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"the Donnatal® Effect"

QUIETS THE STRESS / QUELLS THE SPASM

MCV/Q

CONTENTS

Histamine and Thyroid Hormone Function*

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In an earlier paper in this journal I reviewed evidence suggesting that histamine serves as an important regulator of the microcirculatory system (Schayer, 1968). Since the metabolism of cells depends on their internal environment, and this depends on distribution of nutrients and removal of wastes through the capillaries, it seems evident that any hormone with a sustained circulatory effect could cause widespread secondary changes in metabolism.

Based on a microcirculatory function of histamine, a unified theory of glucocorticoid action has been described (Schayer, 1964b, 1967). It is the purpose of the present paper to consider if the histamine-microcirculation concept may help explain the complicated pattern of thyroid hormone effects on metabolism, growth and development.

Briefly, it will be postulated that a major function of thyroid hormone is for slowly developing adaptations of the circulatory system to environmental changes, and that many thyroid hormone effects are secondary to altered perfusion of tissues. There is no known *in vitro* effect of thyroid hormone which can reasonably explain any major number of the *in vivo* effects (Tata, 1964).

Observations on Thyroid Hormone Action

Any unifying theory of thyroid hormone action must attempt an explanation of the following observations in:

A. Homeothermic animals

1. There is a lag period between administration of thyroid hormone and appearance of its effects.

2. A moderate dose of thyroid hormone increases heat production (BMR); in young animals growth increases.

3. In cold adaptation the rise in thyroid output increases heat production but not growth.

4. The increase in BMR seems to relate to norepinephrine action and to induction of enzymes.

5. Thyroid hormone may sensitize the circulatory system to catecholamines, but this is not a consistent finding. The thyroid hormone-catecholamine relationship seems complex and confusing.

6. In hypothyroidism there is weakness, poor growth and development, cold intolerance and metabolic disturbances.

B. Amphibia

1. In tadpoles a moderate increase in thyroid hormone levels induces metamorphosis.

2. In mature amphibia even large doses of thyroid hormone have almost no effect.

Postulates for Circulatory Theory of Thyroid Hormone Action

1. A basic requirement for thyroid hormone may be for normal function of vascular smooth muscle and, possibly, of cardiac muscle. Thyroid hormone molecules may attach to receptors on these muscle cells and enhance their responsiveness to regulators of contraction and relaxation.

2. The principal physiological regulators of vascular smooth muscle are the constrictors, norepinephrine and the unidentified intrinsic "tone-force." Opposing the constrictors are dilators; histamine is of primary importance in the small vessels.

3. Cardiac muscle may also be similarly affected; it is continuous with vascular smooth muscle and is influenced by the same vasoactive substances.

4. The lag period may be the time required for thyroid-induced changes in the contractile mechanism to become evident.

Possible Sequence of Events in Moderate Hyperthyroidism

1. Vascular smooth muscle is sensitized as described under Postulates.

2. Vasoconstrictor forces are potentiated in the arteries, larger arterioles and veins. However, in small vessels the dilator action of intrinsic histamine is enhanced, and precapillary sphincters open.

3. Through the process of "conducted vasodilatation" (Hilton, 1962) the arterial vessels relax, while the venous side remains partially constricted.

4. There is increased heart action, due to direct or indirect causes.

5. The overall circulatory pattern consisting of (a) strong heart action, (b) an open arterial system, (c) an open microcirculation, and (d) a partially constricted venous system permits a generalized overperfusion of tissues.

6. The abnormally rapid perfusion provides optimal nourishment to cells; metabolite-induced activation of enzymes occurs.

7. Responses of cells depend on their genetically predetermined capabilities (Pitt-Rivers and Tata, 1959). In mature homeotherms, which lack potential for growth, metabolic activation produces heat. In immature homeotherms, both energy production and growth occur.

Possible Role of Physiological Activation of Thyroid Hormone Output During Cold Adaptation

The increased energy production of moderate hyperthyroidism is useless in animals at room temperature, and heat must be dissipated. However, thyroid hormone output is increased as a homeostatic measure during cold adaptation; this is evidently the only known case of physiological activiation of the thyroid gland except in rapid growth and development.

1. Vascular smooth muscle is sensitized as in moderate hyperthyroidism.

2. The sympathetic nervous system is activated by cold stress; more norepinephrine is released, and vascular responsiveness to norepinephrine is enhanced.

3. The circulatory pattern is modified by increased sympathetic activity; blood flow to most vascular beds is reduced (Folkow, Heymans and Neil, 1965) and diverted to heart, lung and skeletal muscle.

4. Overperfusion occurs mainly in skeletal muscle. Increased metabolite levels induce activation of enzymes; in muscle they are primarily concerned with energy production. This energy is used to maintain body temperature.

The Thyroid-Norepinephrine Relationship in Cold Adaptation

Cold-acclimated animals show increased thyroid output (Barker, 1964) as well as sympathetic stimulation. There is considerable evidence that norepinephrine, not epinephrine, is of prime importance in regulating metabolic rate in cold-acclimated animals through the process of non-shivering thermogenesis (Hsieh and Carlson, 1957; Himms-Hagen, 1967). According to Himms-Hagen, "The mechanism by which the sympathetic nervous system produces this regulation is not at all understood."

The reasons for this lack of un-

derstanding are readily seen, for unlike epinephrine, norepinephrine has very little, if any, ability to stimulate metabolism directly. In fact, its only really potent action is vasoconstriction (Goodman and Gilman, 1965). Vasoconstriction, per se, cannot increase the metabolic rate, since it markedly reduces nutritive blood flow in skeletal muscle; muscle is the major site of thyroid-induced increase in BMR. Accordingly, it seems necessary either to postulate a wholly obscure energy-producing function for norepinephrine, or to enquire whether sympathetic vasoconstriction, suitably modified, might lead to increased metabolic rates.

A possible clue is the abundant flow of blood through skeletal muscle during exercise, despite an activated sympathetic nervous system. A dilator mechanism opens the small vessels in muscle, the arterial side relaxes reflexly, and the circulatory picture described under Postulates develops. I believe the dilator mechanism to involve histamine (Schayer, 1964a, 1968).

In cold adaptation, dilatation at the level of the small vessels could presumably produce a similar circulatory picture. Norepinephrine may activate compensatory production of histamine in microvascular smooth muscle cells of skeletal muscle. We have observed norepinephrine induction of histidine decarboxylase in skeletal muscle, skin and lung of mice, but not in other tested tissues (Schayer, 1960, 1962). Leblanc (1963) assayed urine of rats during cold adaptation and found large increases in norepinephrine and histamine levels, the latter possibly being of microvascular origin.

Effect of Increased Thyroid Hormone Levels in Amphibia

In the tadpole, the enzymatic potential of cells is oriented toward metamorphosis. If thyroid hormone causes a generalized overperfusion

of tissues, the abundant supply of blood-borne nutrients, perhaps including certain rate-limiting substances, may trigger metabolite-induced activation of many enzymes and permit cells to achieve their fullest potential consistent with other existing environmental factors.

In the mature amphibian, however, further growth or development is not possible. Since the cells evidently have no enzymic mechanisms significantly concerned with heat production, thyroid hormone, even in large doses, has almost no effect in a frog (Barker, 1964).

The Thyroid Hormone-Catecholamine Relationship

Many studies have related thyroid hormone effects to potentiation of action of catecholamines, particularly norepinephrine; however, there are conflicting reports, and the picture is confusing (Brewster et al., 1956; Barker, 1964; Harrison, 1964; Theilen and Wilson, 1967).

If it is assumed that thyroid hormone has a primary circulatory action and involves histamine, experimental findings on thyroid-catecholamine interaction might be complicated for the following reasons:

1. Histamine is an antagonist of norepinephrine; it is found in high concentrations in perivascular mast cells and in sympathetic nerves.

2. Injection or release of catecholamines may release preformed histamine (Beck, 1965).

3. Injection or release of catecholamines may increase the rate of histamine formation (Schayer, 1960, 1962).

4. The status of the adrenal cortex is of great importance to the experimental outcome; glucocorticoids reduce microcirculatory actions of histamine and potentiate those of catecholamines (Schayer, 1964b, 1967).

In addition, other homeostatic mechanisms, not included in the present thesis, are involved.

Specificity of Thyroid Hormone Action

In liver, the tissue most frequently studied for induction of enzymes, a number of hormones, including thyroid hormone, initiate the same sequence of events in early stages of protein synthesis, i.e., increased nuclear RNA polymerase activity and increased RNA synthesis. Subsequently, however, there is some discrimination, for the pattern of activated enzymes differs for each hormone.

Although a solution to this problem is undoubtedly difficult, the importance of circulatory factors, at present often overlooked by biochemists, must certainly be recognized. Some of these factors are:

1. Hepatic cells are not metabolically identical; the metabolic status of each cell depends on its local nutrient environment, and this varies with the position of the cell along the sinusoid.

2. Any factor which alters liver hemodynamics may alter local nutrient supplies and, hence, affect the level of activity of hepatic enzymes (Brauer, 1963; Rappaport, 1963).

3. Hormones may release histamine and other vasoactive substances (Szego, 1965) or interact with vasoactive substances through potentiation, inhibition, impaired synthesis, or other means. Presumably a sufficient dose of any hormone will cause catecholamine release.

4. Because of the complexity of the hepatic vascular system and the heterogeneous metabolic characteristics of the hepatic cells, metabolic changes arising from circulatory disturbances would be complex and, at present, unpredictable.

In addition, some hormones may affect nutrient levels by other means, e.g., by changing permeability of cell or organelle membranes in liver or in other tissues.

Thyroid hormone activates hepatic respiratory enzymes; the fact that these enzymes are localized in a particular region, Zone 1 of the liver acinus (Rappaport, 1963), may be relevant to the apparent specificity of the hormone.

In skeletal muscle, the tissue which undergoes the greatest increase in thyroid-induced BMR, there seems to be no problem of specificity; evidently no other hormone produces comparable effects in muscle.

Hypothyroidism

In terms of the present thesis, vascular responsiveness would be subnormal in hypothyroid animals. The symptoms, e.g., weakness, poor growth and development, cold intolerance and metabolic disturbances, could result from impaired nutritive blood flow and inadequate cell nutrition.

Summary of Evidence and Arguments Supporting a Primary Vascular Function for Thyroid Hormone

1. Many investigators have reported that excessive levels of thyroid hormone sensitize the cardiovascular system to catecholamines (Brewster et al., 1956; Barker, 1964).

2. During increased thyroid output in cold acclimation, norepinephrine is much more potent than epinephrine in increasing non-shivering thermogenesis (Hsieh and Carlson, 1957; Himms-Hagen, 1967.) Yet norepinephrine is almost exclusively a vasoconstrictor; unlike epinephrine, it has very little ability to stimulate metabolism directly.

