2	20	314.2	20	314.2
4	54	2,290.2	52	2,123.7	54	2,290.2	56	2,463.0	54	2,290.2	52	2,290.2
TOTAL AREA		6,506.2		6,336.6		6,880.1		6,861.2		7,008.9		6,880.1
% Control Area		100		97.4		105.7		105.5		107.7		105.7
VEINS												
1	68	3,631.7	66	3,421.2	66	3,421.2	68	3,631.7	66	3,421.2	68	3,631.7
2	40	1,256.6	42	1,385.4	40	1,256.6	42	1,385.4	40	1,256.6	40	1,256.6
3	48	1,809.6	48	1,809.6	50	1,963.5	48	1,809.6	50	1,963.5	50	1,963.5
4	48	1,809.6	48	1,809.6	46	1,661.9	44	1,520.5	44	1,520.5	46	1,661.9
5	30	706.9	32	804.2	32	804.2	32	804.2	32	804.2	30	706.9
TOTAL AREA		9,214.4		9,230.0		9,107.4		9,151.4		8,966.0		9,220.6
% Control Area		100		100.2		98.8		99.3		97.3		100.1

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 56

ACTION OF PHENTOLAMINE ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 10 micrograms phentolamine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PHENTOLAMINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	66	3,421.2	62	3,019.1	64	3,217.0	66	3,421.2	64	3,217.0	66	3,421.2
2	70	3,848.5	64	3,217.0	72	4,071.5	70	3,848.5	72	4,071.5	70	3,848.5
3	30	706.9	28	615.8	28	615.8	32	804.2	30	706.9	28	615.8
4	18	254.5	18	254.5	16	201.1	20	314.2	18	254.5	18	254.5
TOTAL AREA		8,231.1		7,106.4		8,105.4		8,388.1		8,249.9		8,140.0
% Control Area		100		86.3		98.5		101.9		100.2		99.0
VEINS												
1	37	1,075.2	36	1,017.9	38	1,134.1	36	1,017.9	38	1,134.1	38	1,134.1
2	45	1,590.4	40	1,256.6	44	1,520.5	44	1,520.5	46	1,661.9	42	1,385.4
3	33	855.3	34	907.9	32	804.2	34	907.9	34	907.9	35	962.1
4	26	530.9	26	530.9	28	615.8	26	530.9	28	615.8	28	615.8
TOTAL AREA		4,051.8		3,713.3		4,074.6		3,977.2		4,319.7		4,097.4
% Control Area		100		91.6		100.6		98.2		106.6		101.1

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 57

ACTION OF PHENTOLAMINE ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 10 micrograms phentolamine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PHENTOLAMINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	54	2,290.2	54	2,290.2	56	2,463.0	52	2,123.7	54	2,290.2	56	2,463.0
2	46	1,661.9	44	1,520.5	42	1,385.4	44	1,520.5	44	1,520.5	46	1,661.9
3	52	2,123.7	50	1,963.5	50	1,963.5	50	1,963.5	52	2,123.7	52	2,123.7
TOTAL AREA		6,075.8		5,774.2		5,811.9		5,607.7		5,934.4		6,248.6
% Control Area		100		95.0		95.7		92.3		97.7		102.8
VEINS												
1	50	1,963.5	50	1,963.5	52	2,123.7	54	2,290.2	52	2,123.7	52	2,123.7
2	66	3,421.2	66	3,421.2	64	3,217.0	64	3,217.0	64	3,217.0	66	3,421.2
3	46	1,661.9	48	1,809.6	48	1,809.6	46	1,661.9	50	1,963.5	48	1,809.6
4	38	1,134.1	34	907.9	36	1,017.9	34	907.9	34	907.9	30	706.9
5	36	1,017.9	38	1,134.1	36	1,017.9	38	1,134.1	40	1,256.6	36	1,017.9
TOTAL AREA		9,198.6		9,236.3		9,186.1		9,211.1		9,468.7		9,079.3
% Control Area		100		100.4		99.9		100.1		102.9		98.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 58

ACTION OF PHENTOLAMINE ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 10 micrograms phentolamine in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PHENTOLAMINE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	50	1,963.5	52	2,123.7	50	1,963.5	52	2,123.7	52	2,123.7	50	1,963.5
2	62	3,019.1	60	2,827.4	62	3,019.1	60	2,827.4	60	2,827.4	60	2,827.4
3	40	1,256.6	36	1,017.9	38	1,134.1	42	1,385.4	40	1,256.6	42	1,385.4
TOTAL AREA		6,239.2		5,969.0		6,116.7		6,336.5		6,207.7		6,176.3
% Control Area		100		95.7		98.0		101.6		99.5		99.0
VEINS												
1	36	1,017.9	38	1,134.1	36	1,017.9	38	1,134.1	40	1,256.6	38	1,134.1
2	40	1,256.6	40	1,256.6	40	1,256.6	40	1,256.6	42	1,385.4	42	1,385.4
3	68	3,631.7	66	3,421.2	68	3,631.7	66	3,421.2	66	3,421.2	66	3,421.2
4	50	1,963.5	50	1,963.5	48	1,809.6	48	1,809.6	50	1,963.5	52	2,123.7
TOTAL AREA		7,869.7		7,775.4		7,715.8		7,621.5		8,026.7		8,064.4
% Control Area		100		98.8		98.0		96.8		102.0		102.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 59

A) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 10 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	24	452.4	18	254.5	12	113.1	10	78.5	20	314.2	24	452.4
2	36	1,017.9	10	78.5	10	78.5	8	50.3	12	113.1	14	153.9
3	30	706.9	12	113.1	10	78.5	8	50.3	22	380.1	23	415.5
TOTAL AREA		2,177.2		446.1		270.1		179.1		807.4		1,021.8
% Control Area		100		20.5		12.4		8.2		37.1		46.9
VEINS												
1	44	1,520.5	42	1,385.4	46	1,661.9	44	1,520.5	46	1,661.9	46	1,661.9
2	25	490.9	28	615.8	30	706.9	24	452.4	22	380.1	20	314.2
3	48	1,809.6	52	2,123.7	56	2,463.0	50	1,963.5	54	2,290.2	50	1,963.5
4	28	615.8	30	706.9	30	706.9	28	615.8	26	530.9	24	452.4
TOTAL AREA		4,436.8		4,831.8		5,538.7		4,552.2		4,863.1		4,392.0
% Control Area		100		108.9		124.8		102.6		109.6		99.0

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 60

A) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 10 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	60	2,827.4	20	314.2	50	1,963.5	60	2,827.4	60	2,827.0		-
2	55	2,375.8	25	490.9	50	1,963.5	50	1,963.5	55	2,375.8		-
3	35	962.1	30	706.9	40	1,256.6	40	1,256.6	40	1,256.6		-
4	16	201.1	10	78.5	10	78.5	10	78.5	15	176.7		-
TOTAL AREA		6,366.4		1,590.5		5,262.1		6,126.0		6,635.5		-
% Control Area		100		25.0		82.7		96.2		104.2		-
VEINS												
1	40	1,256.6	45	1,590.4	45	1,590.4	40	1,256.6	45	1,590.4		-
2	20	314.2	42	1,385.4	25	490.9	25	490.9	20	314.2		-
3	25	490.9	25	490.9	25	490.9	30	706.9	25	490.9		-
4	30	706.9	30	706.9	35	962.1	35	962.1	30	706.9		-
TOTAL AREA		2,768.6		4,173.6		3,534.3		3,416.5		3,102.4		-
% Control Area		100		150.7		127.7		123.4		112.1		-

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 61

A) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 10 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	34	907.4	12	113.1	20	314.2	28	615.8	30	706.9	28	615.8
2	26	530.9	18	254.5	16	201.1	20	314.2	20	314.2	26	530.9
3	18	254.5	5	19.6	14	153.9	14	153.9	12	113.1	10	78.5
4	38	1,134.1	14	153.9	36	1,017.9	34	907.9	30	706.9	22	380.1
TOTAL AREA		2,827.4		541.1		1,687.1		1,991.8		1,841.1		1,605.3
% Control Area		100		19.0		59.7		70.4		65.1		56.8
VEINS												
1	32	804.4	32	804.4	38	1,134.1	32	804.4	36	1,017.9	38	1,134.1
2	34	907.9	42	1,385.4	34	907.9	32	804.4	38	1,134.1	36	1,017.9
3	28	615.8	40	1,256.6	32	804.4	36	1,017.9	30	706.9	32	804.4
4	24	452.4	24	452.4	28	615.8	22	380.1	22	380.1	20	314.2
TOTAL AREA		2,780.5		3,898.8		3,462.2		3,006.8		3,239.0		3,270.6
% Control Area		100		140.2		124.5		108.1		116.5		117.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 62

A) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 4.

Local injection of 10 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	50	1,963.5	38	1,134.1	42	1,385.4	46	1,661.9	50	1,963.5	50	1,963.5
2	42	1,385.4	36	1,017.9	40	1,256.6	40	1,256.6	38	1,134.1	40	1,256.6
3	20	314.2	18	254.5	16	201.1	18	254.5	20	314.2	22	380.1
4	18	254.5	10	78.5	16	201.1	14	153.9	16	201.1	18	254.5
5	18	254.5	12	113.1	16	201.1	14	153.9	16	201.1	14	153.9
TOTAL AREA		4,172.1		2,598.1		3,245.3		3,480.8		3,814.0		4,008.6
% Control Area		100		62.3		77.9		83.4		91.4		96.1
VEINS												
1	32	804.2	30	706.9	40	1,256.6	38	1,134.1	36	1,017.9	32	804.2
2	26	530.9	30	706.9	32	804.2	34	907.9	28	615.8	26	530.9
3	28	615.8	30	706.9	32	804.2	32	804.2	28	615.8	26	530.9
4	30	706.9	36	1,017.9	44	1,520.5	44	1,520.5	34	907.9	32	804.2
5	18	254.5	22	380.1	28	615.8	30	706.9	24	452.4	22	380.1
TOTAL AREA		2,912.3		3,518.7		5,001.3		5,073.6		3,609.8		3,050.3
% Control Area		100		120.9		171.7		174.2		124.0		104.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 63

A) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 5.

Local injection of 10 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	72	4,071.4	50	1,963.5	64	3,217.0	68	3,631.7	70	3,848.4	68	3,631.7
2	88	6,082.1	52	2,123.7	68	3,631.7	74	4,300.8	78	4,778.4	74	4,300.8
3	62	3,019.1	54	2,290.2	58	2,642.1	58	2,642.1	60	2,827.4	62	3,019.1
4	70	3,848.5	38	1,134.1	62	3,019.1	64	3,217.0	68	3,631.7	70	3,848.5
TOTAL AREA		17,021.1		7,511.5		12,509.9		13,791.6		15,085.9		14,800.1
% Control Area		100		44.1		73.5		82.2		88.6		87.0
VEINS												
1	42	1,385.4	50	1,963.5	50	1,963.5	50	1,963.5	48	1,809.6	42	1,385.4
2	56	2,463.0	68	3,631.7	68	3,631.7	66	3,421.2	64	3,217.0	64	3,217.0
3	48	1,809.6	54	2,290.2	52	2,123.7	50	1,963.5	52	2,123.7	48	1,809.6
4	45	1,590.4	52	2,123.7	48	1,809.6	48	1,809.6	48	1,809.6	50	1,963.5
TOTAL AREA		7,248.4		10,009.1		9,528.5		9,157.8		8,959.9		8,375.5
% Control Area		100		137.8		131.5		126.3		123.6		115.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 64

A) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 6.

Local injection of 10 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	30	706.9	12	113.1	16	201.1	20	314.2	28	615.8	28	615.8
2	40	1,256.6	20	314.2	14	153.9	24	452.4	37	1,075.2	40	1,256.6
3	28	615.8	10	78.5	12	113.1	22	380.1	30	706.9	30	706.9
4	34	907.9	12	113.1	16	201.1	24	452.4	30	706.9	34	907.9
5	20	314.2	8	50.3	10	78.5	10	78.5	12	113.1	14	153.9
TOTAL AREA		3,801.4		669.2		747.7		1,677.6		3,217.9		3,641.1
% Control Area		100		17.6		19.7		44.1		84.7		95.8
VEINS												
1	35	962.1	39	1,194.6	36	1,017.9	34	907.9	34	907.9	38	1,134.1
2	34	907.9	24	452.4	30	706.9	30	706.9	28	615.8	30	706.9
3	38	1,134.1	40	1,256.6	42	1,385.4	46	1,661.9	40	1,256.6	40	1,256.6
4	47	1,734.9	50	1,963.5	48	1,809.6	52	2,123.7	56	2,463.0	50	1,963.5
5	44	1,520.5	50	1,963.5	52	2,123.7	48	1,809.6	48	1,809.6	46	1,661.9
TOTAL AREA		6,259.5		6,830.6		7,043.5		7,210.0		7,052.9		6,723.0
% Control Area		100		109.1		112.5		115.2		112.7		107.4

D = Diamater in microns. Area = Area in microns^2.

SUPPORTING TABLE 65

B) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 5 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	60	2,827.4	48	1,809.6	50	1,963.5	52	2,123.7	46	1,661.9	34	907.9
2	42	1,385.4	40	1,256.6	40	1,256.6	38	1,134.1	30	706.9	28	615.8
3	44	1,520.5	36	1,017.9	48	1,809.6	40	1,256.6	32	804.2	26	530.9
TOTAL AREA		5,733.3		4,084.1		5,029.7		4,514.4		3,173.0		2,054.6
% Control Area		100		71.2		87.7		78.7		55.3		35.8
VEINS												
1	62	3,019.1	68	3,631.7	76	4,536.5	72	4,071.5	70	3,848.5	72	4,071.5
2	34	907.9	38	1,134.1	40	1,256.6	42	1,385.4	40	1,256.6	46	1,661.9
3	26	530.9	26	530.9	30	706.9	28	615.8	32	804.2	30	706.9
4	78	4,778.4	80	5,026.5	80	5,026.5	76	4,536.5	78	4,778.4	80	5,026.5
TOTAL AREA		9,236.3		10,323.2		11,526.5		10,609.2		10,687.7		11,466.8
% Control Area		100		111.7		124.8		114.9		115.7		124.1

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 66

B) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 5 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	28	615.8	16	201.1	20	314.2	18	254.5	20	314.2	28	615.8
2	26	530.9	10	78.5	16	201.1	16	201.1	18	254.5	22	380.1
3	20	314.2	8	50.3	12	113.1	10	78.5	14	153.9	18	254.5
4	14	153.9	4	12.6	8	50.3	10	78.5	10	78.5	12	113.1
TOTAL AREA		1,614.8		342.5		678.7		612.6		801.1		1,363.5
% Control Area		100		21.2		42.0		37.9		49.6		84.4
VEINS												
1	24	452.4	36	1,017.9	30	706.9	30	706.9	26	530.9	24	452.4
2	28	615.8	30	706.9	28	615.8	30	706.9	28	615.8	28	615.8
3	36	1,017.9	38	1,134.1	38	1,134.1	34	907.9	34	907.9	34	907.0
4	26	530.9	30	706.9	30	706.9	28	615.8	26	530.9	26	530.9
TOTAL AREA		2,617.0		3,565.8		3,123.7		2,937.5		2,585.5		2,507.0
% Control Area		100		136.3		120.9		112.2		98.8		95.8

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 67

B) ACTION OF ISOPROTERENOL ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 5 micrograms isoproterenol in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ISOPROTERENOL INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	20	314.2	17	227.0	18	254.5	18	254.5	20	314.2	18	254.5
2	15	176.7	7	38.5	10	78.5	12	113.1	13	132.7	13	132.7
3	12	113.1	8	50.3	11	95.0	12	113.1	12	113.1	12	113.1
4	21	346.4	16	201.1	14	153.9	18	254.5	19	283.5	20	314.2
TOTAL AREA		950.4		516.9		581.9		735.2		843.5		814.5
% Control Area		100		54.4		61.2		77.4		88.8		85.7
VEINS												
1	42	1,385.4	42	1,385.4	45	1,590.4	42	1,385.4	40	1,256.6	40	1,256.6
2	37	1,075.2	44	1,520.5	47	1,734.9	45	1,590.4	42	1,385.4	40	1,256.6
3	29	660.5	41	1,320.3	46	1,661.9	45	1,590.4	40	1,256.6	38	1,134.1
4	37	1,075.2	39	1,194.6	40	1,256.6	38	1,134.1	34	907.9	38	1,134.1
5	38	1,134.1	40	1,256.6	43	1,432.2	40	1,256.6	40	1,256.6	41	1,320.3
TOTAL AREA		5,330.4		6,677.4		7,696.0		6,956.9		6,063.1		6,101.7
% Control Area		100		125.3		144.4		130.5		113.7		114.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 68

ACTION OF LACTIC ACID ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 100 micrograms lactic acid in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF LACTIC ACID INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	32	804.2	30	706.9	34	907.9	36	1,017.9	34	907.9	34	907.9
2	42	1,385.4	46	1,661.9	48	1,809.6	48	1,809.6	48	1,809.6	42	1,385.4
3	36	1,017.9	40	1,256.6	42	1,385.4	46	1,661.9	42	1,385.4	38	1,134.1
TOTAL AREA		3,207.5		3,625.4		4,102.9		4,489.4		4,102.9		3,427.4
% Control Area		100		113.0		127.9		140.0		127.9		106.9
VEINS												
1	30	706.9	34	907.9	36	1,017.9	34	907.9	36	1,017.9	32	804.2
2	42	1,385.4	44	1,520.5	44	1,520.5	44	1,520.5	42	1,385.4	42	1,385.4
3	44	1,520.5	46	1,661.9	50	1,963.5	48	1,809.6	48	1,809.6	46	1,661.9
4	38	1,134.1	46	1,661.9	46	1,661.9	48	1,809.6	50	1,963.5	48	1,809.6
TOTAL AREA		4,746.9		5,752.2		6,163.8		6,047.6		6,176.4		5,661.1
% Control Area		100		121.2		129.8		127.4		130.1		119.3

