EVENTS

NU SIGMA NU LECTURE
March 7, 1956

MECHANISMS OF PULMONARY EDEMA. By Mark D. Altschule, Harvard Medical School, Boston, Massachusetts.

Many discrepancies between the left ventricular failure hypothesis of pulmonary edema and clinical observations suggest that this mechanism is not the entire explanation of this common clinical syndrome. For instance, pulmonary edema is less frequent in the aortic stenosis than in aortic insufficiency, yet the strain on the left ventricle is as great in the former. Again, the prolonged left ventricular strain of chronic hypertension rarely produces edema in contrast to its common occurrence in sudden hypertension. In the left-sided failure theory the rise in pulmonary capillary pressure determines edema formation. In mitral stenosis, however, pulmonary capillary pressures of 60 mm. Hg probably exist, yet in its uncomplicated form this clinical entity remains comparatively free from pulmonary edema.

An alternative explanation of the experimental and clinical observations takes into account the cumulative effects of many mechanisms. These may conveniently be divided into those which increase the amount of transudate, those which inhibit the reabsorption of the fluid, and those which tend to increase the total body water. Decreased plasma protein levels, increased pulmonary blood flow and raised capillary pressure certainly increase transudation. Epinephrine injection in animals can cause pulmonary edema; exponents of the left ventricular failure theory offer this as inferential evidence that hypertension in man may cause enough left-sided strain to produce edema. The isolation of abundant histamine from animal and human lung tissue provides a more logical relationship. Epinephrine is known to release histamine, and, experimentally, histamine can be shown to cause venous constriction and, perhaps, increased capillary permeability. Both of these latter may contribute to edema formation in man.

Pulmonary edema secondary to hypothalamic lesions in cats and following skull fractures in man may indicate central nervous and reflex mechanisms. The laboratory observation that sudden carotid sinus distension produces pulmonary venoconstriction provides a good explanation for the increased incidence of pulmonary edema in aortic insufficiency and acute hypertension. In chronic hypertension and aortic stenosis this distension is neither so sudden nor so great. Bronchospasm, in an unexplained manner, also contributes to transudate formation.

The experiments of Drinker indicate the highly important rôle of pulmonary lymphatics in reabsorption of pulmonary transudates. General cardiac decompensation manifest by increased systemic venous pressure may contribute to edema formation as much by decreasing lymphatic flow and thereby decreasing transudate reabsorption as by increasing pulmonary capillary pressure. The accumulation of excess body water, as in anemia, nephrosis, or beri-beri, also contributes to edema formation.
These and other mechanisms may be involved; no one factor is enough but the combined effects of many probably tip the balance in favor of pulmonary edema. Fortunately, treatment of this condition differs little no matter which explanation one adopts. Acceptance of this multi-factorial reasoning does, however, militate for the use of digitalis only in those cases of pulmonary edema in which heart failure plays a significant rôle.

R. I. B.

YALE MEDICAL SOCIETY
March 12, 1956

STUDIES IN EXTRACORPOREAL CIRCULATION WITH AN ARTIFICIAL HEART LUNG APPARATUS. By Bert K. O. Kusserow, Research Fellow in Pathology, Yale University School of Medicine.

The heart and lungs may be temporarily excluded from the circulation, either totally or partially, by the substitution of an apparatus which consists of a pumping component and an oxygenating component. Blood is withdrawn from the subject's venous system, delivered to the oxygenator, and returned to the arterial system by a balanced output double perfusion pump. The latter is a single diaphragm, double-chambered pumping unit which functions simultaneously as withdrawal and return pumps whose outputs are identical. This characteristic prevents any imbalance in the subject's blood volume during perfusion. The pump valves operate on the principle of modified stopcocks.

Oxygenation and carbon dioxide removal are effected by the injection of tiny oxygen bubbles directly into the blood as it courses through the oxygenating component. The bubbles are produced by passing oxygen through a microporous porcelain filter. Excess oxygen and carbon dioxide are removed from the blood by the action of a constant delivery, slowly spinning centrifuge.

The apparatus has substituted for the respiratory, or cardiorespiratory, function of sixteen dogs for periods up to forty-three minutes. Nine of the last thirteen dogs have been permanent survivors.

B. K. O. KUSSEROW

CHROMOSOMAL SEX DIFFERENTIATION BY CYTOLOGICAL TECHNIQUES. By Walter Herrmann, Department of Obstetrics and Gynecology, Yale University School of Medicine.