3. Heat production in hyperthyroid animals is reduced by several types of drugs which reduce catecholamine effects.

4. In hyperthyroid animals adrenergic blockade reduces the BMR to euthyroid levels, not to hypothyroid levels. This and other evidence indicate that metabolic effects of thyroid hormone cannot

be entirely attributed to action of adrenergic amines (Barker, 1964). The present view suggests that vasoconstriction is essential for increased BMR, but that there is an alternative to mediation by catecholamines. A vasoconstrictor "tone-force" exists which is not referable to any known blood-borne substance (Barcroft, 1963) and which is unaffected by any drug acting through reduction of catecholamine action. This tone-force is particularly strong in skeletal muscle, the major site of energy production in hyperthyroidism (Tata, 1964).

5. From the evidence outlined above, it seems highly probable that thyroid-induced heat production relates to vasoconstriction. However, vasoconstriction, per se, strongly reduces nutritive blood flow in a resting animal. In order to provide extra energy for prolonged periods, nutritive blood flow must rise above resting levels. Accordingly, to reconcile thyroid-induced vasoconstriction with the observed activation of metabolism, there must also be a mechanism for opening precapillary sphincters.

6. Thyroid hormone sensitizes animals to the lethal effects of histamine (Spencer and West, 1961). Since this enhanced sensitivity is blocked by glucocorticoids, it seems probable that the point of sensitization is microvascular smooth muscle.

7. If thyroid hormone does sensitize precapillary sphincters to histamine and histamine does relax sphincters during exercise, then thyroid hormone excess plus exercise may yield an exceptionally great blood flow in skeletal muscle. This is actually observed; hyperthyroid patients performing a standard exercise show a markedly exaggerated postexercise hyperemia (Barcroft, 1963).

8. Metamorphosis in amphibians presumably requires activation of a vast number of metabolic processes, all within a relatively short period of time. Since elevated nutrient levels are a primary stimulus

for enzyme induction and for a general acceleration of cell metabolism, and since the availability of *all* normal nutrients could be markedly enhanced by the circulatory pattern previously described, it seems quite reasonable that the transformation of a tadpole into a frog could result from the sequence: thyroid hormone → increased local blood flow → elevation of nutrient levels in cells → triggering of enzyme activation → metamorphosis. In contrast to this simple picture, it is difficult to envisage how a primary hormone action directed, for example, toward some change in carbohydrate or protein metabolism or to an effect on the permeability of certain cells to certain nutrients, could produce such a complex transformation.

9. Thyroid hormone increases the metabolic rate of skeletal muscle, heart, liver, kidney, salivary gland, gastric mucosa and skin but has little, if any, effect on a number of other tissues, e.g., spleen, lymph nodes, thymus, gastrointestinal smooth muscle, lung, gonads. Yet thyroid hormone penetrates all these tissues to a roughly comparable extent (Barker, 1964).

Since there is no major metabolic distinction between these two groups of tissues, the data are not readily explained by a direct metabolic action of thyroid hormone. However, these tissues may show major differences in circulatory responses. For example, different effects of vasoactive substances on capillary blood flow might underlie group differences.

10. Thyroid hormone causes brain changes but evidently does not cross the blood brain barrier. If this is so, a direct action of the hormone on cells of the central nervous system seems unlikely. However, if thyroid hormone attached to receptors on the lumen surface of blood vessels nourishing the brain and subsequently altered microvascular flow, it might cause secondary effects in the brain without having crossed the barrier.

11. Kontos et al. (1965) showed that blood flow is markedly increased in skeletal muscle of thyrotoxic patients. Although oxygen consumption and carbon dioxide production were increased, the arteriovenous difference across skeletal muscle of patients was *reduced* relative to normals. Thus, the increased muscle flow was greater than needed for increased oxygen requirements. These observations are comprehensible if thyroid-induced metabolism changes are secondary to circulatory changes; they do not suggest that muscle circulation increases to sustain increased metabolism.

Summary

The concept that histamine serves as an intrinsic microcirculatory dilator may have important implications for the interpretation of thyroid hormone actions.

It is suggested that thyroid hormone participates in distribution of nutrients to cells of vertebrates by altering responsiveness of vascular smooth muscle to constrictors and dilators, for example, norepinephrine and histamine. From enhanced constriction of larger vessels and histamine-induced reflex vasodilatation of the arterial side, a circulatory pattern comprising open arterioles and precapillary sphincters, partially closed veins, and rapid heart action may cause a generalized expansion of capillary perfusion. The greater availability of nutrients may trigger metabolic activation of cells and produce extra energy and growth in immature homeotherms but only energy in adults. In cold acclimation, activation of sympathetic output as well as thyroid output occurs. Overperfusion may, therefore, be confined largely to heart, lung and skeletal muscle, thus increasing energy production but not the rate of growth. In tadpoles, a generalized increase in tissue perfusion may result in metabolite activation

of the many preset changes involved in metamorphosis. In frogs, however, since potential for growth and heat production is low, even large doses of thyroid hormone have little effect. Some of the symptoms of hypothyroidism—weakness, poor growth and development, cold intolerance, and metabolic disturbances—may result from impaired nutritive blood flow and inadequate cell nutrition.

Evidence favoring a primary circulatory action of thyroid hormone is presented; however, it is not implied that all thyroid hormone effects are derived from circulatory changes. Thyroxine is present in some plants and in certain lower animals. Whatever actions it may have in primitive forms may also be primary actions in higher animals.

References

BARCROFT, H. Circulation in skeletal muscle. In *Handbook of Physiology*. Section 2. *Circulation*. Vol. 2. W. O. Fenn and H. Rahn (eds.). Washington, D. C.: American Physiological Society, 1963, pp. 1353–1385.

BARKER, S. B. Physiological activity of thyroid hormones and analogs. In *The Thyroid Gland*. Vol. 1. R. Pitt-Rivers and W. R. Trotter (eds.). New York: Plenum, 1964, pp. 199–236.

BECK, L. Histamine as the potential mediator of active reflex dilation. *Federation Proc.* 24:1298–1310, 1965.

BRAUER, R. W. Liver circulation and function. *Physiol. Rev.* 43:115–213, 1963.

BREWSTER, W. R., JR., J. P. ISAACS, P. F. OSGOOD AND T. L. KING. The hemodynamic and metabolic interrelationships in the activity of epinephrine, norepinephrine and the thyroid hormones. *Circulation* 13:1–20, 1956.

FOLKOW, B., C. HEYMANS AND E. NEIL. Integrated aspects of cardiovascular regulation. In *Handbook of Physiology*. Section 2. *Circulation*. Vol. 2. W. F. Hamilton and P. Dow (eds.). Washington, D. C.:

American Physiological Society, 1965, pp. 1787–1823.

GOODMAN, L. S. AND A. GILMAN (eds.). *The Pharmacological Basis of Therapeutics*. 3rd Edit. New York: Macmillan, 1965.

HARRISON, T. S. Adrenal medullary and thyroid relationships. *Physiol. Rev.* 44:161–185, 1964.

HILTON, S. M. Local mechanisms regulating peripheral blood flow. *Physiol. Rev.* 42 (Suppl. 5): 265–275, 1962.

HIMMS-HAGEN, J. Sympathetic regulation of metabolism. *Pharmacol. Rev.* 19:367–461, 1967.

HSIEH, A. C. L. AND L. D. CARLSON. Role of adrenaline and noradrenaline in chemical regulation of heat production. *Am. J. Physiol.* 190:243–246, 1957.

KONTOS, H. A., W. SHAPIRO, H. P. MAUCK, JR., D. W. RICHARDSON, J. L. PATTERSON, JR. AND A. R. SHARPE, JR. Mechanism of certain abnormalities of the circulation to the limbs in thyrotoxicosis. *J. Clin. Invest.* 44:947–956, 1965.

LEBLANC, J. Secretion and activity of histamine and serotonin during cold adaptation. *Am. J. Physiol.* 204:520–522, 1963.

PITT-RIVERS, R. AND J. R. TATA. *The Thyroid Hormones*. New York: Pergamon, 1959, pp. 59–98.

RAPPAPORT, A. M. Acinar units and the pathophysiology of the liver. In *The Liver: Morphology, Biochemistry, Physiology*. C. Rouiller (ed.). Vol. 1. New York: Academic, 1963, pp. 275–276.

SCHAYER, R. W. Relationship of stress-induced histidine decarboxylase to circulatory homeostasis and shock. *Science* 131:226–227, 1960.

———. Evidence that induced histamine is an intrinsic regulator of the microcirculatory system. *Am. J. Physiol.* 202:66–72, 1962.

———. Histamine and hyperæmia of muscular exercise. *Nature* 201:195, 1964a.

———. A unified theory of glucocorticoid action. *Perspectives Biol. Med.* 8:71-84, 1964b.

———. A unified theory of glucocorticoid action. II. On a circulatory basis for the metabolic effects of glucocorticoids. *Perspectives Biol. Med.* 10:409–418, 1967.

———. Histamine and a possible unity of autonomous microcircu-

latory dilator responses. *Med. Coll. Virginia Quart.* 4:101–106, 1968.

SPENCER, P. S. J. AND G. B. WEST. Sensitivity of the hyperthyroid and hypothyroid mouse to histamine and 5-hydroxytryptamine. *Brit. J. Pharmacol.* 17:137–143, 1961.

SZEGO, C. M. Role of histamine in mediation of hormone action. *Federation Proc.* 24:1343–1352, 1965.

TATA, J. R. Biological action of thyroid hormones at the cellular and molecular levels. In *Actions of Hormones on Molecular Processes*. G. Litwack and D. Kritchevsky (eds.). New York: Wiley, 1964, pp. 58–131.

THEILEN, E. O. AND W. R. WILSON. Hemodynamic effects of peripheral vasoconstriction in normal and thyrotoxic subjects. *J. Appl. Physiol.* 22:207–210, 1967.

The Interplay of Defense Mechanisms Against Infectious Diseases*

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Defense systems against infectious agents can be subdivided into two broad categories involving humoral and cellular mechanisms. Specific humoral systems comprise the antimicrobial and antitoxic effects of at least three classes (IgG, IgM and IgA) of immunoglobulins. These immunoglobulins in varying patterns may (a) neutralize toxins, (b) neutralize viral infectivity and (c) kill certain gram-negative microorganisms in concert with the complement system. A few microorganisms having "deficient" cell walls, such as mycoplasma, may be inhibited by specific antibodies without the aid of complement. Since IgA does not fix complement, IgG and IgM must play the dominant role in complement mediated reactions. A fourth (d) category of specific immunoglobulin activity involves enhancement of phagocytosis or opsonic action, which illustrates an important interplay between a specific humoral mechanism and phagocytic mechanisms. It is probable that IgG and IgM also play the dominant role in opsonization, because IgA has been reported to lack opsonizing activity (Quie, Messner and Williams, 1968). The major functions of IgA must be to neutralize toxins and the infectivity of viruses.