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 69

ACTION OF LACTIC ACID ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 100 micrograms lactic acid in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF LACTIC ACID INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	50	1,963.5	48	1,809.6	52	2,123.7	56	2,463.0	54	2,290.2	54	2,290.2
2	48	1,809.6	46	1,661.9	50	2,963.5	54	2,290.2	52	2,123.7	50	1,963.5
3	26	530.9	22	380.1	30	706.9	34	907.9	30	706.9	30	706.9
TOTAL AREA		4,304.0		3,851.6		4,794.1		5,661.1		5,120.8		4,960.6
% Control Area		100		89.5		111.4		131.5		119.0		115.3
VEINS												
1	62	3,019.1	68	3,631.7	66	3,421.2	70	3,848.5	66	3,421.2	64	3,217.0
2	60	2,827.4	62	3,019.1	62	3,019.1	66	3,421.2	64	3,217.0	60	2,827.4
3	44	1,520.5	48	1,809.6	46	1,661.9	46	1,661.9	42	1,385.4	38	1,134.1
4	24	452.4	32	804.2	38	1,134.1	36	1,017.9	30	706.9	30	706.9
TOTAL AREA		7,819.4		9,264.6		9,236.3		9,949.5		8,730.5		7,885.4
% Control Area		100		118.5		118.1		127.2		111.7		100.8

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 70

ACTION OF LACTIC ACID ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 100 micrograms lactic acid in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF LACTIC ACID INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	34	907.9	38	1,134.1	40	1,256.6	40	1,256.6	42	1,385.4	40	1,256.6
2	32	804.2	40	1,256.6	44	1,520.5	42	1,385.4	46	1,661.9	40	1,256.6
3	28	615.8	24	452.4	24	452.4	28	615.8	26	530.9	28	615.8
4	18	254.5	20	314.2	18	254.5	22	380.1	24	452.4	20	314.2
TOTAL AREA		2,582.4		3,157.3		3,484.0		3,637.9		4,030.6		3,443.2
% Control Area		100		122.3		134.9		140.9		156.1		133.3
VEINS												
1	26	530.9	28	615.8	30	706.9	30	706.9	32	804.2	30	706.9
2	20	314.2	20	314.2	18	254.5	22	380.1	20	314.2	22	380.1
3	20	314.2	20	314.2	24	452.4	22	380.1	22	380.1	24	452.4
4	32	804.2	36	1,017.9	38	1,134.1	40	1,256.6	36	1,017.9	30	706.9
TOTAL AREA		1,963.5		2,262.1		2,547.9		2,723.7		2,516.4		2,246.3
% Control Area		100		115.2		129.8		138.7		128.2		114.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 71

ACTION OF CORTISONE ACETATE ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 50 micrograms cortisone acetate in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF CORTISONE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	52	2,123.7	52	2,123.7	50	1,963.5	48	1,809.6	48	1,809.6	48	1,809.6
2	50	1,963.5	50	1,963.5	50	1.963.5	46	1,661.9	44	1,520.5	42	1,385.4
3	39	1,134.1	40	1,256.6	38	1,134.1	36	1,017.9	30	706.9	32	804.2
4	18	254.5	22	380.1	24	452.4	24	452.4	20	314.2	22	380.1
TOTAL AREA		5,475.8		5,723.9		5,513.5		4,941.8		4,351.2		4,379.3
% Control Area		100		104.5		100.7		90.2		79.5		80.0
VEINS												
1	56	2,463.0	54	2,290.2	52	2,123.7	50	1,963.5	52	2,123.7	54	2,290.2
2	50	1,963.5	50	1,963.5	48	1,809.6	50	1,963.5	50	1,963.5	50	1,963.5
3	42	1,385.4	38	1,134.1	36	1,017.9	34	907.9	30	706.9	32	804.2
4	48	1,809.6	50	1,963.5	50	1,963.5	50	1,963.5	50	1,963.5	52	2,123.7
5	30	706.9	26	530.9	26	530.9	30	706.9	28	615.8	30	706.9
TOTAL AREA		8,328.4		7,882.2		7,445.6		7,505.3		7,373.4		7,888.5
% Control Area		100		94.6		89.4		90.1		88.4		94.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 72

ACTION OF CORTISONE ACETATE ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 50 micrograms cortisone acetate in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF CORTISONE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	58	2,642.1	60	2,827.4	56	2,463.0	56	2,463.0	60	2,827.4
2	36	1,017.9	34	907.9	38	1,134.1	36	1,017.9	34	907.9	34	907.9
3	62	3,019.1	62	3,019.1	60	2,827.4	60	2,827.4	60	2,827.4	60	2,827.4
TOTAL AREA		6,679.1		6,569.1		6,788.9		6,308.3		6,198.3		6,562.7
% Control Area		100		98.4		101.6		94.4		92.8		98.3
VEINS												
1	24	452.4	22	380.1	22	380.1	20	380.1	22	380.1	24	452.4
2	40	1,256.6	40	1,256.6	38	1,134.1	40	1,256.6	40	1,256.6	40	1,256.6
3	48	1,809.6	46	1,661.9	44	1,520.5	46	1,661.9	48	1,809.6	46	1,661.9
4	42	1,385.4	40	1,256.6	42	1,385.4	40	1,256.6	40	1,256.6	44	1,520.5
TOTAL AREA		4,904.0		4,555.2		4,420.1		4,555.2		4,702.9		4,891.4
% Control Area		100		92.9		90.1		92.9		95.9		99.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 73

ACTION OF CORTISONE ACETATE ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 50 micrograms cortisone acetate in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF CORTISONE INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	20	314.2	20	314.2	18	254.5	20	314.2	22	380.1	20	314.2
2	24	452.4	22	380.1	20	314.2	22	380.1	22	380.1	24	452.4
3	60	2,827.4	62	3,019.1	60	2,827.4	62	3,019.1	60	2,827.4	62	3,019.1
TOTAL AREA		3,594.0		3,713.4		3,396.1		3,713.4		3,587.6		3,785.7
% Control Area		100		103.3		94.5		103.3		99.8		105.3
VEINS												
1	32	804.2	30	706.9	32	804.2	32	804.2	30	706.9	30	706.9
2	38	1,134.1	38	1,134.1	36	1,017.9	36	1,017.9	40	1,256.6	38	1,134.1
3	26	530.9	24	452.4	28	615.8	28	615.8	30	706.9	28	615.8
4	35	962.1	38	1,134.1	38	1,134.1	38	1,134.1	38	1,134.1	34	907.9
TOTAL AREA		3,431.3		3,427.5		3,572.0		3,572.0		3,804.5		3,364.7
% Control Area		100		99.9		104.1		104.1		110.9		98.1

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 74

A) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 100 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	60	2,827.4	60	2,827.4	62	3,019.1	62	3,019.1	68	3,631.7	68	3,631.7
2	40	1,256.6	44	1,520.5	46	1,661.9	48	1,809.6	50	1,963.5	52	2,123.7
3	28	615.8	30	706.9	30	706.9	30	706.9	32	804.2	30	706.9
4	36	1,017.9	32	804.2	32	804.2	38	1,134.1	32	804.2	32	804.2
5	58	2,642.1	62	3,019.1	66	3,421.2	64	3,217.0	62	3,019.1	60	2,827.4
TOTAL AREA		8,359.8		8,878.1		9,613.3		9,886.7		10,222.7		10,093.9
% Control Area		100		106.2		115.0		118.3		122.3		120.8
VEINS												
1	84	5,541.8	82	5,281.0	82	5,281.0	80	5,026.5	82	5,281.0	82	5,281.0
2	58	2,642.1	56	2,463.0	54	2,290.2	48	1,809.6	50	1,963.5	56	2,463.0
3	76	4,536.5	76	4,536.5	78	4,778.4	72	4,071.5	72	4,071.5	72	4,071.5
4	54	2,290.2	56	2,463.0	58	2,642.1	60	2,827.4	58	2,642.1	52	2,123.7
5	26	530.9	24	452.4	24	452.4	28	615.8	28	615.8	24	452.4
TOTAL AREA		15,541.5		15,195.9		15,444.1		14,350.8		14,573.9		14,391.6
% Control Area		100		97.8		99.4		92.3		93.8		92.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 75

A) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 100 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	80	5,026.5	92	6,647.6	90	6,361.7	88	6,082.1	88	6,082.1	84	5,541.8
2	72	4,071.5	72	4,071.5	78	4,778.4	82	5,281.0	80	5,026.5	78	4,778.4
3	30	706.9	32	804.2	40	1,256.6	44	1,520.5	42	1,385.4	38	1,134.1
4	78	4,778.4	80	5,026.5	84	5,541.8	82	5,281.0	88	6,082.1	86	5,674.5
TOTAL AREA		14,583.3		16,549.8		17,938.5		18,164.6		18,576.1		17,128.8
% Control Area		100		113.5		123.0		124.6		127.4		117.5
VEINS												
1	122	11,689.9	120	11,309.7	114	10,207.0	122	11,689.9	118	10,936.0	118	10,936.0
2	84	5,541.8	82	5,281.0	80	5,026.5	80	5,026.5	82	5,281.0	82	5,281.0
3	34	907.9	32	804.2	36	1,017.9	38	1,134.1	42	1,385.4	40	1,256.6
4	92	6,647.6	94	6,939.8	92	6,647.6	88	6,082.1	90	6,361.7	90	6,361.7
TOTAL AREA		24,787.2		24,334.7		22,899.0		23,932.6		23,964.1		23,835.3
% Control Area		100		98.2		92.4		96.6		96.7		96.2

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 76

A) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 100 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	58	2,642.1	60	2,827.4	62	3,019.1	62	3,019.1	62	3,019.1
2	52	2,123.7	60	2,827.4	58	2,642.1	60	2,827.4	62	3,019.1	64	3,217.0
3	28	615.8	36	1,017.9	38	1,134.1	34	907.9	32	804.2	34	907.9
4	12	113.1	12	113.1	14	153.9	14	153.9	14	153.9	14	153.9
5	14	153.9	12	113.1	14	153.9	14	153.9	16	201.1	14	153.9
TOTAL AREA		4,816.1		6,713.6		6,911.4		7,062.2		7,197.4		7,451.8
% Control Area		100		139.4		143.5		146.6		149.4		154.7
VEINS												
1	50	1,963.5	50	1,963.5	48	1,809.6	50	1,963.5	50	1,963.5	48	1,809.6
2	44	1,520.5	46	1,661.9	44	1,520.5	46	1,661.9	44	1,520.5	46	1,661.9
3	42	1,385.4	36	1,017.9	34	907.9	34	907.9	36	1,017.9	38	1,134.1
4	44	1,520.5	38	1,134.1	34	907.9	36	1,017.9	40	1,256.6	42	1,385.4
5	48	1,809.6	50	1,963.5	48	1,809.6	50	1,963.5	50	1,963.5	50	1,963.5
TOTAL AREA		8,199.5		7,740.9		6,955.5		7,514.7		7,722.0		7,954.5
% Control Area		100		94.4		84.8		91.6		94.2		97.0

D = Diamater in microns. Area = Area in microns^2.

SUPPORTING TABLE 77

A) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 4.

Local injection of 100 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	40	1,256.6	42	1,385.4	44	1,520.5	50	1,963.5	46	1,661.9
2	28	615.8	24	452.4	24	452.4	30	706.9	32	804.2	40	1,256.6
3	36	1,017.9	38	1,134.1	40	1,256.6	48	1,809.6	46	1,661.9	46	1,661.9
4	22	380.1	24	452.4	32	804.2	30	706.9	30	706.9	32	804.2
5	20	314.2	22	380.1	30	706.9	28	615.8	24	452.4	26	530.9
6	18	254.5	18	254.5	20	314.2	20	314.2	22	380.1	20	314.2
TOTAL AREA		4,392.1		3,930.1		4,919.7		5,673.9		5,959.0		6,229.7
% Control Area		100		89.4		112.0		129.2		135.9		141.8
VEINS												
1	52	2,123.7	48	1,809.6	50	1,963.5	48	1,809.6	46	1,661.9	58	2,642.1
2	44	1,520.5	42	1,385.4	42	1,385.4	38	1,134.1	40	1,256.6	34	907.9
3	58	2,642.1	60	2,827.4	58	2,642.1	54	2,290.2	58	2,642.1	58	2,642.1
4	46	1,661.9	50	1,863.5	52	2,123.7	52	2,123.7	50	1,963.5	48	1,809.6
5	40	1,256.6	32	804.2	30	706.9	28	615.8	26	530.9	24	452.4
TOTAL AREA		9,204.8		8,790.1		8,821.6		7,973.4		8,055.0		8,454.1
% Control Area		100		95.5		95.8		86.6		87.5		91.8

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 78

A) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 5.

Local injection of 100 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	60	2,827.4	66	3,421.2	60	2,827.4	60	2,827.4	60	2,827.4
2	60	2,827.4	62	3,019.1	72	4,071.5	68	3,631.7	64	3,217.0	62	3,019.1
3	36	1,017.9	40	1,256.6	44	1,520.5	40	1,256.6	38	1,134.1	34	907.9
TOTAL AREA		6,487.4		7,103.1		9,013.2		7,715.7		7,178.5		6,754.4
% Control Area		100		109.5		138.5		118.9		110.7		104.1
VEINS												
1	50	1,963.5	46	1,661.9	46	1,661.9	50	1,963.5	48	1,809.6	50	1,963.5
2	16	201.1	16	201.1	16	201.1	18	254.5	18	254.5	20	314.2
3	48	1,809.6	44	1,520.5	40	1,256.6	42	1,385.4	44	1,520.5	44	1,520.5
4	62	3,019.1	56	2,463.0	50	1,963.5	58	2,642.1	58	2,642.1	60	2,827.4
TOTAL AREA		6,993.3		5,846.5		5,083.1		6,245.5		6,226.7		6,625.6
% Control Area		100		83.6		72.7		89.3		89.0		94.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 79

A) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 6.

Local injection of 100 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	38	1,134.1	34	907.9	34	907.9	34	907.9	36	1,017.9	38	1,134.1
2	36	1,017.9	32	804.2	40	1,256.6	40	1,256.6	42	1,385.4	40	1,256.6
3	34	907.9	30	706.9	38	1,134.1	38	1,134.1	38	1,134.1	34	907.9
TOTAL AREA		3,059.9		2,419.0		3,298.6		3,298.6		3,537.4		3,298.6
% Control Area		100		79.1		107.8		107.8		115.6		107.8
VEINS												
1	40	1,256.6	38	1,134.1	34	907.9	32	804.2	38	1,134.1	40	1,256.6
2	42	1,385.4	40	1,256.6	40	1,256.6	38	1,134.1	38	1,134.1	38	1,134.1
3	42	1,385.4	44	1,520.5	42	1,385.4	40	1,256.6	42	1,385.4	44	1,520.5
4	28	615.8	28	615.8	30	706.9	30	706.9	28	615.8	28	615.8
TOTAL AREA		4,643.2		4,527.0		4,256.8		3,901.8		4,269.4		4,527.0
% Control Area		100		97.5		91.7		84.0		91.9		97.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 80

B) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 500 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	36	1,017.9	50	1,963.5	50	1,963.5	48	1,809.6	40	1,256.6	38	1,134.1
2	20	314.2	26	530.9	30	706.9	28	615.8	26	530.9	20	314.2
3	12	113.1	20	314.2	22	380.1	18	254.5	14	153.9	14	153.9
4	45	1,590.4	52	2,123.7	58	2,642.1	58	2,642.1	52	2,123.7	46	1,661.9
TOTAL AREA		3,035.6		4,932.3		5,692.6		5,322.0		4,065.1		3,264.1
% Control Area		100		162.5		187.5		175.3		133.9		107.5
VEINS												
1	60	2,827.4	62	3,019.1	60	2,827.4	60	2,827.4	58	2,642.1	60	2,827.4
2	50	1,963.5	46	1,661.9	50	1,963.1	44	1,520.5	48	1,809.6	46	1,661.9
3	30	706.9	26	530.9	26	530.9	22	380.1	26	530.9	26	530.9
4	32	804.2	32	804.2	30	706.9	34	907.9	36	1,017.9	32	804.2
TOTAL AREA		6,302.0		6,016.1		6,028.3		5,635.9		6,000.5		5,824.4
% Control Area		100		95.5		95.7		89.4		95.2		92.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 81

B) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 500 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	32	804.2	30	706.9	40	1,256.6	44	1,520.5	40	1,256.6	38	1,134.1
2	26	530.9	30	706.9	34	907.9	38	1,134.1	38	1,134.1	36	1,017.9
3	28	615.8	28	615.8	30	706.9	32	804.2	32	804.2	30	706.9
TOTAL AREA		1,950.9		2,029.6		2,871.4		3,458.8		3,194.9		2,858.9
% Control Area		100		104.0		147.2		177.3		163.8		146.5
VEINS												
1	44	1,520.5	38	1,134.1	38	1,134.1	36	1,017.9	38	1,134.1	38	1,134.1
2	32	804.2	30	706.9	30	706.9	28	615.8	30	706.9	30	706.9
3	44	1,520.5	46	1,661.9	44	1,520.5	40	1,256.6	42	1,385.4	44	1,520.5
4	20	314.2	20	314.2	18	254.5	20	314.2	18	254.5	22	380.1
TOTAL AREA		4,159.4		3,817.1		3,616.0		3,204.5		3,480.9		3,741.6
% Control Area		100		91.8		86.9		77.0		83.7		90.0