Chromosomal sex may be determined from cheek scrapings. A discoid intranuclear chromatin mass adjacent to the nuclear membrane appears in 0-4 per cent of the cells of men and 10-32 per cent of the cells of women. In one patient with adrenal hyperplasia and two with gonadal dysgenesis, anatomical sex was shown to differ from chromosomal sex.

J. P. G
PHYSIOLOGY SEMINAR

March 12, 1956

Physiological Changes in the Circulation at Birth. By Geoffrey S. Dawes, Director of the Nuffield Institute for Medical Research, Oxford, England.

The fetal circulation of sheep, obtained by cesarean section, has been studied for the purposes of elucidating the factors regulating blood flow through the placenta, the changes in blood flow through the lungs at birth, the closure of the ductus arteriosus, and the relationship of oxygen consumption to the partial pressure of oxygen in the blood.

The autonomic nervous system rather than the placenta appears to be responsible for controlling the placental blood flow. Full-term pregnancy in sheep lasts 147 days. Between the 90th and 100th day, the autonomic nervous system begins to function. At this time, but not before, the fetus responds to anoxia by an increase in the blood pressure; this, in turn, increases the blood flow through the umbilical vessels. The response to anoxia increases progressively as the fetus approaches birth. These relationships are species specific and are not applicable to the rabbit and certain other species in which the autonomic nervous system is poorly developed before birth.

During the fetal period, only ten per cent of the ventricular output is pumped through the lungs. At birth the pulmonary blood flow increases ten-to twenty-fold. The mechanism responsible for this change is primarily mechanical, rather than nervous or humoral. Perfusion experiments on isolated fetal lungs indicate that distention of the lungs with a gas is of "paramount importance." While the density of the gas may produce variations in the pulmonary resistance and blood flow, this appears to be a minor factor.

Two mechanisms have been elucidated for the constriction of the ductus arteriosus. The criteria employed for ductus closure in the experiments to be discussed include the disappearance of the characteristic presystolic murmur, electrocardiographic reversion to normal pattern, and actual reduction in the external diameter of the ductus arteriosus. In one group of experiments, closure of the ductus is obtained by raising the oxygen saturation in the carotid arteries from that normally present (72%-80%) to about 95%. In another series of experiments, closure is obtained by subjecting the fetus to a short period of asphyxia. This procedure is attained by an increase in blood pressure which is mediated by the autonomic system (as discussed above). The blood pressure effect is apparently of significance inasmuch as the sympathetic amines also produce constriction of the ductus arteriosus. It is of interest that while the rôle of an increased blood oxygen saturation may be difficult to explain in ductus closure, the rôle of asphyxia may be related to the period during which the umbilical cord is separated from the placenta at birth.

In the fetal sheep, a reduction in the oxygen saturation of blood is attended by a corresponding reduction in oxygen consumption. While
studies in human babies and in puppies show a similar relationship, it has been known in the past that the adults of these species do not demonstrate any relationship between oxygen consumption and blood oxygen saturation level. The significance of this phenomenon is, as yet, a matter of conjecture; it is of particular interest in relation to the very low values of oxygen saturation normally present in the human fetus.

STANLEY HARRIS

ALPHA OMEGA ALPHA ANNUAL LECTURE
March 13, 1956

AN EXPERIMENTAL ANALYSIS OF THE DEFENSE OF THE HOST IN ACUTE BACTERIAL PNEUMONIA. By Barry Wood, Johns Hopkins University, Baltimore, Maryland.

Aspects of the problem of host defense in pneumococcus infection include: histopathology of lesion, inflammatory response, operation of cellular defense, lines of cellular defense, and relationship of cellular defense to curative action of penicillin.

The lesion can be divided into several zones. The outermost is the edema zone in which bacteria multiply rapidly. Central to this are the zones of early and late consolidation in which the alveoli are filled with leukocytes, and the zone of resolution with macrophages predominating and cocci in resting metabolic stage.

Using transparent chambers inserted into the ears of rabbits, the development of the inflammatory response can be observed. The phagocytes adhere to the capillary walls, first to the side nearer the inflammation, later to the entire wall of the vessel. The leukocytes then leave the vessel by diapedesis and accumulate at the site of infection.