In addition to specific humoral mechanisms, several nonspecific humoral defense mechanisms exist. Two such factors are β-lysin, which is released during blood clot formation (Tew, Hess and Donaldson, 1969), and lysozyme, which is probably secreted and/or released from several cell types. It is significant that lysozyme can act in concert with the antibody-complement system and augment the bactericidal and lytic effects of this system against certain gram-negative microorganisms (Amano et al., 1954). Lysozyme is usually present in lysosomes of phagocytic cells and may be secreted by mononuclear cells (Heise and Myrvik, 1967). Other potentially active nonspecific factors secreted from living cells or released from disrupted and necrotic cells include cationic substances, lactate, interferon, viral inhibitors and a recently described antibacterial system involving peroxidase, thiocyanate and H_2O_2 (Hirsch, 1960; Klebanoff, Clem and Luebke, 1966; Wolstenholme and O'Connor, 1967; Zeya and Spitznagel, 1968).

If a microorganism is not inactivated by the humoral mechanisms present in the microenvironment at the site of infection, phagocytic cells promptly come into play, and, if conditions permit, the infecting microorganisms will be ingested. The polymorphonuclear (PMN) cell is usually the first line of phagocytic cells to engage microorganisms. However, if the infection continues and is not contained by the PMNs, mononuclear phagocytes (macrophages)

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eventually engulf the parasite and, if necessary, can enter into a long-term engagement with the infectious agent. During this interaction both nonspecific and specific humoral factors may participate prior to and perhaps even conjointly with the intracellular events. It is generally considered that the phagosomes in PMNs and macrophages receive antibacterial factors and hydrolytic enzymes from lysosomes as the result of a fusion process between lysosomes and the membrane surrounding the phagocytized particle (Hirsch, 1962).

It would be expected that the least virulent of all microorganisms might be highly susceptible to the nonspecific humoral systems of defense. Such microorganisms would be represented by *Sarcina lutea* (sensitive to lysozyme) and *Bacillus subtilis* (sensitive to β-lysin). The next hierarchy of pathogenic microorganisms to evolve would be expected to be resistant to the humoral mechanisms and capable of resisting phagocytosis unless specific opsonizing antibody is present. *Diplococcus pneumoniae* is a representative of this type of host-parasite relationship. However, *D. pneumoniae* is fully susceptible to the normal intracellular bactericidal mechanisms once the organism has been ingested. In this case there is no evidence that specific opsonizing antibody contributes significantly to the normal intracellular bactericidal and digestive activities of PMNs and macrophages except for mediating phagocytosis.

The ultimate evolutionary step reached by microorganisms has involved not only resistance to the humoral systems of defense, but also resistance to the normal baseline cellular systems of defense. *Mycobacterium tuberculosis* is a classic example of a parasite reaching this stage of host-parasite evolution. In fact, all of our so-called chronic granulomatous diseases (tuberculosis, brucellosis, listeriosis, histoplasmosis, tularemia,

etc.) are chronic and granulomatous because of a persisting intracellular infection of the phagocytic cells of the reticuloendothelial system. Characteristically the infectious lesion in these host-parasite relationships is composed primarily of macrophages, epithelioid cells, giant cells and lymphoid cells.

Macrophages in a "status quo" nonimmunized animal are essentially incapable of resisting the intracellular growth of virulent tubercle bacilli. Furthermore, the PMNs fail, in all probability, because their life span is too short to effectively bring to bear their bactericidal and digestive systems against an organism with such challenging substrates and biochemical armor as the virulent tubercle bacillus. Accordingly, the ultimate in parasite evolution has resulted in microorganisms with complex cell walls and "capsular" substrates that are refractory to the normal bactericidal and/or digestive processes of the phagocytic cell systems. An alternative to this possibility could involve toxic moieties secreted or released intracellularly by a pathogenic microorganism which could disrupt the chain of events leading to an effective phagosome or block differentiation to an increased immunologic potential.

In this regard, PMNs are quite capable of digesting *Mycobacterium smegmatis* within three hours, which illustrates their potential for killing an avirulent species of mycobacteria (Leake and Myrvik, 1966). Consequently, virulent mycobacteria are biochemically structured in a way which allows them to survive the intracellular potential of the PMN and makes them candidates ultimately for phagocytosis by macrophages. Normal macrophages appear to undergo a form of non-immunologic mediated differentiation and can kill *M. smegmatis* after about four to six days of intracellular residence. However, macrophages can cope only with virulent myco-

bacteria after they have differentiated *in vivo* under the blanket of an immunologic stimulus. Accordingly, there is good evidence to support the concept that normal macrophages are relatively immature cells and can differentiate upon demand by either stimulation with "substrate" or some specific immunological mechanism (Evans and Myrvik, 1968). In addition, these forms of stimulation may lead to mitosis, resulting in a more favorable host cell-parasite ratio. Undoubtedly, macrophages activated by a specific immunologic mechanism develop a population of "immune" phagocytes sooner than by way of the "substrate" principle of stimulation. For example, sodium stearate will develop a characteristic epithelioid cell granuloma which has the same rate of formation regardless of the number of injections. In contrast, repeated injections of mycobacteria illustrate the development of so-called accelerated or allergic granulomas (Myrvik, Leake and Oshima, 1962).

The PMN normally emerges from the bone marrow as a mature cell with a constitutive load of antibacterial and digestive factors packaged in lysosomes. It thus appears that opsonizing antibody is the main specific immunologic component that interplays directly with the PMN. It is also feasible in certain instances for bactericidal antibody plus complement to interplay with lysozyme and, possibly, other antibacterial agents that are transferred to the phagosome. In addition, certain components of complement have been demonstrated to exert positive chemotactic effects on PMNs (Müller-Eberhard, 1968). However, chemotaxis of PMNs also can be prompted by components resulting from tissue damage apart from specific antigen-antibody-complement reactions or other specific sensitivity responses. There is no evidence that PMNs proliferate in tissues as a result of a specific immunologic stimulus.

Therefore, mobilization to any lesion is dependent on blood-borne transport.

In contrast, macrophages commonly circulate or exist in tissues as relatively undifferentiated cells with a sparse number of lysosomes and a low level of hydrolases as well as a baseline level of metabolic activity (Heise, Myrvik and Leake, 1965; Myrvik and Evans, 1967; Leake and Myrvik, 1968). It is of interest that normal alveolar macrophages, even of a low order of activation, can readily kill and digest avirulent strains of *Listeria monocytogenes* but not virulent strains of this organism (Evans, 1968). However, BCG-(*Mycobacterium bovis*) activated alveolar macrophages are capable of killing virulent strains of *L. monocytogenes*. These findings indicate that, once a macrophage is activated by interaction with one type of microorganism, it also has an increased potential to contain and destroy certain unrelated microorganisms. It should be emphasized that this generalization does not hold when BCG-activated macrophages are presented with virulent *Pasteurella tularensis*. On the other hand, macrophages from *P. tularensis*-vaccinated animals are capable of handling *P. tularensis* (Nutter and Myrvik, 1966).

Whereas the role of specific antibodies and their interplay with PMNs is reasonably well understood, our concepts concerning the interplay of specific antibodies and acquired immunity to facultative intracellular parasites (the ultimate in evolution of microbial pathogens) is obscure. Speculation is our only *modus operandi* for discussing this facet of cellular immunity. There is compelling evidence that with most facultative intracellular parasites opsonizing antibody is not the limiting factor. For example, there appears to be an adequate concentration of opsonins in normal sera for mycobacteria and listeria. These opsonins could be the result of long-

term contact with similar or related organisms in the environment. Accordingly, opsonins (if needed with these organisms) are usually normally present, and, thus, phagocytic uptake by macrophages is not the limiting step following primary infection with these organisms. This does not exclude the possibility that phagocytosis of some facultative intracellular parasites may be dependent on antibodies present only in the specifically immune host. Nevertheless, the key point in our understanding of the host-parasite relationship in the so-called granulomatous diseases rests on the fact that normal macrophages are incapable of suppressing the intracellular parasite even if sufficient time is allowed for "substrate" activation. This is exemplified in the case of tuberculosis, where the generation time of the parasite is probably two to four days *in vivo*. In this host-parasite relationship, it is quite apparent that only immune macrophages can significantly suppress the growth of tubercle bacilli.

Assuming that the macrophages which mediate immunity to tuberculosis are derived as the result of some specific immunologic activation process, an interplay of specific and nonspecific factors in cellular immunity must be postulated.

Current knowledge in this area supports the concept that immune lymphocytes are activated following contact with the corresponding antigen. As a result, these lymphocytes undergo transformation and secrete either specific antibody with cytophilic properties for macrophages or a product (Granger's lymphotoxin?) which can activate macrophages (Granger and Kolb, 1968; Heise, Han and Weiser, 1968). If cytophilic antibody is involved, the macrophages passively receive a recognition system (cytophilic antibody) which could function to specifically activate macrophages when they have made contact with the appropriate antigen.

On the other hand, if a nonspecific secretion product of the specifically activated immune lymphoid cells is responsible, specificity of the response would not exist on the macrophage level. However, it is unlikely that the effector cell (macrophage) of antibacterial cellular immunity is totally devoid of specific components. Cytophilic antibodies on macrophages could function in an "antitoxic" capacity on the intracellular level. This possibility is best exemplified by the lack of immune expression of BCG-activated (immune) macrophages against *P. tularensis*. In contrast, macrophages derived from *P. tularensis*-immune animals express definite cellular immunity against *P. tularensis*. The possibility that certain types of antibody could function on the intracellular level to protect the macrophage against toxic products secreted by intracellular pathogens warrants investigation.

In transplantation immunity it appears likely that immune lymphoid cells act directly as effector cells. In this case, macrophages may act only as a secondary participant, which is in contrast to the primary role macrophages play in antibacterial cellular immunity. The case for a lymphotoxin being an effector agent in transplantation immunity is attractive and deserves further study.

Summary

The total complex of immune expression is an interplay between nonspecific antimicrobial humoral systems plus specific antibodies and accessory factors. These systems are backstopped by the phagocytic functions of PMNs. If these fail, mononuclear phagocytes respond as a second line of defense to carry out chronic engagements. In addition to a direct activation process by "substrate," macrophages may be activated and mobilized by a lymphocyte-mediated immunologic reaction which probably in-

volves either a "lymphotoxin" and/or a specific antibody cytophilic for macrophages. Immunologically activated lymphocytes appear to be the primary effector cells of anti-tissue (transplantation) cellular immunity, whereas immunologically activated macrophages appear to be the primary effector cells of anti-bacterial cellular immunity.

References

AMANO, T., S. INAI, Y. SEKI, S. KASHIBA, K. FUJIKAWA AND S. NISHIMURA. Studies on the immune bacteriolysis. I. Accelerating effect on the immune bacteriolysis by lysozyme-like substance of leucocytes and egg-white lysozyme. *Med. J. Osaka Univ.* 4:401–418, 1954.

EVANS, D. G. *Glucose metabolism of normal and immune alveolar macrophages,* thesis, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina, 1968.

EVANS, D. G. AND Q. N. MYRVIK. Studies on glucose oxidation during the interaction of alveolar macrophages and bacteria. *Ann. N.Y. Acad. Sci.* 154:167–176, 1968.

GRANGER, G. A. AND W. P. KOLB. Lymphocyte *in vitro* cytotoxicity: Mechanisms of immune and non-immune small lymphocyte mediated target L cell destruction. *J. Immunol.* 101:111–120, 1968.