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 82

B) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 500 micrograms E. coli 026:B6 lipopolysaccharide in 0.05 ml. Ringer's solution into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	26	530.9	30	706.9	30	706.9	32	804.2	30	706.9	28	615.8
2	18	254.5	20	314.2	24	452.4	22	380.1	22	380.1	22	380.1
3	22	380.1	28	615.8	32	804.2	34	907.9	32	804.2	30	706.9
4	12	113.1	12	113.1	14	153.9	14	153.9	14	153.9	14	153.9
TOTAL AREA		1,278.6		1,750.0		2,117.4		2,246.1		2,045.1		1,856.7
% Control Area		100		136.9		165.6		175.7		159.9		145.2
VEINS												
1	24	452.4	20	314.2	22	380.1	22	380.1	20	314.2	20	314.2
2	26	530.9	26	530.9	26	530.9	24	452.4	24	452.4	24	452.4
3	20	314.2	14	153.9	14	153.9	10	78.5	18	254.5	20	314.2
4	44	1,520.5	34	907.9	34	907.9	30	706.9	30	706.9	34	907.9
TOTAL AREA		2,818.0		1,906.9		1,972.8		1,617.9		1,728.0		1,988.7
% Control Area		100		67.7		70.0		57.4		61.3		70.6

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 83

C) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 0.05 ml. crude extract E. coli 026:B6 antigen into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	38	1,134.1	42	1,385.4	42	1,385.4	40	1,256.6	40	1,256.6	40	1,256.6
2	32	804.2	38	1,134.1	40	1,256.6	40	1,256.6	42	1,385.4	36	1,017.9
3	20	314.2	18	254.5	22	380.1	22	380.1	20	314.2	18	254.5
4	10	78.5	10	78.5	12	113.1	12	113.1	14	153.9	10	78.5
5	12	113.1	12	113.1	12	113.1	10	78.5	12	113.1	10	78.5
TOTAL AREA		2,444.1		2,965.6		3,248.3		3,084.9		3,223.2		2,686.0
% Control AREA		100		121.3		132.9		126.2		131.9		109.9
VEINS												
1	20	314.2	20	314.2	22	380.1	18	254.5	20	314.2	20	314.2
2	24	452.4	22	380.1	20	314.2	22	380.1	22	380.1	20	314.2
3	22	380.1	20	314.2	22	380.1	18	254.5	20	314.2	22	380.1
4	34	907.9	30	706.9	28	615.8	30	706.9	30	706.9	28	615.8
5	32	804.2	28	615.8	28	615.8	26	530.9	28	615.8	30	706.9
TOTAL AREA		2,858.8		2,331.2		2,306.0		2,126.9		2,331.2		2,331.2
% Control Area		100		81.5		80.7		74.4		81.5		81.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 84

C) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 0.05 ml. crude extract E. coli 026:B6 antigen into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	28	615.8	20	314.2	22	380.1	30	706.9	36	1,017.9	32	804.2
2	26	530.9	20	314.2	22	380.1	28	615.8	32	804.2	30	706.9
3	20	314.2	16	201.1	16	201.1	20	314.2	22	380.1	20	314.2
TOTAL AREA		1,460.9		829.5		961.3		1,636.9		2,202.2		1,825.3
% Control Area		100		56.8		65.8		112.0		150.7		124.9
VEINS												
1	28	615.8	24	452.4	26	530.9	26	530.9	26	530.9	26	530.9
2	32	804.2	32	804.2	32	804.2	30	706.9	28	615.8	30	706.9
3	30	706.9	28	615.8	30	706.9	28	615.8	30	706.9	32	804.2
4	36	1,017.9	30	706.9	28	615.8	30	706.9	34	907.9	32	804.2
TOTAL AREA		3,144.8		2,579.3		2,657.8		2,560.5		2,761.5		2,846.2
% Control Area		100		82.0		84.5		81.4		87.8		90.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 85

C) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 0.05 ml. crude extract E. coli 026:B6 antigen into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	58	2,642.1	52	2,123.7	54	2,290.2	60	2,827.4	60	2,827.4	58	2,642.1
2	36	1,017.9	40	1,256.6	38	1,134.1	42	1,385.4	40	1,256.6	40	1,256.6
3	32	804.2	38	1,134.1	40	1,256.6	38	1,134.1	40	1,256.6	38	1,134.1
4	40	1,256.6	40	1,256.6	48	1,809.6	44	1,520.5	42	1,385.4	40	1,256.6
TOTAL AREA		5,720.8		5,771.0		6,490.5		6,867.4		6,726.0		6,289.4
% Control Area		100		100.9		113.5		120.0		117.6		109.9
VEINS												
1	70	3,848.5	70	3,848.5	64	3,217.0	64	3,217.0	62	3,019.1	66	3,421.2
2	52	2,123.7	46	1,661.9	44	1,520.5	38	1,134.1	38	1,134.1	40	1,256.6
3	30	706.9	30	706.9	28	615.8	28	615.8	30	706.9	30	706.9
4	36	1,017.9	36	1,017.9	34	907.9	32	804.2	34	907.9	36	1,017.9
TOTAL AREA		7,697.0		7,235.2		6,261.2		5,771.1		5,768.0		6,402.6
% Control Area		100		94.0		81.3		75.0		74.9		83.2

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 86

D) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 0.05 ml. E. coli filtrate into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	12	113.1	18	254.5	18	254.5	22	314.2	22	380.1		-
2	25	490.9	48	1,809.6	48	1,809.6	52	2,123.7	52	2,123.7		-
3	52	2,123.7	52	2,123.7	54	2,290.2	58	2,642.1	54	2,290.2		-
TOTAL AREA		2,727.7		4,187.8		4,354.3		5,080.0		4,794.0		-
% Control Area		100		153.5		159.6		186.2		175.8		-
VEINS												
1	34	908.0	32	804.2	34	908.0	34	908.0	28	615.8		-
2	30	706.9	22	380.1	24	452.4	28	615.8	24	452.4		-
3	28	615.8	24	452.4	28	615.8	22	380.1	22	380.1		-
4	24	452.4	28	615.8	10	78.5	20	314.2	20	314.2		-
TOTAL AREA		2,683.1		2,252.5		2,054.7		2,218.1		1,762.5		-
% Control Area		100		84.0		76.6		82.7		65.7		-

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 87

D) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 0.05 ml. E. coli filtrate into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	40	1,256.6	42	1,385.4	36	1,017.9	54	2,290.2	46	1,661.9	52	2,123.7
2	36	1,017.9	32	804.2	32	804.2	40	1,256.6	40	1,256.6	48	1,809.6
3	18	254.5	16	201.1	18	254.5	30	706.9	32	804.2	34	907.9
TOTAL AREA		2,529.0		2,390.7		2,076.6		4,253.7		3,722.7		4,841.2
% Control Area		100		95.3		82.1		168.1		147.1		191.3
VEINS												
1	40	1,256.6	34	907.9	32	804.2	36	1,017.9	30	706.9	28	615.8
2	18	254.5	20	314.2	14	153.9	20	314.2	12	113.1	14	153.9
3	16	201.1	14	153.9	20	314.2	20	314.2	16	201.1	18	254.5
4	30	706.9	24	452.4	22	380.1	24	452.4	22	380.1	24	452.4
5	18	254.5	14	153.9	16	201.1	18	254.5	14	153.9	14	153.9
TOTAL AREA		2,673.6		1,982.3		1,853.5		2,353.2		1,555.1		1,630.5
% Control Area		100		74.1		69.4		88.0		53.2		61.0

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 88

D) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 0.05 ml. E. coli filtrate into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF ENDOTOXIN INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	30	706.9	30	706.9	34	907.9	40	1,256.6	36	1,017.9	38	1,134.1
2	12	113.1	12	113.1	18	254.5	12	113.1	12	113.1	12	113.1
3	12	113.1	12	113.1	20	314.2	18	254.5	16	201.1	16	201.1
TOTAL AREA		933.1		933.1		1,476.6		1,624.2		1,332.1		1,448.3
% Control Area		100		100		158.2		174.0		142.8		155.2
VEINS												
1	38	1,134.1	40	1,256.6	36	1,017.9	38	1,134.1	36	1,017.9	38	1,134.1
2	20	314.2	18	254.5	16	201.1	20	314.2	20	314.2	20	314.2
3	38	1,134.1	34	907.9	34	907.9	30	706.9	32	804.3	36	1,017.9
4	22	380.1	20	314.2	18	254.5	16	201.1	14	153.9	14	153.9
TOTAL AREA		2,962.5		2,733.2		2,381.4		2,356.3		2,290.3		2,620.1
% Control Area		100		92.3		80.4		79.5		77.3		88.4

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 89

E) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 1.

Intravenous injection of 2 mgms. E. coli 026:B6 lipopolysaccharide in 0.5 ml. Ringer's solution and observation of changes in the Hamster Cheek Pouch Microvasculature.

	TIME IN MINUTES AFTER INTRAVENOUS INJECTION OF ENDOTOXIN											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	42	1,385.4	32	804.2	32	804.2	40	1,256.6	38	1,134.1
2	32	804.2	32	804.2	26	530.9	16	201.1	20	314.2	22	380.1
3	40	1,256.6	40	1,256.6	32	804.2	30	706.9	32	804.2	36	1,017.9
4	30	706.9	28	615.8	20	314.2	20	314.2	18	254.5	18	254.5
TOTAL AREA		4,577.3		4,062.0		2,453.5		2,026.4		2,629.5		2,786.6
% Control Area		100		88.7		53.6		44.3		57.4		60.9
VEINS												
1	56	2,463.0	58	2,642.1	54	2,290.2	60	2,827.4	72	4,071.5	62	3,019.1
2	56	2,463.0	56	2,463.0	52	2,123.7	58	2,642.1	62	3,019.1	64	3,217.0
3	28	615.8	30	706.9	28	615.8	28	615.8	30	706.9	32	804.2
4	32	804.2	30	706.9	30	706.9	30	706.9	30	706.9	26	530.9
5	54	2,290.2	52	2,123.7	50	1,963.5	52	2,123.7	58	2,642.1	56	2,463.0
6	32	804.2	28	615.8	32	804.2	38	1,134.1	40	1,256.6	36	1,017.9
TOTAL AREA		9,440.4		9,258.4		8,504.3		10,050.0		12,403.1		11,052.1
% Control Area		100		98.1		90.1		106.4		131.4		117.1

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 90

E) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 2.

Intravenous injection of 2 mgms. E. coli 026:B6 lipopolysaccharide in 0.5 ml. Ringer's solution and observation of changes in the Hamster Cheek Pouch Microvasculature.

	TIME IN MINUTES AFTER INTRAVENOUS INJECTION OF ENDOTOXIN											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	34	907.9	36	1,017.9	18	254.5	18	254.5	16	201.1	20	314.2
2	78	4,778.4	70	3,848.5	38	1,134.1	46	1,661.9	44	1,520.5	42	1,385.4
3	82	5,281.0	82	5,281.0	32	804.2	40	1,256.6	38	1,134.1	48	1,809.6
TOTAL AREA		10,967.3		10,147.4		2,192.8		3,173.0		2,855.7		3,509.2
% Control Area		100		92.5		20.0		28.9		26.0		32.0
VEINS												
1	61	2,922.5	61	2,922.5	62	3,019.1	64	3,217.0	68	3,631.7	72	4,071.5
2	52	2,123.7	48	1,809.6	50	1,963.5	48	1,809.6	46	1,661.9	48	1,809.5
3	50	1,963.5	48	1,809.6	46	1,661.9	42	1,385.4	42	1,385.4	44	1,520.5
4	42	1,385.4	44	1,520.5	44	1,520.5	40	1,256.6	42	1,385.4	42	1,385.4
TOTAL AREA		8,395.1		8,062.2		8,165.0		7,668.6		8,064.4		8,787.0
% Control Area		100		96.0		97.3		91.3		96.1		104.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 91

E) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 3.

Intravenous injection of 2 mgms. E. coli 026:B6 lipopolysaccharide in 0.5 ml. Ringer's solution and observation of changes in the Hamster Cheek Pouch Microvasculature.

	TIME IN MINUTES AFTER INTRAVENOUS INJECTION OF ENDOTOXIN.											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	44	1,520.5	38	1,134.1	40	1,256.6	28	615.8	34	907.9	38	1,134.1
2	20	314.2	20	314.2	18	254.5	14	153.9	12	113.1	18	254.5
3	50	1,963.5	42	1,385.4	40	1,256.6	30	706.9	38	1,134.1	44	1,520.5
TOTAL AREA		3,798.2		2,833.7		2,767.7		1,476.6		2,155.1		2,909.1
% Control Area		100		74.6		72.9		38.9		56.7		76.6
VEINS												
1	58	2,642.1	50	1,963.5	52	2,123.7	40	1,256.6	42	1,385.4	50	1,963.5
2	64	3,217.0	56	2,463.0	54	2,290.2	42	1,385.4	46	1,661.9	50	1,963.5
3	42	1,385.4	42	1,385.4	40	1,256.6	36	1,017.9	40	1,256.6	38	1,134.1
4	70	3,848.5	58	2,642.1	58	2,642.1	52	2,123.7	58	2,642.1	58	2,642.1
TOTAL AREA		11,093.0		8,454.0		8,312.6		5,783.6		6,946.0		7,703.2
% Control Area		100		76.2		74.9		52.1		62.6		69.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 92

E) ACTION OF ENDOTOXIN ON THE MICROCIRCULATION. EXPERIMENT 4.

Intravenous injection of 2 mgms. E. coli 026:B6 lipopolysaccharide in 0.5 ml. Ringer's solution and observation of changes in the Hamster Cheek Pouch Microvasculature.

			TIME IN MINUTES AFTER INTRAVENOUS INJECTION OF ENDOTOXIN									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	30	706.9	30	706.9	28	615.8	30	706.9	26	530.9		-
2	38	1,134.1	24	452.4	20	314.2	18	254.5	18	254.5		-
3	36	1,017.9	28	615.8	22	380.1	20	314.2	18	254.5		-
4	32	804.2	28	615.8	24	452.4	22	380.1	20	314.2		-
TOTAL AREA		3,663.1		2,390.9		1,762.5		1,655.7		1,354.1		-
% Control Area		100		65.3		48.1		45.2		37.0		-
VEINS												
1	38	1,134.1	40	1,256.6	40	1,256.6	40	1,256.6	38	1,134.1		-
2	48	1,809.6	44	1,520.5	42	1,385.2	42	1,385.2	40	1,256.6		-
3	64	3,217.0	62	3,019.1	60	2,827.4	52	2,123.7	50	1,963.5		-
4	56	2,463.0	56	2,463.0	52	2,123.7	52	2,123.7	54	2,290.5		-
TOTAL AREA		8,623.7		8,259.2		7,592.9		6,889.2		6,644.6		-
% Control Area		100		95.8		88.0		79.9		77.0		-

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 93

ACTION OF NORMAL SERUM ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 0.05 ml. normal human serum (No.1) into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF SERUM INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	50	1,963.5	36	1,017.9	44	1,520.5	46	1,661.9	38	1,134.1	36	1,017.9
2	44	1,520.5	38	1,134.1	46	1,661.9	46	1,661.9	42	1,385.4	40	1,256.6
3	28	615.8	20	314.2	30	706.9	30	706.9	30	706.9	28	615.8
4	18	254.5	16	201.1	20	314.2	22	380.1	18	254.5	18	254.5
TOTAL AREA		4,354.3		2,667.3		4,203.5		4,410.8		3,480.9		3,144.8
% Control Area		100		61.3		96.5		101.3		79.9		72.2
VEINS												
1	40	1,256.6	40	1,256.6	42	1,385.4	42	1,385.4	40	1,256.6	42	1,385.4
2	38	1,134.1	36	1,017.9	38	1,134.1	40	1,256.6	38	1,134.1	36	1,017.9
3	18	254.5	18	254.5	20	314.2	20	314.2	20	314.2	20	314.2
4	30	706.9	26	530.9	28	615.8	28	615.8	28	615.8	26	530.9
5	62	3,019.1	58	2,642.1	60	2,827.4	56	2,463.0	56	2,463.0	60	2,827.4
TOTAL AREA		6,371.2		5,702.0		6,276.9		6,035.0		5,783.7		6,075.8
% Control Area		100		85.5		98.5		94.7		90.8		95.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 94

ACTION OF NORMAL SERUM ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 0.05 ml. normal human serum (No.2) into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF SERUM INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	68	3,631.7	22	380.1	34	907.9	56	2,463.0	62	3,019.1	62	3,019.1
2	72	4,071.5	20	314.2	34	907.9	62	3,019.1	70	3,848.5	72	4,071.5
3	56	2,463.0	18	254.5	22	380.1	38	1,134.1	40	1,256.6	52	2,123.7
4	26	530.9	20	314.2	18	254.5	24	452.4	25	490.9	22	380.1
TOTAL AREA		10,697.1		1,263.0		2,450.4		7,068.6		8,615.1		9,594.4
% Control Area		100		11.8		22.9		66.1		80.5		89.7
VEINS												
1	82	5,281.0	74	4,300.8	80	5,026.5	82	5,281.0	84	5,541.8	82	5,281.0
2	50	1,963.5	44	1,520.5	50	1,963.5	52	2,123.7	50	1,963.5	52	2,123.7
3	122	11,689.9	102	8,171.7	108	9,160.9	106	8,824.7	112	9,852.0	110	9,503.2
4	128	12,868.0	114	10,207.0	118	10,935.9	116	10,568.3	122	11,689.9	120	11,309.6
TOTAL AREA		31,802.4		24,200.0		27,086.8		26,797.7		29,047.2		28,217.5
% Control Area		100		76.1		85.2		84.3		91.3		88.7

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 95

ACTION OF NORMAL SERUM ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 0.05 ml. normal human serum (No.3) into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF SERUM INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	20	314.2	20	314.2	18	254.5	20	314.2	20	314.2	20	314.2
2	38	1,134.1	34	907.9	30	706.9	40	1,256.6	38	1,134.1	40	1,256.6
3	58	2,642.1	42	1,385.4	58	2,642.1	60	2,827.4	60	2,827.4	60	2,827.4
4	62	3,019.1	40	1,256.6	42	1,385.4	60	2,827.4	58	2,642.1	64	3,217.0
TOTAL AREA		7,109.5		3,864.1		4,988.9		7,225.6		6,917.8		7,615.2
% Control Area		100		54.4		70.2		101.6		97.3		107.1
VEINS												
1	34	907.9	32	804.2	38	1,134.1	36	1,017.9	32	804.2	34	907.9
2	59	2,734.0	60	2,827.4	62	3,019.1	58	2,642.1	52	2,123.7	56	2,463.0
3	92	6,647.6	90	6,361.7	96	7,238.2	102	8,171.2	100	7,854.0	94	6,939.8
4	70	3,848.5	74	4,300.8	72	4,071.5	70	3,848.5	68	3,631.7	70	3,848.5
TOTAL AREA		14,138.0		14,294.1		15,533.9		15,679.7		14,413.6		14,159.2
% Control Area		100		107.1		109.9		110.9		101.9		100.2

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 96

ACTION OF NORMAL PLASMA ON THE MICROCIRCULATION. EXPERIMENT 1.