Phagocytosis is lethal to pneumococci, the bacteria surviving only fifteen to thirty minutes within the leukocyte. At one time it was thought that phagocytosis occurred only in the presence of host antibodies when the capsule of the pneumococcus became coated with gamma globulin. It has now been shown, however, both in vitro and in vivo that some phagocytosis occurs in the absence of antibodies. In such cases, the leukocyte traps the bacterium between itself and another surface. Surfaces which may be used in this way include the wall of the alveolus, neighboring phagocytes, and fibrin networks found in the exudate.

In pneumococcus infections, bacteria may invade the lymph nodes and blood stream. Phagocytosis in the absence of antibodies occurs in these systems as well as in the lung.

Penicillin is bactericidal only when the cocci are in an active metabolic phase. Therefore, penicillin is effective in the edema zone, but ineffective in the center of the lesion.

Problems for future research involve the mechanism of phagocytic adherence to capillary walls, believed to be related to fibrinogen accumula-
tion, and the nature of the anti-phagocytic action of the pneumococcus capsule.

LISA STEINER

GASTROINTESTINAL STUDY UNIT
March 15, 1956

MODERN CONCEPTS OF SPRUE. By Chester M. Jones, Clinical Professor of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.

Tropical and non-tropical sprue present similar clinical pictures and are very probably the same disease. The frequent occurrence of a folic acid or vitamin B₁₂ correctable macrocytic, hypochromic anemia in the former, as opposed to its less frequent, more refractory counterpart in the latter does not constitute sufficient evidence for considering these as separate entities.

Although no histologic pathology is demonstrable, the basic lesion in this disease is thought to be at the cellular level and causes a decreased absorption of fat, carbohydrate, protein and vitamins by the small bowel. The resulting sprue syndrome consists clinically of fatigue, frequent large bowel movements, weight loss, distension, stomatitis and cutaneous pigmentation. Laboratory evaluation frequently reveals fatty stools, decreased serum calcium and prothrombin time, and a flat oral glucose tolerance curve. Barium swallow studies characteristically show puddling and dilated loops in the small bowel.

Cortisone markedly improves absorption from the small bowel in the sprue syndrome. A large number of patients treated with steroids have shown complete reversal of the disease process, though long term results are not as yet available. Some patients have shown improvement on a gluten free diet.

J. C. C.

ANESTHESIOLOGY SEMINAR
March 26, 1956

ANESTHETICS AND ADRENAL FUNCTION. By Leroy D. Vandam, Department of Anesthesiology, Harvard Medical School, Boston, Massachusetts.

During diethyl ether anesthesia in both man and dog, serum levels of 17-hydroxycorticoids increase and continue to do so for several days after operation. The initial increase is due to the anesthesia, the continuing rise to surgical trauma. The serum levels reflect not only enhanced secretion but decreased destruction and/or excretion of the steroids; this was shown by observing increased levels of serum 17-hydroxycorticoids during anesthesia and surgery on adrenalectomized dogs maintained on adrenal cortical extract. During anesthesia and surgery under hypothermic conditions, the increase in serum 17-hydroxycorticoids is minimal, but the levels increase markedly as normal body temperature is reached and continue high for several days.
In the intact dog ether anesthesia increases cardiac output, but after sympathectomy and adrenalectomy, cardiac output and arterial pressure fall while right auricular pressure rises. Thus, ether anesthesia appears to stimulate the secretion of epinephrine and norepinephrine.

The fear and starvation that precede surgery also stimulate the secretion of epinephrine and norepinephrine. But these emotions do not appear to stimulate the adrenal cortex, for patients who are prepared for surgery but not operated upon show no increase in 17-hydroxycorticoids.

J. P. G.

YALE MEDICAL SOCIETY
April 9, 1956

ATYPICAL HYPOPITUITARISM. By Harold Sheehan, Professor of Pathology, Liverpool University, Liverpool, England.

A carefully selected series of 106 cases of postpartum pituitary necrosis, studied clinically and pathologically, was the basis of a study comparing the extent of the hypophyseal lesion with the clinical course. Patients were grouped on the basis of the percentage of the pituitary tissue lost. It was ascertained that adjacent hypothalamic and neurohypophyseal regions were intact and no aberrant pituitary tissue was present. The clinical classification was based on three salient features. The first related to the persistence of function of a particular target organ. The second group showed unusual deficiency of a target organ. In the third group there was a complex picture of hormonal interdependence which produced symptomatology related to marked atrophy of one target organ, but which responded to replacement therapy with hormone of another target organ. Where possible, studies of target organ function and histology were carried out.