HEISE, E. R., S. HAN AND R. S. WEISER. *In vitro* studies on the mechanism of macrophage migration inhibition in tuberculin sensitivity. *J. Immunol.* 101:1004–1015, 1968.

HEISE, E. R. AND Q. N. MYRVIK. Secretion of lysozyme by rabbit alveolar macrophages *in vitro. J. Reticuloendothel. Soc.* 4:510–523, 1967.

HEISE, E. R., Q. N. MYRVIK AND E. S. LEAKE. Effect of Bacillus Calmette-Guérin on the levels of acid phosphatase, lysozyme and cathepsin in rabbit alveolar macrophages. *J. Immunol.* 95:125–130, 1965.

HIRSCH, J. G. Antimicrobial factors in tissues and phagocytic cells. *Bacteriol. Rev.* 24:133–140, 1960.

———. Cinemicrophotographic observations on granule lysis in polymorphonuclear leucocytes during phagocytosis. *J. Exp. Med.* 116:827–834, 1962.

KLEBANOFF, S. J., W. H. CLEM AND R. G. LUEBKE. The peroxidase-thiocyanate-hydrogen peroxide antimicrobial system. *Biochim. Biophys. Acta* 117: 63–72, 1966.

LEAKE, E. S. AND Q. N. MYRVIK. Digestive vacuole formation in alveolar macrophages after phagocytosis of *Mycobacterium smegmatis in vivo. J. Reticuloendothel. Soc.* 3:83–100, 1966.

———. Changes in morphology and in lysozyme content of free alveolar cells after the intravenous injection of killed BCG in oil. *J. Reticuloendothel. Soc.* 5:33–53, 1968.

MÜLLER-EBERHARD, H. J. Chemistry and reaction mechanisms of complement. *Advan. Immunol.* 8:1, 1968.

MYRVIK, Q. N. AND D. G. EVANS. Effect of Bacillus Calmette Guérin on the metabolism of alveolar macrophages. *Advan. Exp. Med. Biol.* 1:203–213, 1967.

MYRVIK, Q. N., E. S. LEAKE AND S. OSHIMA. A study of macrophages and epithelioid-like cells from granulomatous (BCG-induced) lungs of rabbits. *J. Immunol.* 89:745–751, 1962.

NUTTER, J. E. AND Q. N. MYRVIK. In vitro interactions between rabbit alveolar macrophages and *Pasteurella tularensis. J. Bacteriol.* 92:645–651, 1966.

QUIE, P. G., R. P. MESSNER AND R. C. WILLIAMS, JR. Phagocytosis in subacute bacterial endocarditis. Localization of the primary opsonic site to Fc fragment. *J. Exp. Med.* 128:553–570, 1968.

TEW, J. G., W. M. HESS AND D. M. DONALDSON. Lysozyme and β-lysin release stimulated by antigen-antibody complexes and bacteria. *J. Immunol.* 102:743–750, 1969.

WOLSTENHOLME, G. E. W. AND M. O'CONNOR (eds.). *CIBA Foundation Symposium on Interferon.* Boston: Little, Brown, 1967.

ZEYA, H. I. AND J. K. SPITZNAGEL. Arginine-rich proteins of polymorphonuclear leucocyte lysosomes: Antimicrobial specificity and biochemical heterogeneity. *J. Exp. Med.* 127:927–941, 1968.

Carbon Monoxide Poisoning: Some Aspects of the Problem in Great Britain

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In Great Britain, until recently, domestic gas was made from coal and was always referred to as "coal gas." Today we are beginning to use natural gas, and the term coal gas is being replaced by "town gas." Most of the domestic supply, however, is still coal gas, which has a high though variable percentage of carbon monoxide (Mant, 1964). In any event it is always present in a highly lethal concentration. As coal gas is so readily available, it has been the most popular suicidal poison for many years, although the recent figures show that barbiturates are overtaking it in popularity. Nevertheless, out of the 5,000 odd suicides that occur annually in England and Wales, some two-fifths are due to coal gas poisoning. Perhaps even more alarming are the 1,000 odd persons each year who die from some form of accidental carbon monoxide poisoning, usually due to the accidental release of coal gas.

Suicide by coal gas rarely presents any medico-legal problem. In the majority of cases the suicide makes himself or herself comfortable for the act of self-destruction. The most popular method is to use the gas oven, and in a typical case the oven shelves are removed and a pillow or cushion, upon which the suicide puts his head, is placed inside. In some cases a blanket or coat is thrown over the oven, and some gesture may be made to seal the doors and windows. In a relatively small number of cases a suicide note is left, although the more thoughtful may pin a warning on the kitchen door —"Danger—Gas." In other cases the suicide may make up a bed on the floor near a gas point, or go to bed and lead a flexible tube from the gas point beneath the bedclothes. Coal gas suicides only become suspicious when relatives or friends alter the scene in an endeavour to mislead the authorities.

Cases of *accidental* carbon monoxide poisoning, however, are of great medico-legal interest. Accidental deaths from this cause have risen rapidly since World War II and now stand at over 1,000 per annum. The increase during the last 20 years is not as great as it would at first appear. Until the end of the last war the numbers of autopsies carried out on old persons who had apparently died a natural death were relatively few. Today they are frequent in all large urban areas, and, as a result, many completely unsuspected cases of carbon monoxide poisoning—up to 40% in some series—are being discovered (Mant, 1960; Simpson, 1954). A number of cases of carbon monoxide poisoning are unassociated with the simple accidental release of coal gas, but are usually due to faulty ventilation where some form of gaseous, liquid or solid fuel burner is operating. This last group provides the greater medico-legal challenge.

Where death is due to the accidental release of coal gas, the vast

majority of deaths occurs among the very old. These old people have frequently lost their sense of smell, are deaf and partially blind, and their memories for very recent events are bad. Accidents usually occur because the old person has either turned on the gas and omitted to light it or made an attempt to light it and failed, without realizing the fact. In some cases where there are a number of burners on the top of a gas stove, one will be lit and another turned on but unlit. On examining the scene of such a fatality, one usually finds a kettle or some cooking appliance on the gas ring with unignited gas escaping. Spent matches or a faulty ignitor are usually evident. The deceased may not necessarily be found in the kitchen but in some other room, perhaps even on another floor. When one questions the relatives or neighbours, one frequently finds a history of the deceased having turned the gas on and failed to light it. In order to prevent this hazard the Gas Board has developed a number of safety appliances where the gas cannot flow unless a pilot light is first lit. The pilot light heats a bimetal strip which opens the valve when it is hot, and when the gas flows, it is ignited automatically. There are other devices which will automatically shut off the supply of gas to a piece of apparatus if the gas pressure should fall in the main supply. The gas will not flow through the apparatus when the pressure returns without the valve being deliberately released.

Many of the prewar hazards have now been neutralised. These included badly designed taps that could be turned on accidentally and burners which would operate with only some of the jets ignited, thus allowing the escape of gas into the room.

A number of deaths occurred towards the end of the war, and shortly thereafter, as the result of bomb damage to mains and old, inadequately maintained installations. Again it was the aged who were the principal victims, as they could not smell the escaping gas.

Deaths from inadequate ventilation or incomplete combustion of fuel are slightly more common in the 20-50 age group. It is this group of cases which emphasizes the great toxicity of carbon monoxide (Mant, 1964).

Fatalities occur in houses, bungalows, trailers or any other establishment where some form of combustion is used to provide heat and cooking facilities. In all cases there is some error in ventilation or in the efficiency of the system in use. Weather may be a precipitating factor. With normal weather conditions three complete air changes per hour take place in an average room when the windows and doors are closed. When there is thick fog these air changes may not take place, and so a heating system which is adequately efficient under normal conditions may convert a room, or even a house, into a lethal chamber.

The dangers associated with different kinds of heating systems will now be described.

Solid fuel boilers

Solid fuel boilers are used for central heating and supplying domestic hot water. A certain type of oven is also heated by solid fuel. Most of the fatalities are seen with the boiler which heats the domestic water supply. The apparatus itself is comparatively small and may have hand- or automatically controlled ventilation. Fatalities occur when soot or other debris blocks some part of the chimney system, or when the chimney becomes cracked and develops a leak. Some systems have a damper in the actual flue pipe that regulates the draught, and if the damper is closed, or the flue becomes partially blocked and too much ventilation is permitted below the boiler, the products of combustion, containing a variable volume of carbon monoxide, will escape into the room. In most fatal cases associated with solid fuel boilers, one finds that the flue pipe has been blocked by a fall of soot or the chimney itself has been obstructed by soot at one of its angles.

In a typical case one finds the deceased lying in bed or in a chair as if asleep. If there are dogs in the house, they are frequently found dead with their noses pressed to the underside of the door, having died while endeavouring to breathe uncontaminated air.

Solid fuel boilers are also used to heat trailers which are permanently sited as year-round residences. In this group of fatalities it is invariably found that all forms of ventilation have been blocked.

Gas appliances

Any gas appliance, whether it burns coal gas, natural gas or butane, will produce carbon monoxide if it is used in a vitiated atmosphere. Fatalities have been seen where small flueless gas fires have been used for long periods in unventilated rooms and where unorthodox apparatus, such as a bucket with a long flange, has been used for boiling clothes over a gas ring. The initial coolness of the water and the air space due to the flange prevent the complete combustion of gas and, hence, cause the production of carbon monoxide.

In one case a young man was found dead in a trailer. The trailer was heated by a single-element butane gas fire. When the caravan was opened, the fire was noticed to be burning with a smoky flame which soon became clear when fresh air was admitted. A heavy deposit of soot lay beneath the element. Every ventilator in the caravan was blocked. It was found that even under these conditions the fire burned for four hours quite safely, but after this time the atmosphere became so vitiated that carbon monoxide evolved in an increasingly lethal concentration.

Liquid fuel burners

Kerosene is used for central heating, portable space heaters and small cooking heaters. I have never seen a fatality associated with a central heating system, but I have seen several associated with the use of kerosene space heaters in trailers and bungalows. In one case a man used the popular type of kerosene pressure cooking ring in his caravan as a space heater and died from carbon monoxide poisoning. In each case evidence of incomplete combustion was apparent from the deposit of soot in the room where the heater was in use.

It is important to remember that where there is smoke there is incomplete combustion. A few years ago I examined an elderly couple who died from carbon monoxide poisoning which evolved from charring potatoes in a saucepan that had been allowed to burn dry over a paraffin heater.

The final example I shall give you is of a type of fatality already described (Mant, 1961). It is a case which really emphasizes the danger of carbon monoxide and the small volume necessary in the atmosphere to cause death. In this case a night worker returned home one foggy morning to find his wife dead in the kitchen. On the stove was a bucket on a simmering gas, and in the bottom of the bucket were six charring handkerchieves. Under normal weather conditions there was adequate air space around the two closed doors and through the air brick to provide regular changes of air. It was found that no incomplete combustion occurred under the bucket when the gas was alight, even when full on, but when material equivalent to six handkerchieves was allowed slowly to char in the bucket, a lethal concentration of carbon monoxide was present in the atmosphere after some 20 minutes.