Local injection of 0.05 ml. normal human plasma (No. 1) into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	66	3,421.2	68	3,631.7	68	3,631.7	68	3,631.7	64	3,217.0	-	
2	52	2,123.7	54	2,290.2	56	2,463.0	58	2,642.1	60	2,827.4	-	
3	30	706.9	32	804.2	30	706.9	24	452.4	30	706.9	-	
4	64	3,217.0	60	2,827.4	58	2,642.1	62	3,019.1	62	3,217.0	-	
TOTAL AREA		9,468.8		9,553.5		9,443.7		9,745.3		9,968.3	-	
% Control Area		100		100.9		99.7		102.9		105.3	-	
VEINS												
1	68	3,631.7	70	3,848.4	70	3,848.4	64	3,217.0	64	3,217.0	-	
2	58	2,642.1	62	3,019.1	64	3,019.1	58	2,642.1	54	2,290.2	-	
3	42	1,385.4	40	1,256.6	40	1,256.6	36	1,017.9	38	1,134.1	-	
4	26	530.9	24	452.4	20	314.2	26	530.9	24	452.4	-	
TOTAL AREA		8,190.1		8,576.5		8,438.3		7,407.9		7,093.7	-	
% Control Area		100		104.7		103.0		90.4		86.6	-	

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 97

ACTION OF NORMAL PLASMA ON THE MICROCIRCULATION. EXPERIMENT 2.

Local injection of 0.05 ml. normal human plasma (No.2) into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	42	1,385.4	42	1,385.4	44	1,520.5	44	1,520.5	46	1,661.9	46	1,661.9
2	46	1,661.9	46	1,661.9	44	1,520.5	46	1,661.9	46	1,661.9	46	1,661.9
3	44	1,520.5	42	1,385.4	42	1,385.4	44	1,520.5	40	1,256.6	42	1,385.4
4	18	254.5	18	254.5	16	201.1	20	314.2	16	201.1	18	254.5
TOTAL AREA		4,822.3		4,687.2		4,627.5		5,017.1		4,781.5		4,963.7
% Control Area		100		97.2		96.0		104.0		99.2		102.9
VEINS												
1	58	2,642.1	56	2,463.0	56	2,463.0	54	2,290.2	56	2,463.0	58	2,642.1
2	30	706.9	32	804.2	30	706.9	32	804.2	30	706.9	30	706.9
3	35	962.1	36	1,017.9	34	907.9	34	907.9	36	1,017.9	32	804.2
4	56	2,463.0	56	2,463.0	58	2,642.1	60	2,827.4	60	2,827.4	60	2,827.4
TOTAL AREA		6,774.1		6,748.1		6,719.9		6,829.7		7,015.2		6,980.6
% Control Area		100		99.6		99.2		100.8		103.6		103.0

D = Diameter in microns. Area = Area in $microns^2$.

SUPPORTING TABLE 98

ACTION OF NORMAL PLASMA ON THE MICROCIRCULATION. EXPERIMENT 3.

Local injection of 0.05 ml. normal human plasma (No.3) into the Hamster Cheek Pouch.

	TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH											
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	62	3,019.1	60	2,827.4	60	2,827.4	58	2,642.1	58	2,642.1	58	2,642.1
2	60	2,827.4	62	3,019.1	60	2,827.4	60	2,827.4	60	2,827.4	58	2,642.1
3	48	1,809.6	46	1,661.9	44	1,520.5	42	1,385.4	38	1,134.1	40	1,256.6
TOTAL AREA		7,656.1		7,508.4		7,175.3		6,854.9		6,603.6		6,540.8
% Control Area		100		98.1		93.7		89.5		86.3		85.4
VEINS												
1	56	2,463.0	56	2,463.0	56	2,463.0	56	2,463.0	58	2,642.1	58	2,642.1
2	40	1,256.6	42	1,385.4	40	1,256.6	40	1,256.6	38	1,134.1	42	1,385.4
3	52	2,123.7	50	1,963.5	50	1,963.5	54	2,290.2	56	2,463.0	54	2,290.2
4	36	1,017.9	34	907.9	34	907.9	34	907.9	32	804.2	32	804.2
TOTAL AREA		6,861.2		6,719.8		6,591.0		6,917.7		7,043.4		7,121.9
% Control Area		100		97.9		96.1		100.8		102.7		103.8

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 99

ACTION OF PLASMA FROM PATIENTS WITH BACTERAEMIC SHOCK. EXPERIMENT 1.

Local injection of 0.05 ml. plasma from patient (F.L.) - in bacteraemic shock - into the Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	30	706.9	38	1,134.1	30	706.9	32	804.2		-
2	42	1,385.4	32	804.2	30	706.9	24	452.4	28	615.8		-
3	20	314.2	12	113.1	14	153.9	12	113.1	10	78.5		-
4	14	153.9	8	50.3	8	50.3	8	50.3	12	113.1		-
5	18	254.5	12	113.1	14	153.9	16	201.1	18	254.5		-
TOTAL AREA		3,917.6		1,787.6		2,199.1		1,523.8		1,866.1		-
% Control Area		100		45.6		56.1		38.9		47.6		-
VEINS												
1	50	1,963.5	54	2,290.2	52	2,123.7	52	2,123.7	50	1,963.5		-
2	36	1,017.9	40	1,256.6	38	1,134.1	40	1,256.6	42	1,385.4		-
3	34	907.9	34	907.9	28	615.8	32	804.2	32	804.2		-
4	40	1,256.6	32	804.2	40	1,256.6	38	1,134.1	42	1,385.4		-
5	42	1,385.4	40	1,356.6	44	1,520.5	42	1,385.4	42	1,385.4		-
TOTAL AREA		6,531.3		6,515.5		6,650.7		6,704.0		6,923.9		-
% Control Area		100		99.8		101.8		102.6		106.0		-

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 100

ACTION OF PLASMA FROM PATIENTS WITH BACTERAEMIC SHOCK. EXPERIMENT 2.

Local injection of 0.05 ml. plasma from patient (T.T.) - in bacteraemic shock - into the Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	42	1,385.4	42	1,385.4	40	1,256.6	32	804.2	34	907.9	44	1,520.5
2	48	1,809.6	42	1,385.4	38	1,134.1	36	1,017.9	36	1,017.9	44	1,520.5
3	36	1,017.9	34	907.9	26	530.9	20	314.2	20	314.2	26	530.9
TOTAL AREA		4,212.9		3,678.7		2,921.6		2,136.3		2,240.0		3,571.9
% Control Area		100		87.3		69.3		50.7		53.2		84.8
VEINS												
1	45	1,590.4	44	1,520.5	44	1,520.5	42	1,385.4	40	1,256.6	42	1,385.4
2	44	1,520.5	42	1,385.4	44	1,520.5	42	1,385.4	44	1,520.5	42	1,385.4
3	20	314.2	20	314.2	18	254.5	18	254.5	20	314.2	20	314.2
4	32	804.2	32	804.2	30	706.9	30	706.9	32	804.2	34	907.9
TOTAL AREA		4,229.3		4,024.3		4,002.4		3,732.2		3,895.5		3,992.9
% Control Area		100		95.2		94.6		88.2		92.1		94.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 101

ACTION OF PLASMA FROM PATIENTS WITH BACTERAEMIC SHOCK. EXPERIMENT 3.

Local injection of 0.05 ml. plasma from patient (C.M.) into the Hamster Cheek Pouch, followed in 30 mins. by injection of 10 micrograms phenoxybenzamine.

	TIME IN MINUTES AFTER INJECTION OF PLASMA AND PHENOXYBENZAMINE INTO CHEEK POUCH																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	30	706.9	20	314.2	12	113.1	10	78.5	10	78.5	18	254.5	22	380.1	22	380.1	24	452
2	32	804.2	10	78.5	10	78.5	10	78.5	8	50.3	20	314.2	24	452.4	20	314.2	26	530
3	18	254.5	8	50.3	8	50.3	8	50.3	4	12.6	10	78.5	12	113.1	12	113.1	18	254
TOTAL AREA		1,765.6		443.0		241.9		207.3		141.4		647.2		945.6		807.4		1,237
% Control Area		100		25.1		13.7		11.7		8.0		36.7		53.6		45.7		70
VEINS																		
1	20	314.2	22	380.1	22	380.1	24	452.4	20	314.2	24	452.4	24	452.4	24	452.4	22	380
2	28	615.8	24	452.4	20	314.2	20	314.2	18	254.5	20	314.2	20	314.2	22	380.1	20	314
3	14	153.9	16	201.1	16	201.1	10	78.5	0	0	16	201.1	14	153.9	18	254.5	18	254
4	38	1,134.1	38	1,134.1	26	530.9	24	452.4	22	380.1	26	530.9	30	706.9	32	804.2	30	706
TOTAL AREA		2,218.0		2,167.7		1,426.3		1,297.3		948.8		1,498.6		1,627.4		1,891.2		1,401
% Control Area		100		97.7		64.3		58.5		42.8		67.6		73.4		85.3		63

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 102

ACTION OF PLASMA FROM PATIENTS WITH BURNS. EXPERIMENT 1.

Local injection of 0.05 ml. plasma from patient (L.R.) into Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF PLASMA									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	48	1,809.6	22	380.1	26	530.9	26	530.9	24	452.4	26	530.9
2	46	1,661.9	20	314.2	22	380.1	24	452.4	22	380.1	24	452.4
3	24	452.4	12	113.1	12	113.1	14	513.9	8	50.3	14	153.9
4	20	314.2	0	0	8	50.3	10	78.5	0	0	10	78.5
5	26	530.9	12	113.1	14	153.9	16	201.1	14	153.9	20	314.2
TOTAL AREA		4,769.0		920.5		1,228.3		1,416.8		1,036.7		1,529.9
% Control Area		100		19.3		25.8		29.7		21.7		32.1
VEINS												
1	28	615.8	28	615.8	26	530.9	26	530.9	22	380.1	28	615.8
2	24	452.4	22	380.1	22	380.1	24	452.4	20	314.2	22	380.1
3	42	1,385.4	40	1,256.6	38	1,134.1	42	1,385.4	40	1,256.6	40	1,256.6
4	30	706.9	28	615.8	30	706.9	30	706.9	30	706.9	30	706.9
5	34	907.9	34	907.9	32	804.2	30	706.9	28	615.8	32	804.2
TOTAL AREA		4,068.4		3,776.2		3,556.2		3,782.5		3,273.6		3,763.6
% Control Area		100		92.8		87.4		93.0		80.5		92.5

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 103

ACTION OF PLASMA FROM PATIENTS WITH BURNS. EXPERIMENT 2.

Local injection of 0.05 ml. plasma from patient (S.W.) into Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	50	1,963.5	26	530.9	32	804.2	28	615.8	30	706.9	32	804.2
2	44	1,520.5	22	380.1	26	530.9	24	452.4	26	530.9	28	615.8
3	38	1,134.1	12	113.1	14	153.9	10	78.5	10	78.5	12	113.1
TOTAL AREA		4,618.1		1,024.1		1,489.0		1,146.7		1,316.3		1,533.1
% Control Area		100		22.2		32.2		24.8		28.5		33.2
VEINS												
1	30	706.9	22	380.1	24	452.4	26	530.9	22	380.1	24	452.4
2	32	804.2	28	615.8	28	615.8	28	615.8	24	452.4	26	530.9
3	28	615.8	24	452.4	26	530.9	24	452.4	28	615.8	30	706.9
4	36	1,017.9	32	804.2	32	804.2	30	706.9	30	706.9	36	1,017.9
TOTAL AREA		3,144.8		2,252.5		2,403.3		2,306.0		2,155.2		2,708.1
% Control Area		100		71.6		76.4		73.3		68.5		86.1

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 104

ACTION OF PLASMA FROM PATIENTS WITH BURNS. EXPERIMENT 3.

Local injection of 0.05 ml. plasma from patient (F.J.) into Hamster Cheek Pouch.

			TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH									
	Control		3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	38	1,134.1	26	530.9	22	380.1	24	452.4	28	615.8	32	804.2
2	40	1,256.6	30	706.9	24	452.4	25	490.9	28	615.8	30	706.9
3	18	254.5	12	113.1	20	314.2	14	153.9	12	113.1	18	254.5
TOTAL AREA		2,645.2		1,350.9		1,146.7		1,097.2		1,344.7		1,765.6
% Control Area		100		51.1		43.4		41.5		50.8		66.7
VEINS												
1	32	804.2	34	907.9	34	907.9	34	907.9	32	804.2	34	907.9
2	30	706.9	30	706.9	30	706.9	28	615.8	28	615.8	30	706.9
3	24	452.4	26	530.9	28	615.8	27	572.6	26	530.9	28	615.8
4	16	201.1	14	153.9	16	201.1	14	153.9	18	254.5	16	201.1
5	18	254.5	14	153.9	16	201.1	20	314.2	14	153.9	14	153.9
TOTAL AREA		2,419.1		2,299.6		2,632.8		2,564.4		2,359.3		2,585.6
% Control Area		100		95.1		108.8		106.0		97.5		106.9

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 105

ACTION OF PLASMA FROM PATIENTS WITH BURNS. EXPERIMENT 4.

Local injection of 0.05 ml. plasma from patient (M.C.) into Hamster Cheek Pouch.

	Control		TIME IN MINUTES AFTER INJECTION OF PLASMA INTO CHEEK POUCH									
			3 mins.		6 mins.		15 mins.		30 mins.		60 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	54	2,290.2	52	2,123.7	50	1,963.5	52	2,123.7	52	2,123.7	52	2,123.7
2	22	380.1	22	380.1	24	452.4	2 4	452.4	22	380.1	20	314.1
3	40	1,256.6	38	1,134.1	40	1,256.6	38	1,134.1	40	1,256.6	38	1,134.1
4	26	530.9	28	615.8	28	615.8	28	615.8	26	530.9	26	530.9
TOTAL AREA		4,457.8		4,253.7		4,288.2		4,326.0		4,291.3		4,102.8
% Control Area		100		95.4		96.2		97.0		96.3		92.0
VEINS												
1	48	1,809.6	48	1,809.6	50	1,963.5	50	1,963.5	48	1,809.6	50	1,963.5
2	52	2,123.7	50	1,963.5	48	1,809.6	50	1,963.5	48	1,809.6	48	1,809.6
3	62	3,019.1	62	3,019.1	60	2,827.4	62	3,019.1	62	3,019.1	60	2,827.4
4	46	1,661.9	47	1,734.9	48	1,809.6	48	1,809.6	48	1,809.6	50	1,963.5
TOTAL AREA		8,614.3		8,527.1		8,410.1		8,755.7		8,447.9		8,564.0
% Control Area		100		99.0		97.6		101.6		98.1		99.4

D = Diameter in microns. Area = Area in microns^2.

SUPPORTING TABLE 106

ACTION OF PLASMA FROM PATIENT (G.S.) IN BACTERAEMIC SHOCK RECEIVING INTRAVENOUS NORADRENALINE.

Local injection of 0.05 ml. plasma from patient (G.S.) into the Hamster Cheek Pouch, followed in 30 mins. by injection of 10 micrograms phentolamine in 0.05 ml. Ringer's solution.