Certain women after a typical episode of postpartum pituitary necrosis maintained ovarian function as evidenced by occasional uterine bleeding, typical menstruation, or subsequent pregnancy. The ovaries lacked Graafian follicles but the primordial ova remained. No correlation was found between the extent of pituitary damage and continued ovarian function. The persistence of target organ function is perhaps produced by a minimal production of tropic hormone which is stored and periodically released. Alternatively, it has been postulated that the persistent functioning of a target organ may be related to a preponderance of cells producing its tropic hormone in the remaining pituitary tissue. This is unsupported by histological evidence.

Extreme target organ atrophy was studied in the thyroid and adrenals. Severe thyroprivic and adrenal insufficiency states were noted in these cases. Again there was no correlation between the extent of damage to the pituitary and target organ function. These instances may represent people who normally had little reserve in a particular target organ so that removal of the tropic hormone led to severe failure of function with concomitant atrophy. The picture is complicated by cases which showed no functioning target organ tissue on clinical testing but failed to develop severe symptoms referable to that organ.
Most confusing were those cases where symptomatology was primarily related to one target organ but responded to therapy with the hormone of another, as in secondary myxedema controlled by cortisone. These cases sharply illustrate the lack of information concerning the intricacies of the hormonal interrelationships of the pituitary target organs.

ROBERT S. NEUWIRTH

ANATOMY SEMINAR
April 17, 1956

THE FINE STRUCTURE OF THE CORNEA. By Marie A. Jakus, The Retina Foundation, Boston, Massachusetts.

An electron microscopic study of the cornea has disclosed a complex fine structure.

The most superficial layer of the corneal stratified epithelium consists of a pavement of squamous cells which interdigitate with one another by means of stubby cytoplasmic processes, like fasteners in a zipper. The comparative looseness of the “zippering” in this layer suggests that the cells are rather readily desquamated. Except for fine filaments, the cytoplasm of the squamous cells is not remarkable. In the embryonic chick cornea, however, the undifferentiated cytoplasm of these cells is filled with granular endoplasmic reticulum, now identified with the ergastoplasm of light microscopy. The nucleus of the adult squamous cell appears as a lobulated, ovoid aggregation of electron-opaque granules, bounded by a double membrane. The long axis of the nuclear profile is roughly parallel to the plane of the squamous cell. Deep to the squamous pavement is the intermediate layer of cells. The larger cytoplasmic processes of these cells probably effect a tighter “zippering” than occurs in the squamous layer. The nucleus of the intermediate cell resembles that of the squame. The stratified epithelium is completed by a basal layer of tightly “zippered” round cells containing lobulated, spheroid nuclei.

A thin band of moderate electron-opacity, seen beneath the basal cells, represents the basement membrane of the epithelium. Occasionally this membrane displays a finely fibrillar or lamellar architecture. On the surface of the membrane subjacent to the basal epithelial layer, a regular granulation or pseudo-striation is visible.

Bowman’s membrane, an essentially homogeneous band in the light microscope, is revealed in the electron microscope as a feltwork of randomly oriented filaments. In favorable preparations the filaments show a periodicity approximating that of the collagen fibers in the corneal stroma. The appearance of periodicity in these filaments is frequently obscured, perhaps by absorbed substances of appropriate electron-opacity, presumably containing mucopolysaccharide. The filaments measure about 180-190 Å in diameter in the electron micrographs, some 40-50 Å narrower than the stromal collagen fibers.

Beneath the membrane of Bowman lies the corneal stroma, composed of lamellae of collagen fibers. The fibers within any lamella are parallel to the
plane of the corneal surface and to each other; thus, each fibrous lamella may be said to have one axis of orientation to which its constituent fibers are essentially parallel. Since in alternate lamellae these axes of orientation are perpendicular to each other, a criss-cross pattern occurs among the lamella. The diameters of the intralamellar collagen fibers are characteristic for species (man 230 Å; rat 270-275 Å; mouse 370-375 Å). Scattered among the fibers, and occasionally adherent to them, is a fine, filamentous component, thought to contain elastin or mucopolysaccharide.