References

MANT, A. K. Accidental carbon monoxide poisoning. *Medicolegal J.* 28: 30–39, 1960.

———. Carbon monoxide poisoning —an unusual case. *J. Forensic Med.* 8:134–138, 1961.

———. Accidental carbon monoxide poisoning with special reference to incomplete combustion. *J. Indian Acad. Forensic Sci.* 3:1–10, 1964.

———. The problem of carbon monoxide poisoning in Great Britain. *Virginia Med. Monthly* 91:50–56, 1964.

SIMPSON, K. The danger of accidental carbon monoxide poisoning. A review of 100 cases. *Brit. Med. J.* 2:774–776, 1954.

On the Antiquity of Man

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Man is now lord of the earth and of the beasts and flowers, but he took millions of years to achieve his dominion. Two events more than others made man capable of his exercise of power.

1) A slowly achieved adaptation of man himself increased his potentialities far beyond those of other animals. The first step was man's gradual assumption of the *erect posture*. This put him on his peculiarly successful evolutionary path. It freed his hands and opened the way for the development of the central nervous system which made man unique in his capabilities.

2) A late revolution in man's control of his environment gave him the opportunity to exploit his special capabilities. This was the domestication of plants and animals, the *"food-producing revolution."* It freed man from day-by-day hunting and gathering and permitted the development of civilized communities.

From contemporary investigations we know that the food-producing revolution is recent, while the earliest known forms of man are unexpectedly old. A good many bones have recently been added to the previously scanty fossil record of early man. Potassium-argon dating of these fossil finds indicates that man split off from his common ancestry with the apes and began to assume hominid characteristics more than two million years ago. Yet the earliest civilization, in Mesopotamia, did not arise until nearly 3000 B.C. During almost the entire interval, man lived from hand to mouth, enjoying little greater comfort or safety than his earliest hominid ancestors.

Earliest Known Man

Though evidence concerning still earlier precursors is beginning to accumulate, *Australopithecus* is the most ancient established representative of the *Hominidae* family.

Discovery and Reception of Australopithecus

Australopithecus was named and described by Professor Raymond Dart in 1925 on the basis of a juvenile skull found in the Harts Valley in South Africa (Dart, 1925). The full story of the important find is told in Sir Arthur Keith's *New Discoveries Relating to the Antiquity of Man* (1931).

Though he cautiously called his new fossil type *Australopithecus* ("Southern Ape"), Professor Dart, in commenting on the skull, daringly attributed to the creature extremely advanced capabilities. He surmised, from the forward position of the foramen magnum, that *Australopithecus* walked upright. This meant to Professor Dart that

a greater reliance was being placed by this group upon the feet as organs of progression, and . . . the hands were being freed from their more primitive function of accessory organs of locomotion. Bipedal animals, their hands were assuming a higher evolutionary rôle not only as delicate tactual, examining organs which were adding copiously to the animal's knowledge of its physical environment, but also as instruments of the growing intelligence in carrying out more elaborate, purposeful, and skilled movements, and as organs of offence and defence (Dart, 1925).

Fellow paleontologists were offended by Dart's claims. They were inclined to place *Australopithecus* in the same group or subfamily as the chimpanzee or gorilla (Keith, 1925). (The other conspicuous error of modern paleontologists was their endorsement of the Piltdown fraud.)

Further Australopithecine discoveries were delayed for 16 years. Doctor Robert Broom and co-workers then began to find, in the Transvaal, not only skulls and teeth, but also pelvic structures and portions of extremities (Broom, 1947). Their finds proved that *Australopithecus* had proceeded far along the hominid line of development. As Australopithecine material accumulated, Sir Arthur Keith wrote: "I am now convinced, on the evidence submitted by Dr. Robert Broom, that Prof. Dart was right and that I was wrong; the Australopithecinae are in or near the line which culminated in the human form" (Keith, 1947). The first Pan-African Congress on Prehistory, held in Nairobi in 1947, was largely devoted to a vindication of Dart's point of view.
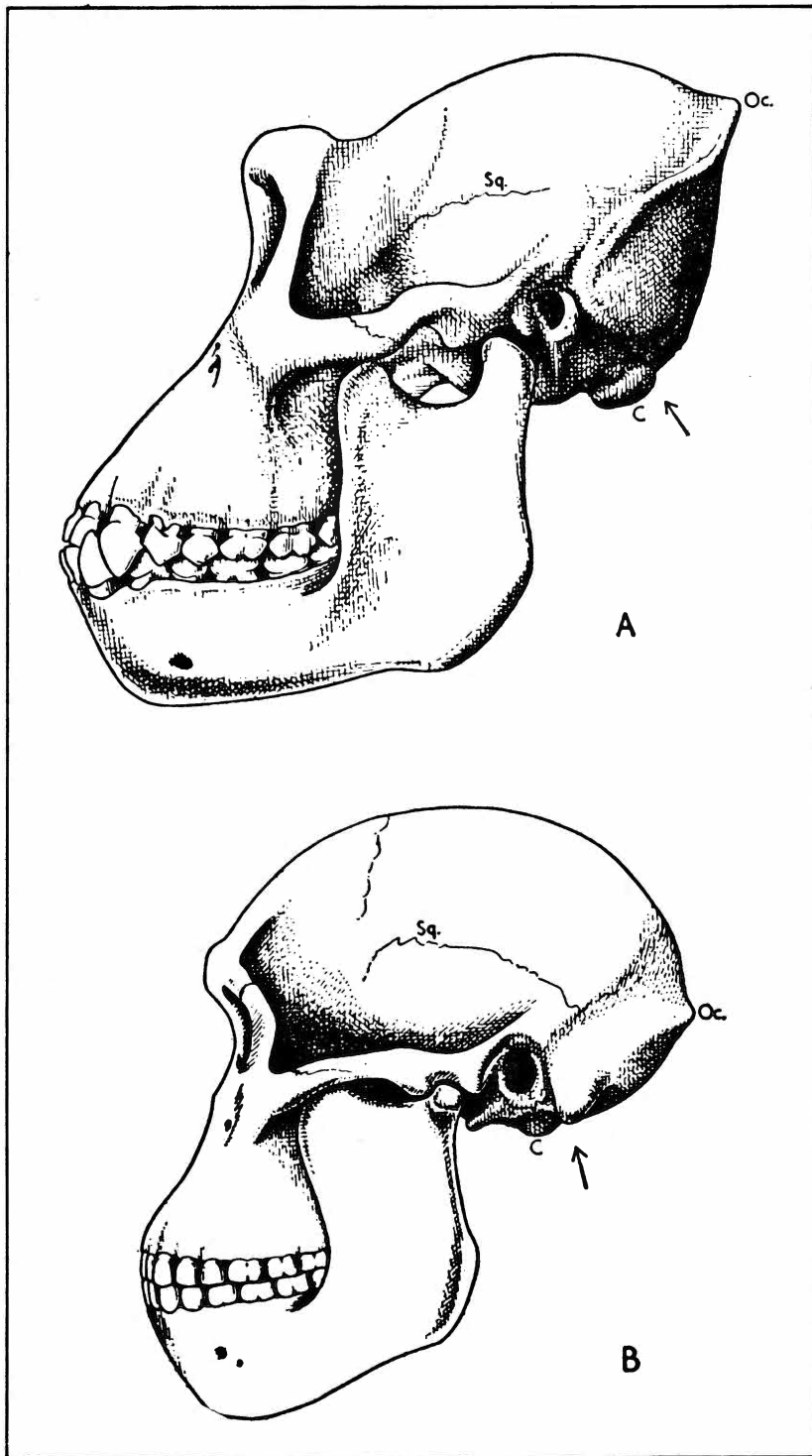
MCV QUARTERLY 5(2): 56-60, 1969

Fig. 1—The skull of a female gorilla, A, compared with the skull of *Australopithecus,* B. Note in *Australopithecus* a lesser degree of prognathism and of supraorbital torus, a more rounded vault, a low-set occipital protuberance, and a more vertical axis of the foramen magnum (arrow). (From W. E. Le Gros Clark, 1964. Courtesy of University of Chicago Press.)

Remains of *Australopithecus* have been found only in South and East Africa. The greatest antiquity established by potassium-argon dating is 2.5 million years. By contrast, evidence of *Homo erectus,* who appeared 500,000 years ago, has been found in South and East Africa, Palestine, and the Far East (Java and Peking man).

Comparison of Australopithecus with the Anthropoid Apes

Detailed description and evaluation of *Australopithecus* and other fossil hominid types can be found in two small books by Sir Wilfrid E. Le Gros Clark entitled *The Fossil Evidence for Human Evolution* (1964) and *Man-Apes or Ape-Men?* (1967).

Most helpful in demonstrating the differences between *Australopithecus* and the apes have been comparisons of the skull, teeth and bony pelvis.

1) *Skull.* In the earliest divergence of the hominid from the pongid (anthropoid ape) line, paleontologists expected the brain to have led the way. This preconception prevented them from giving hominid status to Professor Dart's *Australopithecus,* for the cranial capacity of *Australopithecus* is similar to that of the largest gorillas (only 600 cc). But, though cranial capacity is similar, cranial configuration shows striking differences (Fig. 1). In *Australopithecus* the supraorbital torus is less conspicuous, the cranial vault more rounded, the external occipital protuberance set lower, the location of the foramen magnum much farther forward, the axis of the foramen magnum more vertical, and the face less prognathous.

2) *Dentition.* Unlike the anthropoid apes, *Australopithecus* has small canines and incisors, no gap between canines and incisors, canines flush with the other teeth, and an evenly curved dental arcade (Fig. 2). The palate and teeth of *Australopithecus* look remarkably

like those of modern man, though the size of the structures is considerably greater in *Australopithecus.*

3) *Pelvic Structures.* In anthropoid apes the pelvis is very shallow from front to back. Viewed from the front it is widely splayed. The pelvis of *Australopithecus* is very deep from front to back, allowing for insertion of muscles which help in maintaining the erect posture (Fig. 3). The Australopithecine pelvis is hard to distinguish from that of modern man.

Because of the modernity of the Australopithecine pelvis, it is now believed that assumption of the erect posture led the way, as postulated by Dart, in the development of greater capabilities by the *Hominidae,* as opposed to the anthropoid apes.

A Greek account of the creation anticipated this recent scientific judgment. Epimetheus exhausted himself providing special talents for other creatures and could think

of nothing advantageous for man. Called in to complete the creation, his brother Prometheus gave man the gift of *walking upright,* like the gods (Hamilton, 1963).

The Food-Producing Revolution

About 12,000 years ago a rapid elevation in man's style of life began. It came about through the domestication of plants and animals—called the "food-producing revolution" by Professor R. J. Braidwood (1967).

Sites and Times,
Old World and New

The earliest efforts to trace and understand the food-producing revolution of the Old World were made by Braidwood. He reasoned that the transition from food-gathering to cultivation must have begun on the "hilly flanks" of Mesopotamia. On the hilly flanks (in contrast to the arid alluvial

plains of the "cradle of civilization"), there was enough rainfall for non-irrigative farming; wheat and barley, the first grains to be domesticated, grew wild; sheep, pigs, dogs and cattle were part of the natural ecology.