	TIME IN MINUTES AFTER INJECTION OF PLASMA AND PHENTOLAMINE INTO CHEEK POUCH																	
	Control		3 mins.		6 mins.		15 mins.		30 mins.		3 mins.		6 mins.		15 mins.		30 mins.	
ARTERIES	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA	D.	AREA
1	42	1,385.4	12	113.1	14	153.9	10	78.5	14	153.9	30	706.9	38	1,134.1	36	1,017.9	34	907.
2	20	314.2	0	0	0	0	0	0	4	12.6	12	113.1	18	254.5	18	254.5	16	201.
3	28	615.8	4	12.6	4	12.6	5	19.6	8	50.3	20	314.2	26	530.9	28	615.8	26	530.
4	38	1,134.1	8	50.3	6	28.3	6	28.3	14	153.9	30	706.9	32	804.2	32	804.2	30	706.
TOTAL AREA		3,449.5		176.0		194.8		126.4		370.7		1,841.1		2,723.7		2,692.4		2,346.
% Control Area		100		5.1		5.6		3.7		10.7		53.4		79.0		78.1		68.
VEINS																		
1	64	3,217.0	66	3,421.2	62	3,019.1	60	2,827.4	56	2,463.0	58	2,642.1	60	2,827.4	60	2,827.4	62	3,019.
2	20	314.2	18	254.5	18	254.5	14	153.9	12	113.1	22	380.1	22	380.1	20	314.2	20	314.
3	36	1,017.9	40	1,256.6	40	1,256.6	42	1,385.4	38	1,134.1	40	1,256.6	42	1,385.4	36	1,017.9	38	1,134.
4	52	2,123.7	50	1,963.5	52	2,123.7	48	1,809.6	52	2,123.7	50	1,963.5	50	1,963.5	50	1,963.5	52	2,123.
TOTAL AREA		6,672.8		6,895.8		6,653.9		6,176.3		5,833.9		6,242.3		6,556.4		6,123.0		6,591.
% Control Area		100		103.3		99.7		92.6		87.4		93.5		98.3		91.8		98.

D = Diameter in microns. Area = Area in microns^2.

APPENDIX 4.

CASE HISTORY SUMMARIES 1-31.

CASE 1

Patient E.C., female, age 38 years.

Diagnosis: Traumatic rupture of the duodenum.

Operation: Laparotomy and repair of duodenal laceration.

Clinical Summary: The patient struck a tree with her automobile and sustained facial, head and abdominal injuries. There had been transitory unconsciousness at the time of the accident but when the patient was admitted to hospital she was vomiting and complaining of abdominal pain.

Laparotomy was performed and a traumatic laceration of the duodenum at the junction of the 3rd and 4th parts was repaired and the abdomen closed around a peritoneal drain. Post-operatively the patient developed a marked tachycardia and hypotension. The blood pressure improved with intravenous therapy but over the following ten days the abdomen remained distended and the patient had a continuous pyrexia of 103°F. On the eleventh post-operative day dehiscence of the wound occurred and leakage of fluid suggested a duodenal fistula. On radiological examination, barium administered orally to the patient, was observed to pass out of the duodenum at the site of the previous traumatic rupture. The patient's condition continued to deteriorate and on the 16th day following the accident, she was transferred to the intensive care unit of the Peter Bent Brigham Hospital.

On admission, the patient was found to be acutely ill. Rectal temperature was 102.8°F., arterial blood pressure was 84/60 mm.Hg. and pulse rate was 120 per minute. The wound was gaping and pus was leaking from the drain incisions and from the saphenous vein 'cut-down' sites. White blood count was 33,600 per c.mm. Marked dehydration and electrolyte imbalance were present. Over the next 3 days, in spite of intensive therapy, (intravenous fluids and antibiotics) the temperature rose to 104°F., pulse rate rose to 180 per minute and systolic arterial blood pressure remained below 80 mm.Hg. Bacterial swabs from the abdominal wound grew E. coli and later, blood cultures grew the same organism.

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Case 1 (Contd.)

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On the third day following her transfer, the patient's urinary output was only 180 ml. in 24 hours. She developed respiratory distress and central venous pressure was found to be 20 cms. water. Acute pulmonary oedema developed. Electrocardiography showed no major abnormal finding. Phlebotomy (400 mls. blood), mannitol infusion (12.5 G), dibenzyline (15 mgms.), and low molecular weight dextran (500 mls.) were without effect and the patient died. Terminally the patient's blood pH fell to 7.05; pO_2 was 56 mm.Hg. and pCO_2 was 40 mm.Hg.

A post-mortem examination was not obtained.

CASE 2

Patient J.D., male, age 35 years.

Diagnosis: Multiple injuries.

Operations: Tracheostomy.
Laparotomy for alimentary tract bleeding - gastrectomy.

Clinical Summary: Four days prior to admission the patient had a motor cycle accident. He sustained multiple injuries including broken ribs, fracture of the left tibia and fibula, puncture wounds of the abdomen and concussion. At that time the patient was admitted to a local hospital for emergency treatment. His pulse and blood pressure were unrecordable and he was cold and shocked. With multiple blood transfusions the patient's condition improved. Arterial blood pressure rose to 130/60 mm.Hg. Emergency treatment of the fractures was carried out. Over the next three days the patient's urinary output decreased to 300 mls. per day. Gross haematuria was noted. He was transferred to the intensive care unit of the Peter Bent Brigham Hospital.

On admission the patient's abdomen was tympanitic and in the left upper quadrant there was a palpable mass. X-rays showed comminuted fractures of the left tibia and fibula. There was a large left pleural effusion with some pneumothorax and consolidation at the left base.

Initial Laboratory Data:-

Haematocrit		- 35 per cent.
W.B.C.		- 18,500 per c.mm.
Blood Urea Nitrogen		- 64 mgms. per 100 mls.
Electrolytes	Na	- 110 mEq. per litre.
	K	- 5.7 mEq. per litre.
	Cl.	- 82 mEq. per litre.

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Case 2 (Contd.)

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Blood Gas Estimations

pH	- 6.9
pCO_2	- 43.4 mm.Hg.
Oxygen Saturation	- 68.4 per cent.
CO_2 content	- 14.2 mEq. per litre.

Hospital Course.

Tracheostomy and left thoracentesis were carried out with improvement in the patient's respiratory state. Because of oliguria and a blood urea nitrogen rising rapidly to 176 mgms. per 100 mls. renal injury was suspected, but retrograde pyelography demonstrated bilateral intact collecting systems. Haemodialysis carried out on three occasions lowered the blood urea nitrogen level to 110 mgms. per cent and urinary output increased to 500 mls. in 24 hours. Further progress was complicated by massive alimentary tract bleeding. After six litres of blood had been transfused, emergency laparotomy was carried out. The stomach was full of blood. A left subphrenic abscess was discovered and the spleen and left kidney were involved in dense fibrous tissue. Pseudomonas aeruginosa was cultured from the abscess.

An emergency gastrectomy was carried out. For the following five days the patient's condition remained poor. X-ray of chest showed generalised infiltration of lung fields. Tracheal cultures and blood cultures grew pseudomonas aeruginosa. Hypotension became refractory and the patient died.

Post-Mortem Findings.

At post-mortem examination, the patient was found to have a ruptured spleen, peri-splenic and subhepatic abscesses. The splenic vein and left renal artery and vein were thrombosed with infarction of the spleen and left kidney. The right kidney showed signs of acute tubular necrosis. Prostatic abscesses were present. Further abscesses were present in the liver and pancreas. Peptic ulceration was present in the gastric remnant and there was acute inflammation of the serosal surfaces of the stomach and duodenum. Diffuse bilateral bronchopneumonia with pulmonary emboli and an abscess of the right middle pulmonary lobe was found. Death was due to widespread sepsis with respiratory and renal failure.

CASE 3

Patient R.M., male, age 29 years.

Diagnosis: Abdominal Injuries.

Operation: Splenectomy, Nephrectomy and Colostomy.

Clinical Summary: The patient, a 29 year old man was struck in the left flank by a shell casing which had detonated near him. He was admitted to the local hospital and was taken immediately to the operating theatre where a ruptured spleen and fragmented left kidney were removed. There was a laceration of the splenic flexure of the colon and a fracture of a lumbar vertebra with severe bleeding from dural veins and a cauda equina injury. A colostomy was fashioned and packing was required to control retroperitoneal bleeding.

A few hours later the patient had to return to the operating theatre for further control of haemorrhage from epidural veins. With massive blood transfusions the patient's blood pressure was maintained but after 24 hours anuria, he was transferred for haemodialysis to the Peter Bent Brigham Hospital.

A blood urea nitrogen of 150 mgms. per 100 ml. and a serum potassium of 7.3 mEq./litre fell to 48 mgms. per 100 ml. and 5.3 mEq./litre respectively after haemodialysis.

Owing to increasing respiratory difficulties, a tracheostomy was carried out and controlled respiration instituted.

On the evening of the second day after his transfer, the patient became drowsy and then comatose. The following day he developed twitching and later, epileptiform seizures.

Blood cultures grew E. coli and later cerebro-spinal fluid also grew E. coli and showed 11,000 white cells per c.mm. The temperature was 102.8°F. (axillary).

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Case 3 (contd.)

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Hypotension was persistent and in spite of the administration of oxygen, hypoxia was progressive. Shortly before death, pO_2 was 35 mm.Hg. during 100 per cent oxygen inflation of the lungs. The patient died six days after the injury.

Post-Mortem Findings.

At necropsy, there was a large traumatic wound of the left flank. A colostomy was present. Spleen and left kidney had been removed. A left subphrenic abscess was present with localised peritonitis.

A large retroperitoneal haematoma was associated with fractured transverse processes and trauma to nerve roots. Acute congestion of liver, stomach, duodenum and small bowel were present. The remaining kidney (right) was the site of acute tubular necrosis. Acute tracheitis and extensive acute broncho-pneumonia were present. There was evidence of meningitis with petechiae on the base of the frontal and temporal lobes of the brain.

CASE 4

Patient C.M., male, age 58 years.

Diagnosis: a) Peritonitis from Diverticulitis.
b) Carcinoma of Stomach.

Operation: 1) Transverse Colostomy and Peritoneal Drainage.
2) Laparotomy for Haematemesis.

Clinical Summary: The patient, a 58 year-old man who had acute lower abdominal pain was admitted to hospital. A diagnosis of diverticulitis was made and laparotomy was performed. A generalised peritonitis was found and there was diverticulitis of sigmoid colon. A transverse colostomy was fashioned and the abdomen closed with peritoneal drainage.

The patient's condition continued to deteriorate over the following seven days and he was transferred from his local hospital to the intensive care unit of the Peter Bent Brigham Hospital. Tracheostomy was performed and tracheal aspiration, associated with assisted respiration with a Bird respirator, improved the patient's respiratory state. Abdominal distension persisted and there was copious aspiration of gastric fluid. Barium swallow and fluoroscopy revealed a chronic posterior gastric ulcer. There was no evidence of perforation of the ulcer.

Blood pressure, haematocrit, blood volume and central venous pressure were normal. White blood count was 13,000 per c.mm. Blood urea nitrogen was normal and intravenous infusions maintained serum electrolyte values within the normal range. Following admission to the intensive care unit the patient's condition gradually improved. On the seventh day after admission however, the patient developed a sudden rigor, and his temperature rose to 105-106°F. Hypotension developed and the extremities became cold, cyanosed and mottled. The abdominal wound appeared infected and several serial blood cultures grew organisms of the serratia species. Urinary output decreased and the blood urea nitrogen rose to

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Case 4 (contd.)

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95 mgms. per 100 ml. There was severe gastro-intestinal haemorrhage with haematemesis and melaena. The bleeding was not controlled by massive blood transfusion (8 litres) and laparotomy was performed. The previously observed posterior-wall gastric ulcer was found to be a necrotic bleeding carcinoma fixed to the pancreas. Gastrectomy was not possible and bleeding was controlled by suture and the abdomen closed. The patient's condition did not improve and he died the following day.

Post-Mortem Findings.

Post-mortem examination confirmed the presence of a carcinoma of stomach with considerable bleeding into the alimentary tract. There was generalised peritonitis with diverticulitis. Acute tracheo-bronchitis with hypostatic pneumonia was present.

CASE 5

Patient B.G., male, age 57 years.

Diagnosis: Mitral Stenosis (Rheumatic).

Operation: Mitral Valve Replacement.

Clinical Summary: This 57 year-old male patient had long standing mitral stenosis. He had rheumatic fever, aged 12 years. Mitral valvuloplasty had been performed in 1944 and two years later re-operation of mitral valvuloplasty was performed, marked calcification being found in the cusps with moderate regurgitation. The patient was re-admitted for assessment. He had increasing shortness of breath with episodes of paroxysmal tachycardia resulting in unconsciousness. After further investigation, open heart operation, using the heart-lung machine, was performed. The mitral valve was excised and replaced with a Harken valve prothesis. Owing to the two previous thoracotomies, there was marked difficulty in clearing the lung from the chest wall.

Immediately after operation the patient's condition was satisfactory. Early on the second post-operative day, the patient was found to be hypotensive with poor urinary output. Blood urea nitrogen was 34 mgms. per 100 mls. The haematocrit was 45 per cent, central venous pressure fluctuated between 8-15 cms. saline, and blood volume estimated with the "Volemetron" using 1 ^{125}. Albumen was normal (5,500 ml.).

The patient complained of lower abdominal pain, and abdominal distension was noted. Fresh blood was aspirated on gastric suction. The abdomen was tender and tympanitic and there was early ecchymosis in the flanks. Serum amylase was 750 units (Somogyi) and lactic acid dehydrogenase was 1400 units.

An X-ray of chest showed opacities on the left side, the right lung field being normal. There was gaseous distension of the small bowel and colon. Intravenous noradrenaline was given but the systolic arterial blood pressure remained below 90 mm.Hg.

On the second post-operative day the /

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patient's abdominal discomfort and distension became more marked. Hypothermia had been used during operation and post-operatively the patient remained on a cooling blanket, the temperature being controlled between 97-98°F. The patient's blood pressure could not be maintained with fluids and vasopressor drugs. Central venous pressure rose to 22 gms. saline. In spite of attempts at resuscitation the patient died.

Post-Mortem Findings.

The patient had rheumatic heart disease. The heart weighed 600 grams. Mitral valve replacement was satisfactory.

There was severe bilateral broncho-pneumonia with scattered intrapulmonary haemorrhages in the left lung. Both kidneys were the site of acute tubular necrosis.

The most striking findings involved the alimentary tract. There were superficial mucosal haemorrhages in the stomach and the oesophagus. There was acute exudative entero-colitis with focal mucosal haemorrhages and necrosis. Death had supervened at the time of almost total intestinal necrosis. No thrombi or emboli were present in the superior mesenteric artery.

COMMENT - This patient's death and post-mortem findings were similar to the severe intestinal changes found in the dog in irreversible haemorrhagic shock. The primary cardiac defect, and operation had produced hypotension with poor tissue perfusion resulting in irreversible intestinal ischaemia.

CASE 6

Patient T.T., male, age 66 years.

Diagnosis: Carcinoma of Bladder.

Operation: 1) Total Cystectomy and Ileal Bladder.
2) Laparotomy for intestinal obstruction.

Clinical Summary: In 1949 the patient had a partial cystectomy for carcinoma of bladder. Within the last year he had chemotherapy and cystodiathermy for recurrence of tumour and one month before present admission cystoscopy revealed extensive tumour of the bladder trigone and intravenous pyelography demonstrated bilateral hydronephrosis.

Total cystectomy and fashioning of an ileal conduit were carried out in a one-stage operative procedure. Twelve days later re-exploration was required for intestinal obstruction. There was atonic dilatation of small bowel but no obvious mechanical obstruction. On the third day after the laparotomy the patient's temperature rose to 105°F., systolic arterial blood pressure fell to 80 mm.Hg. and oliguria (120 mls. urine in 24 hours) was noted. The patient was transferred to the intensive care unit.

Initial Laboratory Findings.

Haematocrit	- 48 per cent.
Blood urea nitrogen	- 203 mgms. per 100 ml.
Electrolytes	
Serum Sodium	- 163 mEq. per litre.
Serum Potassium	- 7.1 mEq. per litre.
Serum Chloride	- 130 mEq. per litre.

Haemodialysis was instituted shortly after admission and blood urea nitrogen fell to 68 mgms. per 100 ml. Serum potassium, sodium and chloride concentrations were 3.5, 142, and 103 mEq. per litre respectively immediately after haemodialysis.

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The patient continued to have pyrexia (103.4°F). Blood pressure was maintained with vasopressor (noradrenaline). Central venous pressure remained low (less than 4 cms. water).

Repeated blood cultures grew pseudomonas aeruginosa. Upper gastro-intestinal bleeding occurred. Clotting time was prolonged (14 mins.), prothrombin concentration was low and platelet count was 92,000 per c.mm.

A tracheostomy did not materially improve hypoxia and respiratory distress. A marked metabolic acidosis was treated with intravenous sodium bicarbonate and Tris. buffer. The patient's condition continued to deteriorate and death occurred nineteen days after the cystectomy.

Post-Mortem Findings.

Necropsy revealed a dehiscence of the left-uretero-ileal anastomosis with generalised peritonitis.

The kidneys were the site of long standing hydronephrosis with acute and chronic pyelonephritis. Acute tubular necrosis was present.

Acute ulceration of oesophagus was found and the stomach was full of clotted blood. Punctate ulcers with a haemorrhagic reaction were present throughout the ileum and colon. Histologically there were thrombi in the small vessels of the bowel and clumps of bacilli in the base of ulcers.

The lungs were consolidated with microabscesses and both bases were involved in acute necrotising bronchopneumonia.

CASE 7

Patient F.R., male, age 75 years.

Diagnosis: Peritonitis — superior mesenteric artery occlusion.

Operation: Laparotomy. Thrombendarterectomy and resection of small bowel.