Descemet's membrane comprises an unusual arrangement of collagen. Indeed, before the preparation of tangential sections of the membrane a satisfactory interpretation of its fine structure from transverse sections was wanting. Descemet's membrane consists of a pile of bidimensional grids of collagen laid parallel to the plane of the corneal surface. Each bidimensional grid is a mosaic of repeating hexagonal units. The corners of each hexagonal unit are marked by dense nodes connected by internodal fibers which, therefore, describe the perimeter of the hexagon. In the center of each hexagon is a single node, connected by radial fibers to the six peripheral nodes at the corners of the hexagon. The grids formed by the repetition of the hexagonal unit are piled so that the corresponding nodes and internodal fibers of all grid layers are in register. (From this description one may envision the original problem in interpretation from transverse sections and its clarification by the examination of tangential sections.)

The deepest stratum of the cornea, a single layer of "zippered" endothelial cells, provides a comparatively plain limiting wall for a tissue of intricate internal architecture.

ALLAN H. MILOFSKY

YALE MEDICAL SOCIETY
May 14, 1956

ACUTE HYPERTENSION IN THE PULMONARY VASCULAR BED OF THE DOG: A PHYSIOLOGICAL STUDY. By S. E. Downing, Fourth-year Student, Yale University School of Medicine.

Although a rather extensive literature on the subject of pressoreceptors on the pulmonary vascular bed has evolved, there is a rather wide divergence of opinion regarding the nature of the reflex response resulting from induced pulmonary hypertension.

In general, the present approach to the problem is to perfuse the left lung of the intact dog with normal saline at body temperature under variable pressures and rates of flow and to measure simultaneously the perfusion pressure and rate of flow, the systemic pressure, the pulse rate, the main pulmonary arterial pressure, and the respiratory rate and depth.

An apparatus was constructed by means of which the perfusion pressure and rate of flow could be regulated and recorded.

In order that the experiments might be performed on the intact animal, it was necessary to construct various cannulae so that the manipulations could be performed on animals with intact chests. Consequently, into each
animal an infusion cannula was placed in the left pulmonary artery, a guide cannula sutured to the main pulmonary artery through which an L.P. needle could be passed for the purpose of measuring the main pulmonary arterial pressure, and two specially designed snares for the pulmonary veins, one for the upper and middle lobe veins and one for the lower lobe veins, by means of which the venous return of the left lung could be occluded or opened at will from the exterior of the animal.

Two groups of animals were prepared surgically, acute and chronic. Veratridine was used to demonstrate the presence of intact nerve pathways from the pulmonary vascular bed which might have been damaged at the time of surgical preparation.

The results of this study demonstrated that the response of the intact dog to acute hypertension in the peripheral pulmonary vascular bed consists of three components: (i) a drop in systemic pressure, (ii) bradycardia, and (iii) a change in the respiratory pattern. All of the components had their onset simultaneously about six or seven seconds after beginning the perfusion. None of the components were observed to occur following ipsilateral vagotomy. The fact that the response does not occur when the pulmonary vein snares are open, but does readily with the snares closed would suggest that the majority of the receptors are located on the venous side of the pulmonary circuit.

S. E. DOWNING

A Study of Some Aspects of Fatty Acid Metabolism in Man. By Robert McDivitt, Fourth-year student, Yale University School of Medicine.

Five normal humans without evidence of metabolic disease were given 200 micro-curies of acetate-1-C\(^{14}\) each, and blood samples were drawn at intervals up to 96 hours. The plasma lipids were separated into triglycerides, cholesterol esters, and phospholipids with a modified form of Fillerup and Mead's method of silicic acid chromatography. Following this, an aliquot from each fraction was saponified and the amount of radioactivity in each fatty acid sample determined, using a liquid scintillation counter. Further aliquots of fatty acids from each triglyceride, phospholipid, and cholesterol ester fraction were chromatographed on hyflow-supercel reverse phase columns to effect separation of individual fatty acids. It was found that incorporation of radioactivity was much greater and more rapid in the triglyceride fatty acid fraction than in either the phospholipid or the cholesterol ester fatty acid fractions, peak specific activity of this fraction occurring within two hours after administration of the acetate. The maximum specific activity of the phospholipid fatty acid fraction occurred at 12 hours, while that of the cholesterol ester fatty acid fraction occurred between 24-48 hours. It was further observed that the greatest concentration of stearic and other saturated fatty acids occurred in the triglyceride fraction, while the unsaturated fatty acids were found in greatest concentration in the cholesterol ester fraction. Possible correlation between fatty acid composition of these compounds and difference in rates of incorporation of radioactivity from acetate-1-C\(^{14}\) was discussed.

ROBERT MCDIVITT