Working with paleobotanists, Braidwood found at Jarmo (fl. 6750 B.C.) barley, the two primitive kinds of wheat, flint sickles, mortars, ovens, stone bowls and evidence of animal domestication. The wheats were divided half and half between wild and domesticated forms. Thus, Jarmo appeared to exemplify a very early stage in the food-producing revolution. Braidwood's hilly flanks hypothesis seemed confirmed.

Later research in Syria, Turkish Anatolia, Iran and Jericho upset Jarmo's priority. Jericho, at 1100 feet below sea level and dating to before 8000 B.C., was already a large village with a dependable food supply long before Jarmo was occupied. The precise
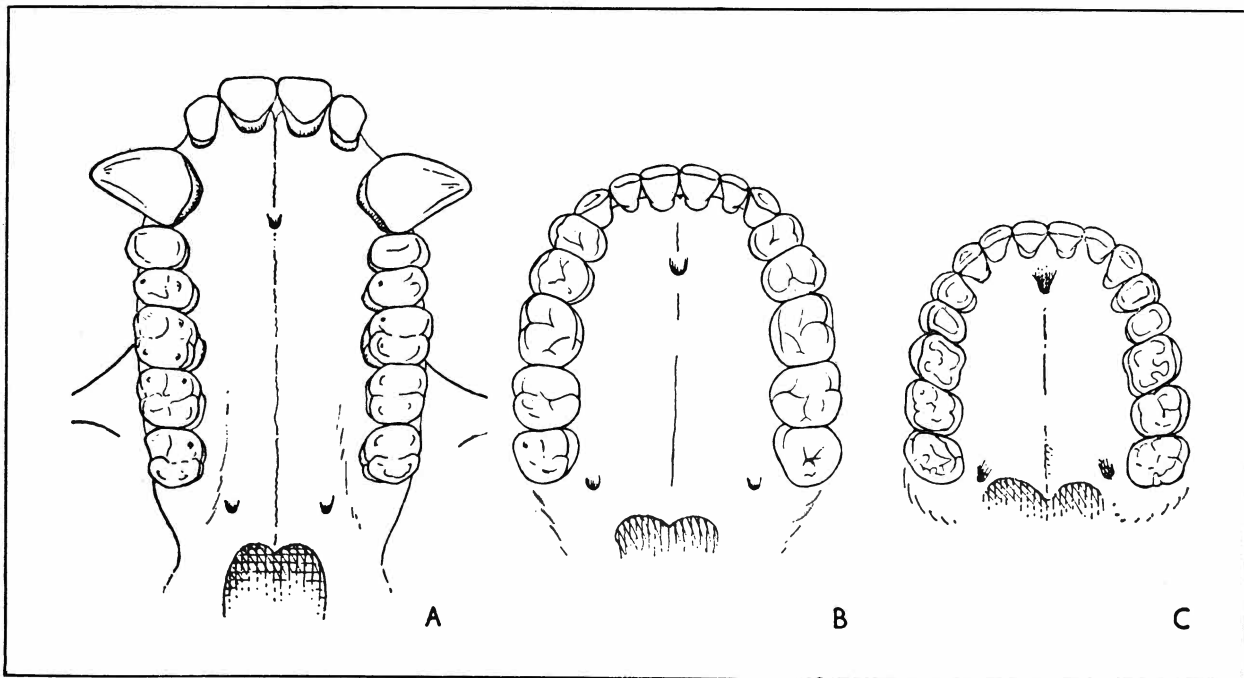

Fig. 2—The palate and upper dentition of a male gorilla, A; *Australopithecus,* B; and Australian bushman, C. Note in *Australopithecus* the relatively small canines and incisors, the absence of a diastema, and the evenly curved dental arcade. (From W. E. Le Gros Clark, 1964. Courtesy of University of Chicago Press.)

locale in which the Old World food-producing revolution took place remains undetermined.

The food-producing revolution took place independently in the Old and New Worlds. Plants and animals resulting from this revolution in Ancient America show little overlap with plants and animals domesticated in the Old World.

Cotton was grown and the dog domesticated in both hemispheres, but ancient Peruvians cultivated maize (corn), beans, squashes, peanuts, sweet potatoes, many varieties of "Irish" potato, pineapple, avocado, guava, tobacco and numerous other plants not found in the Old World. The first animal domesticated in Peru was the guinea pig. Stone tunnels were incorporated into prehistoric Peruvian dwellings as quarters for the guinea pigs, who were fed principally on anchovies (Lanning, 1967). Modern Peruvian householders continue to breed and eat guinea pigs.

By the fourth millennium B.C., the Coxcatlan people in the Tehuacan Valley of Mexico possessed domesticated chili, squash, maize, beans and gourds (MacNeish, 1964), and in the Chilca Valley on the central coast of Peru gourds, cotton and beans were being cultivated.

No one center in the New World is singly credited with the domestication of plants. Instead, it is felt that corn was domesticated in the Tehuacan Valley, pumpkins in northeastern Mexico, sunflowers in the southwestern United States, and potatoes and lima beans in the highlands of South America (MacNeish, 1964).

How the Wild Wheats Were Domesticated

The way in which the wheats became domesticated was made clear by the Danish paleobotanist, Hans Helbaek, working with Professor Braidwood.

The wild wheats first domesticated were emmer and einkorn. In the dominant forms of these wheats the spike axis holding each tuft is brittle, as are the articulation points which connect the individual spikelet with the spike axis. But in the wild wheats there is also a recessive form which has a tough spike axis. Spikelets from the dominant form are released individually and are transported readily
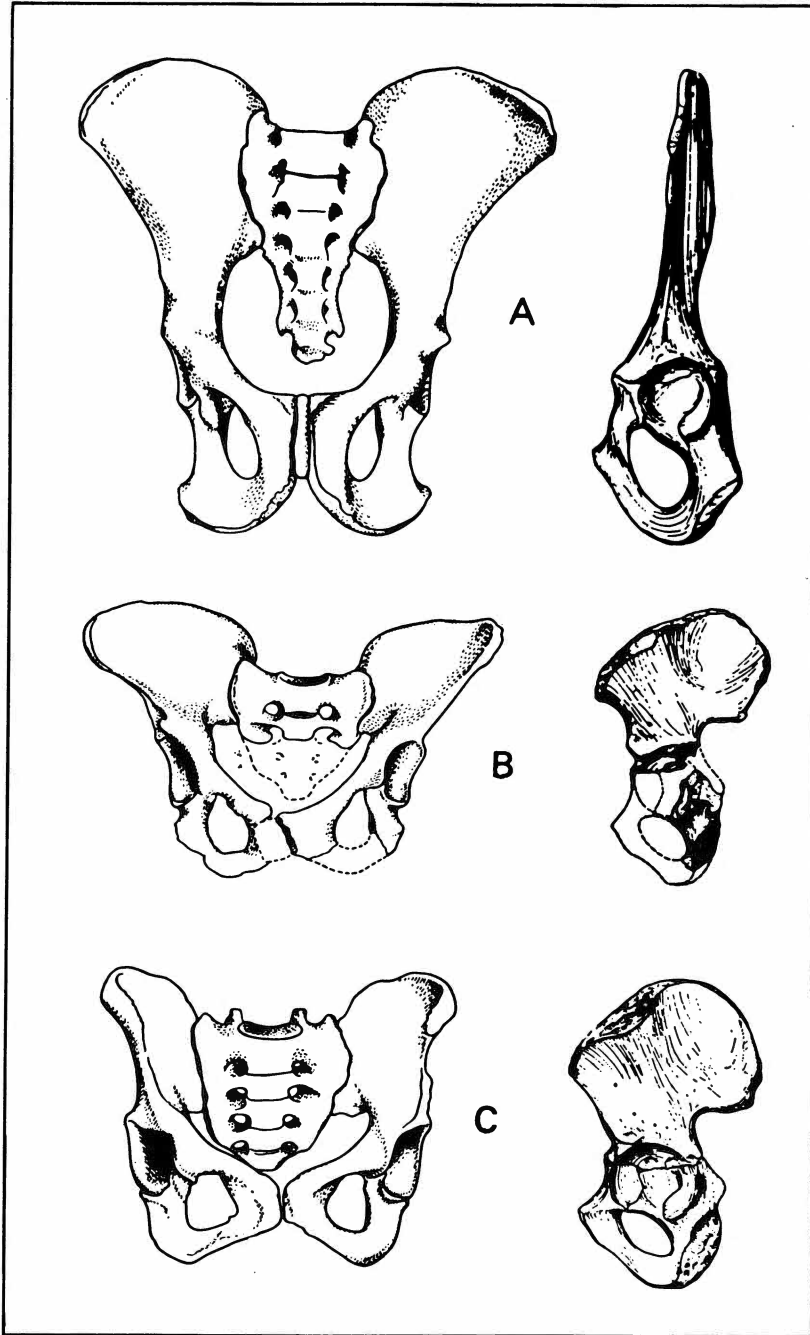

Fig. 3—The pelvis of a chimpanzee, A; *Australopithecus,* B; and Australian bushman, C. Note in *Australopithecus* the depth of ilium, the sharply angulated sciatic notch, and the strong development of the anterior inferior iliac spine. (Adapted from W. E. Le Gros Clark, 1964. Courtesy of University of Chicago Press.)

by wind and animals. Grains from the tough spike recessive form fall with the spike in one spot. Almost all such grains perish in the competition for survival.

In harvesting the wild wheats, man accumulated more and more of the tough spike recessive types. Eventually *only* the tough spikes were recovered. In the words of Helbaek: "This was the actual act of domestication, as the tough-axis cereals were no longer able to exist without the agency of man. They had become the serfs of man, but at the same time man had become the servant of the cereals, having made his new mode of life dependent upon them" (Helbaek, 1959).

An analogous dependence on man came to pass in the development of maize, whose evolution was clarified by Mangelsdorf and his associates (Mangelsdorf, Mac-Neish and Galinat, 1964). Unlike ancient maize, whose grains were individually housed, the entire ear of modern corn is inescapably wrapped in the husks. Thus, "cultivated maize has no mechanism for the dispersal of its seeds and hence is no longer capable of reproducing itself without man's intervention" (Mangelsdorf, 1965).

Effect of the Food-Producing Revolution

Prior to the food-producing revolution man had already become entirely modern in physique and intellect. His paintings in the caves of France and Spain excite our wonder and admiration. Yet he remained dependent on the daily kill or catch and the basket of recently gathered food.

Development of high-yield cultivable grains and manageable herds gave man a year-round food supply. The period which followed was one of astonishing social acceleration. A span of less than 10,000 years separates the hunter and gatherer from the highly developed civilizations of Mesopotamia and Egypt.

References

BRAIDWOOD, R. *Prehistoric Men*. Glenview, Ill.: Scott, Foresman, 1967, pp. 88–110.

BROOM, R. Discovery of a new skull of the South African ape-man, *Plesianthropus*. *Nature* 159:672, 1947.