Clinical Summary: The patient, a 75 year-old man who had recent recurrent abdominal cramps was admitted to hospital with acute abdominal pain and rigidity. Laparotomy was carried out, and the superior mesenteric artery was found to be occluded. Thrombendartectomy was performed with restoration of blood flow to the distal small bowel. The proximal small bowel remained ischaemic however and the proximal $\frac{2}{3}$rds was resected.

The patient developed acute renal failure on the first post-operative day. Peritoneal dialysis was instituted on the second post-operative day when serum potassium rose to 7.5 mEq. per litre and the blood urea nitrogen concentration was 140 mgms. per 100 ml. The patient's condition continued to deteriorate. Hypotension which developed did not respond to vasopressors and intravenous fluids and death occurred on the 3rd post-operative day.

Post-Mortem Findings.

There was generalised atherosclerosis with acute occlusion of the superior mesenteric artery. There was old complete occlusion of the left renal artery. Atherosclerosis involved the coronary vessels and there was marked atheroma of lower aorta and iliac vessels.

The remaining ileo-jejunal segments of small bowel on either side of the anastomosis were infarcted and peritonitis was present. Acute haemorrhagic gastritis was found and there was acute congestion of the liver and spleen. Multiple calculi were present in the right kidney. The lungs showed bilateral bronchopneumonia. Escherichia coli, isolated from the peritoneal fluid at the time of operation was also isolated from post-mortem cultures taken from heart blood, lung and peritoneum.

CASE 8

Patient F.R., male, age 58 years.

Diagnosis: Carcinoma of Bladder.

Operation: 1) Ileal Bladder.
2) Resection and anastomosis of small bowel.

Clinical Summary: The patient, a 58 year-old male, who had previous radiotherapy for a carcinoma of bladder was admitted to hospital and on the second hospital day an ileal-loop diversion was performed as a preliminary to cystectomy. Post-operatively the patient developed a pyrexia and on the 14th post-operative day there were signs of generalised peritonitis associated with hypotension. Exploratory laparotomy showed generalised peritonitis due to a breakdown in the ileal anastomosis. E. coli was cultured from the peritoneal exudate. A resection and anastomosis of ileum were performed. Post-operatively the patient required vasopressors to sustain a satisfactory blood pressure. There was pyrexia (temperature 103°F). Pneumonic consolidation of the lower lung lobes occurred. Tracheostomy was performed with mechanical respiration to overcome hypoxia. It was noted that the patient had a low platelet count and a prolonged bleeding and clotting time.

A bone marrow examination showed marked megakaryocytic and myeloid hyperplasia. An isologous Cr_{51} labelled platelet transfusion study showed an increased destruction or sequestration of platelets. Renal function which was initially poor promptly improved. Blood volume studies showed a marked expansion of the effective blood volume after operation. The blood volume fell to normal levels over the following days and was associated with a marked diuresis. The patient's general condition steadily improved and he was discharged from hospital, afebrile 3 weeks after the second operation. On discharge from hospital blood urea nitrogen levels, white blood cells and platelet concentrations were normal. Main Table 41 summarises the patient's hospital course.

CASE 9

Patient K.W., male, age 64 years.

Diagnosis: Abdominal aortic aneurysm.

Operation: Resection of abdominal aneurysm.

Clinical Summary: This 64 year-old man had been receiving medical treatment for hypertension. Six weeks before admission to hospital the patient complained of low back pain which radiated around the abdomen. X-ray examination (Aortography) confirmed the clinical diagnosis of an aortic aneurysm about 10 cms. in diameter and 12 cms. in length. Both common iliac arteries were dilated and the aneurysm extended up to just below the renal vessels. X-ray of lumbar spine, intravenous renal pyelography and a gastro-intestinal barium series demonstrated no other cause for the persistent low back pain.

At operation the aneurysm was found to be extremely adherent to the surrounding structures, particularly to the duodenum and to the inferior mesenteric vein. The posterior wall of the aneurysm was absent and the false membrane was composed of the anterior spinal ligaments. A knitted Dacron bifurcation prosthesis was used to replace the resected aneurysm.

The patient's immediate post-operative course was good. Urinary output was maintained at 50-60 ml. per hour. On the seventh post-operative day there was dehiscence of the abdominal wound. Under general anaesthesia protruding small bowel was replaced and secondary suture of the wound performed. Following the resuture of the abdominal wound, the patient's temperature became elevated to 101°F and did not settle. White blood count on the 16th day following the primary operation was 37,000 per c.mm. Later the same day the patient had a shaking chill lasting 15 minutes. Temperature rose to 102°F and within two hours, the blood pressure, normally 180/120 mm.Hg. fell to 96/60 mm.Hg. Several blood cultures were sterile. Blood gas analysis and blood pH were normal. An electrocardiograph suggested antero-septal ischaemia. Blood volume and haematocrit were satisfactory. Intravenous fluids were given and

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noradrenaline infusion restored the blood pressure to normal levels. Urinary output was low (less than 30 ml. per hour) and blood urea nitrogen rose to 114 mgms. per 100 ml.

The following day the patient had another hypotensive episode with blood pressure falling to 60/40 mm.Hg. Temperature remained elevated and X-ray of chest showed atelectasis and consolidation of the right lung base. Antibiotics, steroids and intravenous fluids (including low molecular weight dextran) were administered. The patient's condition continued to deteriorate and he died early the following morning.

Post-Mortem Findings.

The patient had generalised athero-sclerosis. The dacron graft aortic prosthesis was satisfactory. There were mucosal and submucosal haemorrhages in the stomach and small bowel. Multiple duodenal ulcers were present and there was necrosis and perforation of the third part of the duodenum with a large retroperitoneal abscess. Acute pancreatitis with focal fat necrosis was present. Multiple recent small pulmonary emboli were present in both lungs and there was atelectasis and consolidation of the right lower lobe.

CASE 10

Patient E.F., male, age 75 years.

Diagnosis: Carcinoma of head of pancreas.

Operation: Pancreatico-duodenectomy.

Clinical Summary: This 75 year-old man was admitted to hospital for investigation of jaundice associated with abdominal pain and weight loss. The gall-bladder was palpable and there was an epigastric mass mainly on the left side. Occult blood was present in the stool. Serum bilirubin was 5.5 mgms. per 100 ml. and the other liver function tests suggested obstructive jaundice.

At laparotomy a tumour of the head of pancreas involving the ampulla was found. Biopsy of the tumour showed it to be a poorly differentiated adenocarcinoma.

A pancreatico-duodenectomy was carried out, the common bile duct and stomach being anastomosed to the jejunum. Four bottles of blood were given during the operation. For the first post-operative week, the patient's course was satisfactory. He was then noticed to have some mental confusion. The abdomen was distended, urinary output was poor and the blood urea nitrogen concentration was elevated. The patient suddenly became shocked; his systolic arterial blood pressure fell to 65 mm.Hg. and he had a bulky bowel movement containing bright fresh blood. Blood transfusions were given and laparotomy was carried out. At the re-exploration of the peritoneal cavity, a bleeding point on the gastro-jejunostomy suture line was oversewn. Culture of the wound at the time of operation grew Klebsiella-Aerobacter species.

During the following two weeks the patient had intermittent haemorrhage from his abdominal wound. Blood pressure fluctuated and repeated blood transfusions were necessary. Klebsiella-Aerobacter species, Escherichia coli and Staphylococcus aureus were grown from the wound. Serial blood cultures were all sterile.

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Increase in the discharge from the wound suggested a gastro-jejunal fistula, which was confirmed by giving methylene blue by mouth, the wound discharge containing dye. The patient's general condition continued to deteriorate over the following days. The extremities were blue and mottled. Hypotension became irreversible and the patient died.

Post-Mortem Findings.

At post-mortem examination there was generalised peritonitis with marked left para-colicabscess formation. A fistula could not be identified in the inflammatory mass. There was a left nephro-pyelitis with a grossly distended left pyo-ureter. The abdominal abscess grew proteus species and the organisms isolated from cultures of kidney, pelvis, ureter and heart blood, were proteus species and Klebsiella-Aerobacter species.

CASE 11

Patient B.B., male, age 42 years.

Diagnosis: Haematemesis from Duodenal Ulcer.

Operation:
1) Partial Gastrectomy.
2) Laparotomy for post-gastrectomy haemorrhage.

Clinical Summary: This 42 year-old male who had a two year history of peptic ulcer was admitted to hospital suffering from recurrent gastro-intestinal bleeding. After a massive haemorrhage from an ulcer of the second part of the duodenum a polya gastrectomy was performed. Because of the proximity of the ulcer to the ampulla the duodenum was closed above the ulcer. Two weeks later after further alimentary tract haemorrhage the patient was transferred to the intensive care unit at the Peter Bent Brigham Hospital. On admission the patient's temperature was 105°F and his pulse was 120 per minute. Bilateral rales were audible in the chest. The patient's temperature was considered to be due to pneumonia.

Seven hours later further haemorrhage occurred and the patient's blood pressure fell to 70/50 mm.Hg. After blood transfusion, laparotomy was performed and the duodenal ulcer which was still bleeding was excised. A T-tube choledochostomy drain was inserted. (The common bile duct being explored to confirm that it remained intact after the excision of the ulcer in the second part of the duodenum.)

The following day, because of increased respiratory difficulties a tracheostomy was performed. The patient still had a pyrexia and an x-ray of chest showed bilateral basal infiltrates. During the following three days, although there was no further haemorrhage, the patient's condition did not improve. Jaundice was noted and it became progressive. A platelet count was 88,000 c.mm. Haematocrit and blood volume were within normal range. In spite of platelet transfusions the thrombocytopenia persisted. Klebsiella-Aerobacter species were isolated from consecutive blood cultures. The blood pressure fell and became refractory to intravenous fluids and vasopressor drugs. Oedema of the legs and cyanosis

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of the extremities were marked. The patient developed anuria and died one week after the second operation.

Post-Mortem Findings.

There was severe bilateral broncho-pneumonia with consolidation. (Post-mortem cultures from the lungs and heart blood grew Klebsiella-Aerobacter organisms.) The polya gastrectomy anastomosis and choledochostomy were satisfactory. There was no evidence of obstruction in the post-hepatic biliary system. There was an infarct of the spleen and petechiae and recent infarcts in both kidneys.

CASE 12

Patient E.K., female, age 63 years.

Diagnosis: Carcinoma of Rectum.

Operation: 1) Abdomino-perineal excision of rectum.
2) Laparotomy for intestinal obstruction.

Clinical Summary: The patient who had an abdomino-perineal excision of rectum performed for carcinoma of rectum developed oliguria (less than 300 mls. urine per day) and was transferred to the Peter Bent Brigham Hospital where haemodialysis was performed. There was persistent abdominal distension and at laparotomy a small bowel obstruction around the colostomy was found and corrected. Post-operatively the patient's temperature was 102°F. Blood urea nitrogen concentration continued to rise and further haemodialysis was carried out. The clotting time at the end of the dialysis was 18 minutes.

Marked bleeding occurred from the alimentary tract. Blood cultures grew Klebsiella-Aerobacter species. (Four bottles). Hypotension became progressive and the patient died one week after the second operation.

Post-Mortem Findings.

There was acute peritonitis with 1500 ml. pus in the peritoneal cavity. There was no evidence of mechanical obstruction. Blood was present in the stomach and erosions were found in the oesophagus and stomach. Acute necrotising enterocolitis involved most of the small bowel and colon. The kidneys were pale. There was acute tubular necrosis with pyelonephritis. The lungs showed bilateral haemorrhagic bronchopneumonia.

CASE 13

Patient C.T., male, age 50 years.

Diagnosis: Obstructive Jaundice and Cholangitis.

Operation: Reconstruction of stenosed bile duct.

Clinical Summary: Two years prior to the present admission the patient had a cholecystectomy carried out following an attack of jaundice and fever. The common bile duct was not explored. Two months later further laparotomy had been carried out for recurrence of abdominal pain, jaundice and pyrexia. At laparotomy the common bile duct could not be identified in inflammatory adhesions. A sub-hepatic abscess was drained and a biopsy of liver showed chronic active cholangitis with biliary stasis. Intermittent bouts of fever and jaundice persisted. During three separate episodes of fever, organisms (Escherichia coli) were cultured from the blood. A further laparotomy was carried out. Transduodenal exploration of the common bile duct allowed identification and exploration of the common bile duct with T-tube drainage. Following this procedure the patient became hypotensive; he had a chill and rigor and blood cultures again grew Escherichia coli. With antibiotic therapy and intravenous fluids the patient's condition improved. After the T-tube had been removed he was allowed home.

There were minor intermittent attacks of fever and jaundice over the next nine months.

On his present admission following a more severe attack the patient was found to be shocked. His blood pressure was 84/44 mm.Hg. Blood urea nitrogen was 75 mgms. per 100 ml. and serum bilirubin 8 mgms. per cent. The patient complained of fatigue and loss of energy. Temperature was 103.8°F and white blood cell count was 14,860 per c.mm. Blood cultures were once more positive (E.coli). Treatment with intravenous fluid and antibiotics improved the patient's condition but the jaundice persisted and a further laparotomy was performed. The lower surface of the liver was involved in dense

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adhesions. A transhepatic cholangiogram showed a distended upper part to the common bile duct and distended branches. The duodenum was opened and the common bile duct irrigated. There was considerable stenosis and tortuosity of the lower part of the common bile duct. A Roux-Y loop of jejunum was anastomosed to the upper dilated common bile duct and a T-tube drain inserted. Following this procedure, E. coli, proteus species and Pseudomonas aeruginosa were cultured from the bile draining from the T-tube. The wound surface also showed evidence of E. coli but there was no recurrence of pyrexia and further blood cultures were sterile. The serum bilirubin fell to normal levels.

COMMENT:- The patient had recurrent attacks of ascending cholangitis associated with stenosis of the common bile duct. There were episodes of bacteraemia complicated by hypotension on some occasions. Operative correction of the biliary stasis and antibiotic treatment of the residual biliary duct infection cured the patient's symptoms.

CASE 14

Patient A.A., male, age 70 years.

Diagnosis: Cholecystitis.

Operation: 1) Cholecystectomy.

2) Drainage of Subphrenic Abscess.

Clinical Summary: The patient was a 70 year-old man who had diabetes which was poorly controlled. He had a long history of intermittent cholecystitis, and a few months before his present admission he had a cerebral thrombosis producing an incomplete left hemiparesis.

After a further severe episode of cholecystitis the patient was admitted to hospital for cholecystectomy. At operation a large thickened but not tense gall-bladder containing several stones was removed. The common bile duct was normal and was not opened. The following day the patient appeared drowsy; his temperature was 102°F and his arterial blood pressure was 180/80 mm.Hg. (similar pre-operative blood pressure.) Blood sugar was 480 mgms. per 100 ml. and insulin was given. Later the same day the patient perspired freely and his temperature rose to 104°F and his blood pressure fell to 120/70 mm.Hg. The patient's condition then appeared to improve until the eighth post-operative day when he had a sudden shaking chill. He sweated profusely. The skin was dusky violet in colour. The patient was disorientated and the temperature rose sharply to 105°F.

The following day after a further similar rigor, operative exploration of the subhepatic space was carried out and a localised abscess was evacuated and a drain inserted. Blood cultures taken on four separate occasions all grew bacteroides species. After temporary improvement the patient's temperature once more became elevated. He continued to appear toxic and during the third post-operative week, hypotension supervened. Noradrenaline was given with only temporary improvement and the patient died in coma on the 28th post-operative day.

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Post-Mortem Findings.

There was a purulent peritonitis, acute splenitis and a large intrahepatic abscess.

Acute erosions were found in the oesophagus. There was gastromalacia with post-mortem perforations. Multiple acute duodenal ulcers were present and there were copious bloody contents in the whole small bowel. In the respiratory system there was acute tracheo-bronchitis and confluent bronchopneumonia. A large pulmonary embolism was present in the right lower lobe.

CASE 15

Patient G.S., female, age 79 years.

Diagnosis: Acute cholecystitis and acute pancreatitis.

Operation: Cholecystostomy.

Clinical Summary: This was the third hospital admission of this elderly widow who had previously repeatedly refused operative treatment for recurrent cholecystitis. Prior to the present admission the patient had a one week's history of acute upper abdominal pain associated with vomiting.

In hospital the patient appeared acutely ill. White blood count was 21,000 per c.mm., haematocrit was 37 per cent. Blood urea nitrogen and serum electrolytes were normal but the lactic acid dehydrogenase, serum glumatic oxalo-acetic transanimase and serum amylase levels were considerably elevated. Blood volume estimation was normal. At laparotomy an empyema of the gall-bladder associated with acute pancreatitis was found. Cholecystostomy and peritoneal drainage were performed.

Post-operatively the patient's condition remained very poor. Intravenous fluids and noradrenaline did not improve the hypotension. A marked metabolic acidosis was treated with tris buffer (THAM) and sodium bicarbonate. Serial blood cultures grew Aerobacter-Klebsiella species. The patient developed generalised petechiae. There was acrocyanosis of the extremities. The hypotension was refractory to treatment. The acidosis became progressive and the patient died on the third day following admission to hospital.

Post-Mortem Findings.

There was severe acute and chronic cholecystitis and cholelithiasis with haemorrhagic necrosis of the gall-bladder wall. Ascending cholangitis with small intrahepatic abscesses was found. There was thrombosis of the portal vein with infarction of a segment of the liver. Acute pancreatitis with areas of fat necrosis was also found. A fibrinous peritonitis with perisplenitis and perihepatitis was found and there was a generalised severe exudative necrotising enterocolitis. Petechiae and haemorrhages were present in the skin, pleura, oesophagus, stomach and bowel. The kidneys were the site of acute tubular necrosis.

CASE 16

Patient M.C., female, age 66 years.

Diagnosis: Severe burns (60-70% Body Surface).

Operation: Multiple excisions of necrotic skin and skin grafting.

Clinical Summary: This 66 year-old married woman received 60-70 per cent body surface burns when her dressing gown caught fire at her kitchen stove.

Although there was marked facial oedema there did not appear to be any pharyngo-laryngeal injury and tracheostomy was not required. With intensive intravenous therapy, monitored carefully by biochemical and haemodynamic measurements the patient progressed satisfactorily at first and on the twelfth day after the accident excision of some burned areas with autogenous skin grafting was carried out.

On the second post-operative day the patient had a rigor and her temperature rose to 103°F: the bacterial colonization of the burned areas and the bacteriological state of the environment were studied closely. Figure 23 summarises the bacteriological findings during the patient's hospital course.

The initial grafts on the chest wall had taken satisfactorily and ten days later further excision of necrotic areas was performed and homologous cadaveric grafts were applied. Once again, in spite of careful antibiotic therapy, on the 2nd post-operative day the patient had a shaking chill and the temperature rose to 104°F. There was however no hypotension.

Subsequently the burned areas appeared to become more infected. Staphylococcus aureus and pseudomonas aeruginosa (pyocyaneus) were the dominant organisms at this time. Minor excision and grafting procedures were carried out but the patient's general condition continued to deteriorate. Four weeks after admission to hospital the patient became drowsy and then

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comatose. She had a generalised convulsion followed by minor seizures and thereafter appeared to be in a stupor. Temperature remained elevated. Blood cultures, which previously had always been sterile now grew pseudomonas aeruginosa. Hypoglycaemia was found but there was no ketosis and the blood urea nitrogen was normal. The hypoglycaemia and a marked metabolic acidosis were treated rigorously but the patient developed increasing hypotension and died on the fifth week after sustaining the burn injury.

Post-Mortem Findings.

At autopsy the brain had a peculiar sweet smell characteristic of pseudomonas infection. There was severe laryngitis and oesophagitis which had not been suspected clinically.

All the blood had clotted. The peritoneal cavity seemed very dry and there was pre-mortem ischaemia of the bowel.

Bilateral pleural effusions were found and there was bronchopneumonia with focal segmental atalectasis.

CASE 17

Patient L.R., female, age 60 years.

Diagnosis: Burns (70% body surface).

Operation: Multiple excisions of sloughs and skin grafting procedures.

Clinical Summary: This patient was burned when she lit a match while looking for a gas leak in her cottage basement. She was treated at the local hospital with intravenous infusions of electrolyte solutions and blood. Because of oliguria, and the extensive nature of the burns the patient was transferred to Boston for further treatment.

The patient had burns of the face, mouth, chest, arms, legs and abdomen. Later when it was possible to assess the depth of burns, 35% body surface had full skin thickness burns and a further 35% body surface had partial skin thickness burns.

On admission to hospital the patient's haematocrit was 66 per cent and serum sodium was 124 mEq. per litre. With infusion of 3% saline solution the haematocrit fell and urinary output returned to normal.

The bacteriological state of the necrotic burned areas was assessed frequently. A heavy mixed infection of staphylococcus aureus and several gram negative bacteria colonised the burns. After the second week the patient appeared toxic and she developed intermittent pyrexia. Dehydration and hypotensive episodes responded to energetic intravenous fluid therapy. Repeated blood cultures were negative. Antibiotic drug therapy, assessed on bacterial susceptibilities, was changed from time to time. After several operative skin-grafting procedures the patient's condition slowly improved and she was discharged from hospital two months after the accident.

CASE 18

Patient S.W., female, age 66 years.

Diagnosis: Burns. (40% body surface).

Operation: 1) Skin grafting operations.
2) Bilateral common femoral vein ligations.

Clinical Summary: This 66 year-old widow (a sister of L.R., Case 17,)was involved in the same gas explosion accident as her sister and sustained burns. (40% body surface).

The initial progress of the patient was satisfactory although an elevation of the blood urea nitrogen did not fall to normal until the 12th day after the burn injury. Staphylococcus aureus, pseudomonas aeruginosa and Klebsiella-Aerobacter organisms were the main bacteria isolated from the necrotic skin. Multiple skin grafting operations were carried out.

Five weeks after the accident the patient became hypotensive and appeared to have congestive cardiac failure. Subsequently she had sudden left pleuritic pain associated with left calf tenderness. The blood lactic dehydrogenase (L.D.H.) rose to 174 units per cent. Bilateral common femoral vein ligation was performed. Serial blood cultures were sterile. Digitalis and diuretic therapy was instituted and the patient's cardio-respiratory state improved.

As the grafted areas healed, infection subsided slowly. The patient's general condition improved gradually and she was allowed to leave hospital three months after the burns accident.

CASE 19

Patient F.J., male, age 65 years.

Diagnosis: Burns (25% body surface).

Operation: 1) Tracheostomy.
2) Skin-grafting procedures.

Clinical Summary: This patient threw petrol on to a garden fire to make it burn better and sustained flash burns. He was admitted to hospital where he appeared to have 25% body surface burns. As the patient's face was badly burned and as he had laryngeal stridor tracheostomy was performed shortly after his admission to hospital.

At first the burned surfaces were sterile. Subsequently B. subtilis and B. cereus were isolated and later staphylococcus aureus and pseudomonas aeruginosa were isolated from the burned surfaces. Three weeks after the initial injury excision of sloughs and skin grafting were carried out. The following day the patient had a shaking chill and a tachycardia of 160 per minute. Arterial blood pressure which had been stable at 180/80 mm.Hg. fell to 100/60 mm.Hg. and the temperature rose to 104.4°F. An electrocardiogram and an x-ray of chest were both normal and a blood volume estimation was 300 ml. greater than the expected value. A pure culture of staphylococcus aureus was isolated from three blood cultures. The staphylococcus appeared to belong to the same phage type as the staphylococcus isolated from the patient's nose, hands and burned surfaces. (Phage Type U.C. 18).

With intravenous fluid therapy and intravenous and topical antibiotic therapy the patient's condition rapidly improved. Urinary output was maintained at a satisfactory level and the blood urea nitrogen level was not raised.

As the autogenous grafts epithelialised the burned areas the local sepsis subsided, and the patient appeared less toxic. There were no subsequent rigors or hypotensive attacks and the patient's temperature returned to normal.

CASE 20

Patient R.W., male, age 52 years.

Diagnosis: Burns (60% body surface).

Operation: Debridement and skin grafting.

Clinical Summary: This patient sustained severe third degree burns when he was sprayed with burning lighter fuel while igniting a picnic stove. On admission to hospital his haematocrit was 60 per cent, white blood count was 10,000 per c.mm. Blood urea nitrogen was 73 mgms. per 100 ml. and serum electrolytes were within normal limits. He was given intensive electrolyte and colloid intravenous infusions and with the help of 1000 ml. 10% mannitol, urinary output improved and the blood urea nitrogen concentration fell. The haematocrit fell from 60 to 45 per cent. Later when the haematocrit fell further to 29 per cent a whole blood transfusion was given.

On the sixth day the patient was eating well. Electrolytes were normal. Blood urea nitrogen was 26 gms. per 100 ml. Haematocrit was 35 per cent and white blood count was 12,000 per c.mm. Temperature fluctuated between 100-101°F.

Operative debridement and skin grafting were carried out on the seventh hospital day. Immediately post-operatively the patient was hypotensive. Blood pressure was 80/50 mm.Hg. and although massive blood transfusion (4 litres) was given, central venous pressure remained low. The haematocrit was 25 per cent. In the early morning of the second post-operative day the patient again sustained a rapid fall in blood pressure. The systolic arterial blood pressure was below 70 mm.Hg. and urinary output diminished.

Blood transfusion, steroid therapy, oxygen administration and vasopressors were given. The patient became comatose and died on the second post-operative day.

From the blood cultures, taken immediately after the operation and on the first post-

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operative day, pseudomonas aeruginosa was isolated. This organism was also the dominant species cultured from the burn surfaces.

Post-Mortem Findings.

There were extensive thermal burns (3rd degree) involving approximately 60% body surface. Pseudomonas infection was widespread.

There was a recent acute myocardial infarction. The kidneys were swollen and pale - the site of acute tubular necrosis. Acute tracheobronchitis and petechial haemorrhages of the pleura were found. Multiple acute ulcers of oesophagus and stomach were present. There was acute congestion of the liver and spleen and focal fat necrosis of the pancreas. Both adrenal glands showed diffuse hyperplasia.

CASE 21

Patient C.A., male, age 36 years.

Diagnosis: Burns (50% body surface).

Operation: Skin grafting (Multiple procedures).
Drainage of empyema of chest.

Clinical Summary: This 36 year-old man was covered with burning petrol from an exploding engine and sustained 50% body burns. (45% body surface being third degree burns.) The majority of the anterior and posterior portions of the trunk, upper arms and neck were included in the burn area. The initial response was good and by the 5th hospital day the patient was eating regularly.

On the eleventh hospital day 15% body surface burn was debrided and grafted. At this time cultures from the burn surfaces grew mainly alcaligenes faecalis and Klebsiella-Aerobacter species. A further 7% burn area was grafted on the 17th day. Following this procedure the blood urea nitrogen was slightly raised but urinary output was normal. On the evening of the third post-operative day, however, the patient became drowsy. The lethargy increased and the following morning the patient was in coma.

The blood sugar concentration was found to be 1660 mgms. per 100 ml. Blood urea nitrogen was 68 mgms. per 100 ml., serum sodium, potassium and chloride were 160 mEq., 4.6 mEq. and 120 mEq. per litre respectively. The CO_2 combining power was 20.2 millimoles per litre and the serum osmolarity was 459 millimoles per litre. The urine contained a large amount of sugar but no ketones.

Vigorous insulin and fluid therapy rapidly improved the patient's condition. At this time several blood cultures grew alcaligenes faecalis.

Eleven days after the acute hyperglycaemic episode the patient's blood sugar levels were normal and insulin was discontinued. Urinary excretion

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of 7-hydroxy-corticoids which had been high throughout, reached a peak value at the onset of the hyperglycaemic coma when the 24 hour urinary excretion was 34.7 mgms.

Following the coma the patient became more febrile and a right lobar pneumonia was complicated by a right-sided empyema. The right pleura was drained and alcaligenes faecalis, Escherichia coli and Klebsiella-Aerobacter organisms were isolated from the pus.

At the end of the second month after a further debridement and grafting operation the patient had several fainting spells and then became hypotensive and comatose. Blood sugar estimation was 17 mgms. per cent. The patient had received no insulin in the preceding 38 days. Measurement of the serum insulin-like activity was very low (less than 31 micro-units per ml.). Blood sugar rapidly stabilised with glucose therapy and there were no subsequent episodes.

The patient's further progress was steady but slow. The burned areas gradually healed and the patient was discharged home six months after the original accident.

CASE 22

Patient M.N., female, age 54 years.

Diagnosis: Burns (70% body surface).

Operation: Excision of necrotic skin and homologous skin grafting.

Tracheostomy.

Clinical Summary: This 54 year-old married woman sustained grave third degree burns (70% body surface) when a falling lighted cigarette ignited a flannel duster and the patient's clothing.

Initially the patient was given antibiotics, anti-tetanus serum, and an intravenous infusion of electrolyte solutions, dextran and whole blood. The patient was nursed on a Stryker frame with a plaster cast support. There was intermittent pyrexia. The predominant organism infecting the burned surfaces was Proteus vulgaris although staphylococcus aureus, pseudomonas aeruginosa and Klebsiella-Aerobacter species were also isolated from some of the burned areas. On the seventh day after the accident cadaveric skin homografts were applied to excised burned areas and further grafting was carried out on the eleventh day. The wounds however became progressively more septic. The temperature became elevated. Blood cultures on three successive days grew proteus vulgaris. The patient developed lethargy and for the last two days before death was hypotensive and semi-comatose. Tracheostomy performed the day before death was not helpful.

Post-Mortem Findings.

Deep thermal burns (70% body surface), partially replaced with homografts, were necrotic and septic. Evidence of generalised systemic sepsis was found — acute splenitis, tracheobronchitis, bilateral bronchopneumonia and haemorrhagic necrosis of the adrenal gland (especially the zona reticularis). The liver showed passive hyperaemia and there were mucosal haemorrhages in the stomach and urinary bladder.

CASE 23

Patient F.G., male, age 78 years.

Diagnosis: Burns (30% body surface).

Operation: Debridement and skin grafting.

Clinical Summary: This elderly man stated that while sitting in a chair lighting a pipe, the match dropped into his lap igniting his clothes. On admission to hospital shortly after the accident he was noted to have a third degree burn over the entire anterior chest and abdomen. Both upper arms were involved and there was partial thickness burns of the hands. Haematocrit was 38 per cent. White blood count was 21,000 per c.mm. and blood urea nitrogen was 14 mgms. per 100 ml. An electrocardiogram revealed a possible old antero-septal myocardial infarct.

The burn was treated in an open fashion. Antibiotics and fluid replacement therapy were commenced and on the ninth hospital day the patient had an excision and skin-grafting operation. 95% of the autogenous grafts were successful. On the nineteenth hospital day however, the patient became progressively hypotensive. Heart rate was regular (64 per minute). The haematocrit fell from 30 to 26 per cent. The patient appeared dehydrated and he subsequently became oliguric with only 45 ml. urine being produced in 8 hours. Fluid therapy overcame the dehydration but the oliguria persisted. At this time occult blood was present in the stools. A chest film revealed an infiltrate and possible pleural effusion on the right side. Bronchoscopy was performed and Klebsiella-Aerobacter organisms were isolated from the aspirated pus. Despite therapy the patient became progressively more hypotensive and after lapsing into coma, he died three weeks after the burn accident.

Post-Mortem Findings.

At autopsy the burned area was excised and covered with healthy skin grafts. The significant pathological findings were in the respiratory system. Both lungs showed evidence of chronic bronchiectasis with superimposed bilateral bronchopneumonia, the bronchi containing abundant secretion. The coronary vessels were widely patent. There was hepatic congestion and mucosal petechiae in the stomach. The urinary bladder showed erosions and there was arteriolar nephrosclerosis.

CASE 24

Patient B.W., (4-26-45), female, age 26 years.

Diagnosis: Septic abortion.

Operation: 1) Subtotal hysterectomy and right oophoro-salpingectomy.

2) Laparotomy and ligation of bleeding vessel.

Clinical summary: The patient was a 26 year-old married woman who was admitted to hospital following a septic criminal abortion. She had five previous pregnancies. The last menstrual period was 3 to 4 months earlier. Two days before admission the patient had soap suds introduced into the uterus to produce an abortion. In the evening she developed lower abdominal pain and diarrhoea, followed by shaking chills. The following day she had an incomplete abortion. The abdominal pain and fever increased and she was admitted to her local hospital. There she was found to have a temperature of 105°F, peritonitis, hypotension and anuria and was transferred to the Peter Bent Brigham Hospital, Boston.

On admission her blood pressure was 80/40 mm.Hg., her pulse rate was 140 per minute and her respiratory rate was 20 per minute. The patient appeared to be acutely ill and toxic. She complained of generalised abdominal pain. There was slight icterus of the skin and sclerae. Chest examination revealed no abnormality. The abdomen showed an increased girth and the uterus was palpable to just below the umbilicus. There was generalised abdominal tenderness. The uterus was exquisitely tender and hard and crepitus could be elicited on palpation. A straight x-ray film of the abdomen showed concentric gas shadows in the uterus, very suggestive of a clostridial infection. (Figure 24).

Initial Laboratory Findings.

Urine: very scanty and dark brown.

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Haematology: Haematocrit 26 per cent.
Leucocyte count 19,500 per c.mm.
Platelet count 44,000 per c.mm.
Clotting time 15 minutes.
Fibrinogen 100 mgms. per cent.
Serum haemoglobin 227 mgms. per cent.
Serum methaemoglobin 0.4 per cent.
Sulphaemoglobin less than 0.1 per cent.

Blood Chemical Analyses: Blood urea nitrogen 58 mgms. per 100 ml.
Serum bilirubin 2.3 mgms. per 100 ml.

The initial problem was septic abortion with peritonitis, haemolysis and anuria. Investigation was carried out to see if ureteric obstruction was present. Cystoscopy and retrograde pyelograms were normal. At laparotomy the peritoneal cavity contained sero-sanginous fluid. The fundus of the uterus was black and necrotic. Cultures of the peritoneal fluid and of the uterus, grew Cl. perfringens, E. coli, and Klebsiella-Aerobacter organisms.

Blood cultures on the first three consecutive days were all positive for gram-negative organisms of the Klebsiella-Aerobacter group. All subsequent blood cultures were sterile.

Supracervical hysterectomy and right oophoro-salpingectomy were carried out. Antibiotics included penicillin and streptomycin. Later chloramphenicol was used.

After the patient's return from the operating room it was considered that hyperbaric oxygen therapy might be helpful and she was transferred to the hyperbaric chamber and treated under light general anaesthesia for 2 hours at a pressure of 30 pounds per square inch. During this time peak arterial pO_2 was 1150 mm.Hg.; pCO_2 was 34 mm.Hg. and pH was 7.61.