CLARK, W. E. Le G. *The Fossil Evidence for Human Evolution*. Chicago: University of Chicago Press, 1964.

————. *Man-Apes or Ape-Men? The Story of Discoveries in Africa*. New York: Holt, Rinehart and Winston, 1967.

DART, R. A. *Australopithecus africanus:* the man-ape of South Africa. *Nature* 115:195–199, 1925.

HAMILTON, E. *Mythology*. New York: New American Library, 1963, pp. 68–69.

HELBAEK, H. How farming began in the Old World. *Archaeology* 12: 183–189, 1959.

KEITH, A. The fossil anthropoid ape from Taungs. *Nature* 115:234–235, 1925.

————. *New Discoveries Relating to the Antiquity of Man*. London: Williams and Norgate, 1931, pp. 37–59.

————. Australopithecinae or Dartians. *Nature* 159:377, 1947.

LANNING, E. P. *Peru Before the Incas*. Englewood Cliffs: Prentice-Hall, 1967, p. 63.

MACNEISH, R. S. Ancient Mesoamerican civilization. *Science* 143:531–537, 1964.

MANGELSDORF, P. C. The evolution of maize. In *Essays on Crop Plant Evolution*. J. Hutchinson (ed.). Cambridge, Eng.: Cambridge University Press, 1965, pp. 23–49.

MANGELSDORF, P. C., R. S. MACNEISH AND W. C. GALINAT. Domestication of corn. *Science* 143:538–545, 1964.

The Role of Operations Research in a University Hospital
A Review and Bibliography*

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Introduction

Traditionally, the universities have led business and industry in research methods. Since the end of World War II, however, the business world has effected increased efficiency in its many activities by the application of a variety of techniques commonly known as Operations Research (O.R.). More important, however, is the change of attitude that this indicates. It is now felt that the scientific approach (with several major restrictions) can be used to study the organization of groups, with the objective of optimizing the work of the group. Such groups may be composed of cells in a tissue culture, doctors in a hospital, instructors in a school, operators in a factory, or members of a business firm. The approach used is not magical but rather a combination of various new and old techniques from different fields. It is natural to express the logic of the system and the relationships between components of the system in the form of mathematical equations. While such aridity may dissuade some from the adoption of these techniques, the reduction of a particular O.R. problem to its mathematics may reveal its similarity to a problem already considered in the literature. Any specific problem, however, usually requires the collaboration of persons from different areas,

and the strength of O.R. techniques may lie in this interdisciplinarian approach. This includes higher management, for there is little point in a solution which is not used.

The purpose of this paper is to briefly describe some of the methods used in O.R. and to indicate where these can be applied in patient care. (See Levy and Cammarn [1968] for a review of the applications of information systems and computers to medical care.) Hospital administrators are increasingly concerned with the rising costs of hospitalization. Directors of hospitals, as well as those individuals training in hospital administration, should seek to familiarize themselves with O.R. techniques as possible tools in the search for increased efficiency and reduced costs. Likewise, doctors and medical students should find it useful to be acquainted with the methods and philosophy of O.R. Thus, they will better appreciate the actions of the administrator seeking to increase the efficiency of the hospital, and they may, themselves, initiate some O.R. studies within their clinic, practice, or laboratory. The shortage of nurses and other health personnel demands their effective use when on duty. This situation emphasizes the importance not only of selection and training, but of the provision of adequate facilities and an encouraging environment for work. Conditions leading to a high personnel turnover must be discovered

and eradicated, wherever possible. Finally, in attempting to provide better patient care, we must at all times consider the patient and seek advice from him. A system which is efficient for the staff is suboptimal if the patient is severely inconvenienced. Patients talk among themselves of uncomfortable dental chairs, long waits in drafty corridors, nurses who do not answer a buzzer, and dehumanizing treatment at the hands of doctors. This information (even though critical and, at times, uncalled for) should not go unused.

The objective of this paper is to encourage those engaged in medical care and hospital administration to regard the system they are part of, or are responsible for, as a suitable and acceptable area of research. Such research does not require a detailed knowledge of O.R. but does require an intimate knowledge of the system studied and of the objectives of the group or person responsible for its creation and functioning.

In the remainder of this paper various aspects of O.R. methods are described. However, O.R. is best typified by a willingness to examine and to change the system of interest in a systematic way. O.R. is implicitly economic, because it is concerned with optimization procedures. In the business world the objectives are to maximize profits and to minimize costs, and it is easy to quantify these ideas. In medical applications of O.R. we are faced with the need

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to quantify such objectives as giving the patient superior health care. Perhaps our research efforts should be concentrated in the area of definition and quantification of patient care. If this proves impossible, we then need to devise methods other than those described here which can be applied to hospitals, clinics, and general practice to reduce costs and to make our treatment and handling of the patient more effective.

Mathematical Programming

Definition: Here we wish to find the conditions which will maximize or minimize a function of a set of variables subject to a set of constraints.

If the function to be optimized and the constraints are linear equations, then the procedure is called *Linear Programming.* (A weighted sum of a number of variables is said to be linear.)

If the variables are restricted to take only integer values or whole numbers, then the procedure is called *Integer Programming.*

When some of the constraints are defined in terms of random variables (a random variable has a given probability of taking a given value), the procedure is called *Stochastic Programming.* Multistage decision processes are studied by the methods of *Dynamic Programming.*

Comments: Note that mathematical programming is unrelated to computer programming. Confusion between the two has arisen because explicit solutions of realistic problems in mathematical programming are rare, and empirical solutions are sought either by using a variety of computer algorithms or by using the computer to simulate the system to find a heuristic solution.

Examples: The development of hospital diets (Balintfy, 1966) is the classical biomedical example of linear programming. Here one wishes to minimize the cost to the dietary department subject to the

diet containing adequate daily amounts of carbohydrates, fats, proteins, vitamins and other trace elements and subject to the palatability of the recommended diet. The treatment of the patient is a multistage decision process (Rustagi, 1968). Consider the maintenance of anesthesia, for example.

References: Gass (1958) and Chapter 9 of Morse and Bacon (1967) are useful introductory texts to mathematical programming. Riley and Gass (1958) list an extensive bibliography in linear programming, and Praeger (1956) shows how linear programming may be applied to the composition of diets. Ledley (1965) gives examples of the application of linear programming (p452) and dynamic programming (p459) to the treatment of patients. Bellman (1968) gives an excellent nontechnical introduction to the role of dynamic programming in control theory.

Allocation

Definition: Under this heading are listed assignment and transportation problems. In assignment we wish to choose the best way of allocating n facilities to n tasks in order to maximize some criterion such as effectiveness or cost. It is assumed that the effectiveness or cost of each facility to do each task is given. In the transportation situation we wish to find the cheapest way of transporting material from m sources to n destinations. We are given the costs of transportation for each source to each destination, the amount of the commodity at each source and the amount required at each destination.

Comment: Assignment and transportation are extensions of mathematical programming and are often covered under that heading rather than under the separate heading of allocation.

Biomedical Applications: The scheduling of medical personnel, e.g., interns and student nurses, to various services may be considered

a problem in allocation. Scheduling of classrooms and conference rooms at a college, however, would be a problem in transportation in that we would wish to minimize the distance travelled by attendees as well as the number of seats unfilled or the number of people unseated.

References: Chapter 12 of Churchman, Ackoff and Arnoff (1957) and Goddard (1963) give good introductions to allocation problems.

Inventory Control

Definition: Under this heading comes the problem of finding the best reordering policy to minimize inventory costs. The costs are generally made up of the costs of purchases, storage, and the cost of being out of stock. A solution to an inventory control problem will be given as a strategy telling how to decide when to reorder and how much of a given item to reorder.

Production control is clearly a variation of inventory control, and the two may be combined into a study of production and inventory control. Here we are concerned with the ordering and storage of raw material as well as the storage and sale or disposition of the finished product.

Comment: Although inventory control is one of the most widely used techniques of O.R., no general theory has as yet emerged. Individual problems in inventory control are tackled independently, though recourse can be had to other studies with similar characteristics. Note that, while the costs of purchasing and storing are generally available or can be evaluated, the cost of an item in demand but out of stock may be difficult to assess or quantify in the medical field.

Biomedical Applications: Published studies have described straightforward applications in a hospital. Reports #4 and #8 of the Oxford

Regional Hospital Board have given optimum purchasing policy for hospital stores and have published tables for use in implementing the policy. The optimum purchasing policy is validated by reference to the Central Stores of the Churchill Hospital. The reports also show how the choice of purchase by a regional center versus purchase by the hospital will depend upon such factors as demand, lead time, and cost of storage.

Inventory control has been applied to the administration of a blood bank (Rockwell, Barnum and Griffin, 1962; Elston and Pickrell, 1963, 1965). The object here is twofold—to minimize the chance that the bank is depleted and to minimize the volume of blood which becomes unusuable because of ageing.

References: Chapter 8 of Churchman, Ackoff and Arnoff (1957); Arrow (1958); Magee (1958); Chapter 12 of Flagle, Huggins and Roy (1960); and Moran (1960) are basic texts in the theory and application of inventory control.

Queuing Theory

Definition: A study of the "arrival" times and the "waiting" times of "customers" wanting "service" and of the "server" times and the "idle" times of the server.

Queuing situations are typified by:

    (a) the distribution of arrival times of customers;

    (b) the distribution of server times;

    (c) the queue discipline, i.e., whether first come, first served or other arrangement to determine the next waiting customer to be served;

    (d) the number of servers.

Generally one is interested in the average number of customers at any time or the mean queue length when the situation reaches a stationary state, if it ever does. Of interest also are the average waiting time of customers in the queue and the frequency with which the server will be idle. The object of queuing theory is to see whether, by means of small technological or organizational changes, one can drastically improve the queuing situation in terms of the above statistics—mean queue length, mean customer waiting time, frequency of idle server.

The concept of queuing may be expanded to include the situation where there are a number of servers maintaining a number of "machines" which require service intermittently. Here one is interested in the frequency with which a given number of the servers will be idle. Clearly this situation is related to the assignment problem.

Comments: It is obvious that in a queuing situation there is a trade-off between the length of the queue (and, hence, of the mean waiting time) and how busy the server is kept. As the utilization rate of the server increases above 80%, the mean queue length will (in general) increase extremely quickly. At this level, minor perturbations in the system (such as the server taking a coffee break) will have an untoward effect out of all proportion to its size.

Biomedical Applications: All aspects of queuing theory are directly applicable to the organization of patient care. Appointment systems for outpatients have been studied as a queuing process by White and Pike (1964), among others. The Oxford Unit of Biometry is studying the application of queuing theory at St. Thomas' Hospital in order to determine a policy of non-emergency hospital admissions and thereby increase bed utilization.

The description (Chapter 25 of Flagle, Huggins and Roy, 1960) of a study of inpatient care at the Johns Hopkins Hospital is essentially an example of the queuing and assignment problem described above. Instead of machines breaking down or requiring adjustment intermittently from one of a number of servers, we have bedridden patients in a service requiring the attention of one of the nurses on that service. Flagle recommends that, in the context of his study, more efficient use of nurses' time could be achieved by:

    (a) Removing unnecessary chores from the nursing staff. This led him to advocate the use of pre-packaged and disposable items stocked and distributed by a Central Supply department.