On the second hospital day the patient appeared to have improved. With intravenous vasopressors

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(noradrenaline) a systolic blood pressure of 100 mm.Hg. was maintained. The patient remained anuric and an arterio-venous plastic tube shunt was inserted into the left arm. Haemodialysis, using the twin-coil kidney, was carried out three times over the next nine days. On the 10th post-operative day, oozing from the abdominal wound became much more marked and further operative exploration was necessary. Arterial bleeding found in the necrotic tissue of the right parametrium was controlled by suture. There was a serious thrombocytopenia and only on the patient's 15th hospital day did the platelet count rise above 50,000 per c.mm. It subsequently rose to above 110,000 per c.mm. The patient remained almost completely anuric for two weeks. From the 15th day urinary output commenced and associated with an initial post-anuric diuresis there was an accompanying fall in the blood urea nitrogen level. Figure 25 demonstrates the patient's clinical course.

A monilial infection of alimentary, urinary, and respiratory tracts, occurring later in the patient's illness, responded to nystatin therapy.

COMMENT - The patient illustrated the problems associated with severe sepsis from mixed gram-positive and gram-negative infection with hypotension and a low flow state, oliguria and coagulation defects. A satisfactory response was achieved by a combination of surgical treatment, hyperbaric oxygen therapy, haemodialysis, intermittent brief use of vasopressor substances, blood and platelet transfusions and intensive antibiotic therapy.

CASE 25

Patient G.L., female, age 35 years.

Diagnosis: Endometriosis.

Operation: 1) Hysterectomy.
2) Drainage of Pelvic Abscess.

Clinical Summary: The patient, a 35 year-old married woman had four previous admissions to hospital for recurrent respiratory disease (bronchitis and pneumonia). Six days prior to admission to the Peter Bent Brigham Hospital, the patient had a hysterectomy for endometriosis performed at another hospital. On the first post-operative day the patient was noted to have pulmonary congestion and a pyrexia of 101°F. Antibiotic therapy was commenced. During the following few days there was increasing abdominal distension and the patient's temperature rose to 104°F. A diagnosis of pelvic abscess was made and gastric aspiration was commenced. Urinary output was 600-700 ml. per day. The haemoglobin fell from 14 G. per cent to 9.4 G. per cent post-operatively.

On the 6th post-operative day the patient was transferred to the intensive care unit at the Peter Bent Brigham Hospital. On admission her temperature was 103.4°F., respiratory rate 40 per minute, pulse 120 per minute and blood pressure 100/80 mm.Hg. Coarse rhonchi were present throughout the lungs. The abdomen, which was grossly distended was silent to auscultation. X-ray of chest showed a collapsed left lower lobe of lung. On the 9th post-operative day the patient had an infected pelvic haematoma drained. In view of the increasing pulmonary upset a tracheostomy was carried out and intermittent tracheal aspiration was performed. Further x-rays showed bilateral basal consolidation of the lung fields. The pyrexia (104°F) persisted. With assisted respiration the patient's arterial pO_2 rose to 225 mm.Hg. when breathing 100% oxygen.

Dark foul-smelling fluid drained from the vagina. Pulmonary oedema responded to treatment by

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Phlebotomy of 300 ml. blood. A central venous pressure of 10-12 cms. water was recorded and there was no subsequent rise in venous pressure.

The patient's abdominal distension persisted and her pulmonary condition continued to give anxiety. On the 16th post-operative day after the hysterectomy, the patient became acutely cyanotic with marked respiratory distress and hypotension. Tracheal suction produced copious purulent secretions. Controlled respiration with 100% oxygen was carried out. Later an x-ray chest showed a right-sided pneumothorax. A pleural water-seal drain caused only slight improvement. Arterial pO_2 fell to 40 mm.Hg., hypotension was unresponsive and death occurred on the evening of the 16th day.

Laboratory Data on day of Death.

White blood count - 19,300 c.mm.

Prothrombin concentration - 36% of normal.

Blood urea nitrogen - 14 mgms. per 100 ml.

Blood Gas Estimations	(1) 8 a.m.	(2) 10 p.m. (Death at 10.30 p.m.)
pH	7.02	6.93
pO_2	43 mm.Hg.	15 mm.Hg.
pCO_2	70 mm.Hg.	90 mm.Hg.
CO_2 content(plasma)	19 mM/litre.	21 mM/litre.
Serum lactate		29.8 mMols./litre.
Serum pyruvate		0.82 mMols/litre.

On day of death patient had a severe combined respiratory and metabolic acidosis.

Post-Mortem Findings.

1. Generalised peritonitis with fibrinous adhesions.
2. Hepatomegaly (wt 2170 G) with biliary stasis - jaundice.
3. Superficial ulceration of oesophagus, stomach and duodenum.
4. Cystitis.
5. Acute laryngo-trachea-bronchitis.
   Bilateral bronchopneumonia and consolidation.
   Partially organised bilateral pulmonary thrombo-emboli.

CASE 26

Patient H.F., male, age 83 years.

Diagnosis: Urethral Stricture. (Post perineal prostatectomy).

Operation: Urethral bouginage.

Clinical Summary: 17 years previously the patient had a perineal prostatectomy for benign prostatic hypertrophy. Four years before his present admission to hospital the patient had developed a urethral stricture and had attended from time to time for urethral dilatation. Since the last bouginage 2 months previously the patient had intermittent haematuria, increased frequency and hesitancy of micturition.

Urethral dilatation was attempted under local anaesthesia and was unsuccessful. A urethrogram showed some extravasation of dye. Later the same evening the patient had a shaking chill, and was found to have pulmonary oedema. Blood pressure was 60/40 mm.Hg. and temperature was 105°F. The patient was treated with morphia, aminophylline, phlebotomy, oxygen, chloramphenicol and noradrenaline. Large doses of steroid were given by continuous intravenous infusion over the next 48 hours. Suprapubic cystomy was performed. Two days after the onset of symptoms, the white blood count was 40,000 per c.mm. and the blood urea nitrogen was 89 mgms. per cent. Positive blood cultures were not obtained but the urine grew E. coli and Klebsiella-Aerobacter organisms.

After making slow progress over the next two weeks the patient then developed a further attack of pulmonary oedema. He became cold and sweating and developed marked ventricular tachycardia. On this occasion the patient was unresponsive to energetic therapy and died.

Permission for post-mortem examination was not granted.

CASE 27

Patient F.L., male, age 54 years.

Diagnosis: Adenocarcinoma of Prostate.

Operation: Total perineal prostatectomy.

Clinical Summary: One month before admission to hospital, at a medical examination for business purposes the patient was found to have a firm nodule in the prostate. He had occasional dysuria. There was no haematuria or back pain. The patient was admitted to hospital for investigation.

Initial Laboratory Findings.

Urine - mid-stream specimen - sterile.

Blood urea nitrogen - 18 mgms. per 100 ml. blood.

Serum, calcium, phosphorus and phosphatase were normal.

White blood count was 6,600/c.mm. (78% neutrophils).

Haematocrit 45.5 per cent.

X-ray of Chest, Lumbar Spine and Pelvis were normal.

Intravenous pyelography showed normally functioning kidneys.

The bladder outline was normal but a post-micturition cystogram showed some residual urine.

An electrocardiogram showed left ventricular hypertrophy.

On the 3rd hospital day, total perineal prostatectomy was performed. A biopsy of prostate taken at the time of operation confirmed the presence of adenocarcinoma. Later histological examination of the whole specimen demonstrated adenocarcinoma involving perineural lymphacics, peri-prostatic capsule and seminal vesicles. During operation three bottles of blood were given.

The patient's post-operative progress was at first satisfactory.

On the 6th post-operative day the patient developed a shaking chill and his temperature rose to 104.4°F. There was some discharge from perineum.

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Case 27 (contd.)

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The catheter drained urine satisfactorily. Blood pressure which had been steady at 190/100 mm.Hg. fell to 108/60 mm.Hg.

Urine and blood cultures on the 6th and 7th post-operative days grew E. coli. Later blood cultures were sterile.

Blood urea nitrogen never rose above 30 mgms. per cent and daily urinary output remained satisfactory. The patient was given chloramphenicol and streptomycin. In the following days the temperature gradually fell. The patient was allowed home on the 20th post-operative day. Urinary control was satisfactory when the patient was discharged from hospital.

CASE 28

Patient W.K., male, age 24 years.

Diagnosis: Renal Failure from chronic glomerulonephritis.

Operation: Bilateral nephrectomy and splenectomy with renal homotransplantation.

Clinical Summary: This 24 year-old man who had chronic renal failure secondary to chronic glomerulonephritis, had a renal homotransplantation with his mother as donor. Bilateral nephrectomy and splenectomy were performed at the same operation. Early rejection of the homografted kidney was overcome by using azaserine, actinomycin C and prednisolone. The patient was discharged from hospital 5 weeks after the operation and at that time maintenance immuno-suppressive drug therapy consisted of 100 mgms. prednisolone and 200 mgms. asathioprine (Imuran) daily. Three weeks later the patient woke up with sudden severe pains in both knees. He was re-admitted to hospital. Temperature on admission to hospital was 102°F. White blood count was 8,200 per c.mm. and a platelet count was 285,000 per c.mm. X-rays of both knees showed no abnormality. Blood urea nitrogen was 16 mgms. per 100 ml. and urine findings were normal.

A few days later the patient had a shaking chill and his temperature rose to 105°F. He had frequent loose bowel movements. Serial blood cultures were negative and no pathogens were cultured from the stool.

The patient's subsequent hospital course lasted twenty days until the time of death. He had daily spikes of fever (103-105°F). During the last week the patient's temperature never fell below 102°F. Careful examination failed to detect any localised site of infection.

In addition to the diarrhoea the patient developed marked dysphagia. Barium swallow revealed no abnormality. The serum bilirubin rose to 3.2 mgms. per 100 ml. Abdominal distension became

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progressive and the patient had severe enterocolitis. He became hypotensive. Vasopressor drugs were of temporary value. There was marked metabolic acidosis, the blood pH falling below 7.0. Further resuscitation was impossible and the patient died 2 months after kidney homotransplantation operation.

Post-Mortem Findings.

Staphylococcus aureus was isolated from the deeper part of the operation wound. The homotransplanted kidney was healthy and satisfactory. The liver was the site of severe fatty changes with numerous gas pockets apparently from clostridial infection. From liver slices E. coli and alpha-haemolytic enterococci were cultured. E. coli was also isolated from post-mortem heart blood. There was peritonitis with dilatation of small and large intestine. No perforation was found in the alimentary tract.

Confluent bronchopneumonia was present associated with bilateral purulent pleural effusions.

CASE 29

Patient M.D., male, age 24 years.

Diagnosis: Chronic glomerulonephritis with renal failure.

Operation:
1) Homotransplantation of kidney (cadaver kidney)
2) Appendicectomy for acute appendicitis.
3) 2nd Homotransplantation of kidney.
4) Evacuation of Ischio-rectal abscess.

Clinical Summary: This 24 year-old man had chronic azotaemia associated with chronic glomerulonephritis. He had long term intermittent dialysis. At first repeated peritoneal dialysis was performed but later on account of peritoneal sepsis and adhesions haemodialysis was undertaken. In April, 1962 a kidney from a 32 year-old male who died during aortic valve replacement was transplanted into the patient's right iliac fossa. Long term chemotherapy to prevent immunological rejection of the donor kidney was employed using azathioprine (Imuran) and prednisolone. The patient remained in satisfactory health for the following 20 months at which time he was re-admitted to hospital with a temperature of 103°F and acute lower abdominal pain. These symptoms were due to acute appendicitis and appendicectomy was performed. In the following weeks signs of rejection of the donor kidney became marked and to overcome the renal insufficiency a second homotransplantation was carried out. A kidney removed during operation for relief of hydrocephalus in a child (Matson procedure - ventricular drainage via plastic tube into ureter) was transplanted into the patient's left iliac fossa, the failing first transplanted kidney on the right side being undisturbed.

Following the operation the patient developed a persistent wound infection. Pseudomonas aeruginosa, Escherichia coli and staphylococcus aureus were isolated.

The patient had a remittent temperature and later E. coli was isolated from blood cultures. A large ischio-rectal abscess in the perineum was evacuated, pseudomonas aeruginosa and staphylococcus epidermidis

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being cultured from the pus.

A leucocytosis between 20,000 and 42,000 per c.mm. had been maintained for several weeks. Multiple septic foci occurred on the legs. Jaundice and hypotension finally supervened and the patient died six months after the second renal homotransplantation (26 months after the initial transplantation).

Post-Mortem Findings.

The right iliac fossa kidney (1st donor transplant) had been destroyed and was surrounded by dense adhesions. The left donor kidney had fistulae and abscesses. Clumps of gram-negative rods were present in the liver which was enlarged and congested. Linear erosions were present in the oesophagus and multiple superficial ulcers were found in the stomach and duodenum. Multiple thrombi or emboli with small abscesses were scattered throughout both lungs.

CASE 30

Patient W.J., male, age 46 years.

Diagnosis: Polycystic kidney disease. Renal failure.

Operation: Bilateral Nephrectomy, splenectomy and renal homotransplantation.

Clinical Summary: This 46 year-old man had a ten year history of progressive renal failure, uraemia and hypertension associated with bilateral polycystic kidneys.

He had been maintained on a chronic dialysis regime until renal homotransplantation was performed. The donor kidney was from the patient's wife who shared all but two minor blood groups. At operation bilateral huge polycystic kidneys were removed along with the spleen.

After the transplantation operation the patient's progress was good. Blood urea nitrogen fell to 20-30 mgms. per 100 ml. Immuno-suppressive chemotherapy was maintained with a daily dose of 200 mgms. azathioprine (Imuran) and 100 mgms. prednisolone.

Three months after the operation the patient developed a febrile illness and a cough. X-ray demonstrated a poorly circumscribed lesion in the right upper lung field. It was considered that the lesion of the lung might have been tuberculosis, sarcoid, cocidioidomycosis or histoplasmosis. Bronchoscopy was performed with negative results.

Low grade fever persisted for 2-3 weeks at which point the patient developed a sudden shaking chill and his temperature rose to 103°F. Blood cultures at this time were sterile. White blood count was 14,000 per c.mm., platelet count 280,000 per c.mm., haematocrit 35 per cent, and blood urea nitrogen had risen to 82 mgms. per 100 ml. Immuno-suppressive drugs had to be continued as there was evidence of rejection of the kidney. The donor kidney in the right iliac fossa was enlarged and tender and the

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blood urea nitrogen had risen. The patient's condition continued to deteriorate. He looked pale and toxic and the pyrexia persisted. Although the platelet count was maintained at a normal level subsequent white cell counts revealed a leucopenia (the terminal white blood count being in the 1,500-2,500 per c.mm. range).

Hypotension associated with marked respiratory distress developed. The pyrexia increased and blood cultures became positive (E. coli). Further deterioration took place and the patient died 15 weeks after the renal homotransplantation operation.

Post-Mortem Findings.

There was active rejection of the homotransplanted kidney. A large abscess was found in the right lung and E. coli was cultured from it. There was a terminal massive bronchopneumonia. Mucosal petechiae and haemorrhages were found in the stomach, duodenum and small bowel. The parathyroid glands were enlarged.

CASE 31

Patient J.B., male, age 58 years.

Diagnosis: Carcinoma of liver.

Operation: Homotransplantation of liver.

Clinical Summary: This 58 year-old man who had a long history of alcoholism was admitted to hospital with abdominal pain and weight loss. He had never suffered from haematemesis, ascites or convulsions.

Admission examination revealed a fine, nodular liver which was considerably enlarged and which contained discrete hard masses. Rectal examination and sigmoidoscopy were negative. Barium meal and barium enema examinations were also negative and liver function tests were within normal limits. Cholecystography was normal and x-ray of chest and skeleton showed no abnormality.

At laparotomy, an enlarged, fibrosed liver was found to contain multiple tumour deposits. Careful examination of the abdominal cavity revealed no evidence of primary tumour elsewhere. A liver biopsy was taken and the abdomen closed. The histological report of the biopsy confirmed the presence of adenocarcinoma of liver and suggested that the tumour was metastatic to a carcinoma of stomach, colon, pancreas or lung. Chemotherapy was commenced with 'Cytoxan' but one week later a suitable liver became available and the patient underwent liver homotransplantation.

The donor was a 35 year-old policeman who had been shot through the head and who died almost immediately after admission to hospital.

At operation the patient's liver was removed and the donor liver transplanted. The circulation which was established appeared satisfactory. The total donor liver circulation occlusion time was 2 hours, 50 minutes. Immuno-suppressive drug therapy included azathioprine (Imuran), azaserine and cortisone.

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On the day following operation, blood volume estimation, blood urea nitrogen and serum electrolytes were normal. Liver function tests were - bilirubin 3.8 mgms. per cent, alkaline phosphatase 0.9, S.G.O.T. 960 units, lactic acid dehydrogenase (L.D.H.) 620 units, total protein 4.7 G. per cent and albumen 3.5 G. per cent.

During the next seven days the patient developed a marked thrombocytopenia and liver function progressively deteriorated. By the tenth post-operative day the patient had lapsed into coma and the arterial blood pressure fell progressively and was unresponsive to vasopressor drug therapy. Just before death liver function tests demonstrated gross liver failure (bilirubin 42 mgms. per cent, S.G.O.T. 3,000 units and L.D.H. 3,150 units).

Blood cultures had remained sterile but bacteriological specimens from the wound and T-tube bile drainage contained staphylococcus aureus.

Post-Mortem Findings.

There was generalised acute sepsis. Bacteria were found in the liver, heart, lungs and kidneys. Microabscesses were found in the heart muscle and there was bilateral bronchopneumonia.

There was massive hepatic necrosis with thrombosis of the hepatic vessels. Blood was present in the stomach, small and large bowel. Multiple superficial recent gastric and pyloric ulcers were found. A small primary carcinoma was found in the sigmoid colon. The kidneys were the site of acute tubular damage.