    (b) Reduction of other unscheduled duties either by their elimination (e.g., in spite of (a), keeping a small inventory of emergency drugs maintained at the ward to remove the need for a nurse going to the Pharmacy) or by pooling services (e.g., having a centralized messenger and escort service).

    (c) A flexible policy of staffing (e.g., by switching nurses as needed from one ward to the next or by meeting anticipated peaks in demand through scheduling of additional nurses for duty).

    (d) Better selection, training and guidance of new members of the health care team.

Flagle found that direct bedside nursing care varied from 15 to 37 hours in his study ward. This variability is extremely large, and perhaps the most direct way to increase nurse utilization is to seek ways to reduce this variation. By the law of averages, if the size of the ward is increased, the relative variation will decrease; hence, the conclusion that (in general) small self-contained wards are necessarily inefficient.

The other revealing finding in this study which led to (d) is that, of the 359 new employees

followed up, only about *25%* were employed after six months. It is suggested that the fluctuation in workload—from underemployment to overemployment—may have been a factor in this personnel turnover.

References: Cox and Smith (1961) and Khintchine (1960) give a mathematical treatment to queuing theory. Doig (1957) may be consulted for other references to the theory of queuing. Lee (1966) is a readable introduction to queuing theory with examples from aviation. For applications to the hospital, see Connor (1964), Thompson, Avant and Spiker (1960) and Katz (1969).

Decision Theory

Definition: Decision theory is concerned with making the best choice from a number of potential alternative decisions (including the decision to do nothing) or constructing the best strategy in making a series of decisions.

Decision theory seeks to maximize the expected utility or to minimize the expected loss. The expected utility may be defined as:

Gain $\times$ P(decision correct)
$-$ Loss $\times$ P(decision wrong)
where P denotes probability

The other criterion frequently used in decision theory is the minimax loss principle. This is very conservative, since the decision chosen under this criterion is the one which minimizes the maximum loss in all circumstances. The minimax loss principle is illustrated in Table 1.

Decision theory leads naturally to a theory of games. In game theory the objective is to pick the best strategy of operation in repeated competitive situations.

Comments: Since the theory of games is concerned with competitive situations, such as war or business, decision theory may be considered a special case of game theory in which the competitor is

nature and, therefore, is neutral. A special case of statistical decision theory is differential medical diagnosis (or at least its idealized equivalent). In differential diagnosis the emphasis is on the recognition of the underlying disease process rather than on economics or other utilities. However, treatment may be started under varying degrees of knowledge about the condition (Lusted, 1968).

Biomedical Applications: Consider the use of the minimax principle in medical decision making. Assume a hypothetical case of treating a patient who may have one and only one of the possible diseases—A, B, C, D. Further, assume that there are four possible treatments—I, II, III, IV. (There is no reason why the number of treatments [decisions] should correspond to the number of diseases [states of nature].) Furthermore, assume that the result of using any treatment with any condition is measured in terms of the likely number of days the patient will remain hospitalized. Arrange this information in a payoff table as shown in Table 1.

The minimax decision is given by listing the maximum duration of hospitalization for each treatment or row

I	13
II	36
III	8
IV	15

and then choosing that treatment which gives the smallest figure. In

the table this is Treatment III. A patient who may have one of the four conditions, A, B, C, or D, and who is treated by III will be discharged no more than eight days after hospitalization. It may be argued that this is obvious, since III is the best treatment for three of the four conditions. However, at this point we should try to bring into the decision process our knowledge of the relative frequency of the four diseases. This can be done by multiplying the days in bed given in each column of the table by the relative frequency of occurrence of the disease heading that column. If we have no knowledge of those frequencies, we could say that they are equally likely and multiply each column by one-fourth. This, of course, will lead to the same minimax decision to use Treatment III, since the numbers in the payoff table are unchanged relative to each other. Let us now assume, however, either from our experience with other patients or from the symptoms and signs of the current patient, that the probability of the patient's having Condition B is twice that of the other conditions. From this, the probabilities are $P(A) = P(C) = P(D) = 0.2$ and $P(B) = 0.4$.

Multiplying the second column by 0.4 and the others by 0.2 gives the results shown in Table 2.

TABLE 1				
	Disease			
Treatment	A	B	C	D
I	12	3	13	12
II	4	5	36	3
III	1	8	5	0
IV	15	10	12	10

TABLE 2				
	Disease			
Treatment	A	B	C	D
I	2.4	1.2	2.6	2.4
II	0.8	2.0	7.2	0.6
III	0.2	3.2	1.0	0.0
IV	3.0	4.0	2.4	2.0

For each treatment row the maximum is selected

I	2.6
II	7.2
III	3.2
IV	4.0

and the smallest of these occurs with Treatment I which is now the minimax decision. In other words, we have here combined our knowledge of the relative likelihood of the four diseases with the effectiveness of their treatments to give in some sense a "best" decision as to which treatment is to be used. Although this is extremely artificial, the references cited below indicate the progress being made in medical decision theory at other centers.

References: Basic introductions to the theory of decision making are to be found in Wald (1950), Good (1952), and Luce and Raiffa (1957). Morse and Bacon (1967), Chapter 6-2, and Ledley (1965), Chapter 12-6, describe some examples of medical decision making. Others are Katz (1967) and Reale et al. (1968).

Network Analysis

Definition: This procedure seeks to minimize the time and/or the cost of completing a project with a given set of resources. The project typically is broken up into its components, and these are arranged in a logical sequence. The time necessary to complete each component is estimated, and a schedule is arranged. A study of the schedule reveals the "critical path," i.e., the sequence of components in which a delay will delay the completion of the project. The money or resources available may then be reallocated to ensure the earliest completion of the project. Alternatively, the original sequencing of the components may be reordered (where possible) to produce a cheaper or faster method of achieving the project goals. A simple example of network analysis is the cooking of a meal in the shortest time.

A variety of names and abbreviations is used to describe different approaches to network analysis. The most common of these are the Program Evaluation and Review Technique (PERT) and the Critical Path Method (CPM). A glossary of these names and abbreviations is available in Frambes (1964).

Comment: Network analysis is at present unrelated to the study of neural networks, since the latter depends entirely on the pattern of interconnection between neurons (Chuang, Bell and Stacy, 1967). Network analysis is different from the scheduling aspects of mathematical programming. However, these distinctions are likely to become blurred by future research application.

The origins of network analysis may be traced back to the Special Projects Office of the United States Navy, which first used PERT in the development of the Polaris missile, and to du Pont, which developed CPM for the commercial production of consumables. Since that time extensive use has been made of these techniques both in government and in industry. It is likely that the recent successes of NASA with their Apollo program are due to the coordination of research and production via network analysis.

Biomedical Applications: Network analysis could be used in the construction of a new or special health care facility, in the renovation of existing facilities, in the development of new medical schools and medical curricula and in the organization of medical care. Reduction of the time taken in surgical procedures or other complex health care procedures may also be achieved by network analysis.

References: Miller (1962) and Rawle (1964) give good nonmathematical introductions to PERT. Battersby (1964) may be used as an introductory text for network analysis. A recent application of PERT to the organization of a medical research project is given by Woolf, Cass and McElroy (1968).

Other Procedures

There is no firm agreement as to an exhaustive listing of O.R. techniques. Other topics which might have been considered are Cybernetics (Wiener, 1948; Ashby, 1956); Information Theory (Raisbeck, 1963); Evolutionary Operation, or EVOP, (Box, 1957; Hunter and Kittrell, 1966); Computer Simulation (Meyer, 1956; Fetter and Thompson, 1965; Evans, Wallace and Sutherland, 1967); and Operational Gaming (Greene and Sisson, 1959).

Search Theory is concerned with the ability to discriminate among different types. It may be considered as an application of statistical decision theory but is given prominence here because of the importance of medical screening. The objective of search theory is to decide on the optimal allocation of resources to detect an object, e.g., the best way to scan cells in a biopsy to detect abnormalities. These considerations lead, however, to the relationship between the frequency of false positives and false negatives and to the definition of clinical norms (Morse and Bacon, 1967, pp146-155).

Operational Gaming uses a computer to simulate complex systems requiring human intervention. These programs generally are of competitive situations, e.g., military combat and business management, and are used to train military officers and business executives by predicting the response of the system to their decisions. Operational Gaming promises to be a potent method of training medical students in clinical decision making (Feurzeig et al., 1964). A hypothetical patient is described, and the student at the computer console is required to ask questions, call for

hypothetical lab tests and prescribe treatment as he proceeds to form a diagnosis.

Discussion

Figure 1 shows the relationship between the basic academic fields and the biosciences, indicating that all of these contribute to the study and improvement of health care via the O.R. team. An important member of the Health Care research team is the doctor or other specialist delivering the care. Only with his cooperation can the efforts of the team be relevant and, hence, ultimately successful.

It may be of use to state here the basic premises of the O.R. approach and to outline the type of problems that it can tackle. O.R. workers tacitly assume that:

> The system under interest is not wholly indeterminate;

It is possible to experiment or to adjust the system at will and to study its responses (in engineering terms, it is possible to control the system and to gather feedback information);

It is possible to construct a mathematical or other type of model of the system.

It is then possible to study the model and the effects of perturbations on it without interfering with the smooth working of the system.

An alternative way of saying the above is to describe a system suitable for an O.R. study. It is assumed that:

> There is an opportunity for decision among different courses of action;
>
> Quantitive study and measurement is possible;
>
> Past data are available on the performance of the system

or that such data can be collected prospectively;

> Ready evaluation of the results of the study should be possible.

The problem should not be so large and complex as to be beyond definition and modeling. However, while the choice of a discrete area to study is advocated, the relationship of this area to the whole should also be considered. Ignoring this relationship will sometimes lead to suboptimization rather than to optimization. Suboptimization occurs when the solution is correct for the subsystem studied but wrong for the total system which is relevant. A given radiation dose may kill a tumor, but if it also kills the patient or produces severe side effects, it is a suboptimal dose.

Excellent introductions to O.R. procedures are given by Churchman, Ackoff and Arnoff (1957) and Flagle, Huggins and Roy (1960.) Perhaps the best paperback introducing O.R. to the busy executive was written by Duckworth (1965). It needs to be read, however, in conjunction with the present article since it gives no medical applications. Apart from isolated chapters in the texts mentioned above, the only other sources for information on hospital applications of O.R. are the annual listing of Hospital Studies of the National Health Service and the summary of NIH grants.

The Wayne Commission Report, in discussing the obligations and goals of the urban university, states: "The urban university accepts the responsibility to participate fully in the urban problem-solving process. Hence, the various colleges and their faculties accept as one primary objective the development of new ways to meet the unsolved needs of the urban area" (Virginia, 1967, pp33-34). The tools to be used in the solution of these urban problems will include those outlined by this paper. Morse and Bacon (1967) describe some appli-
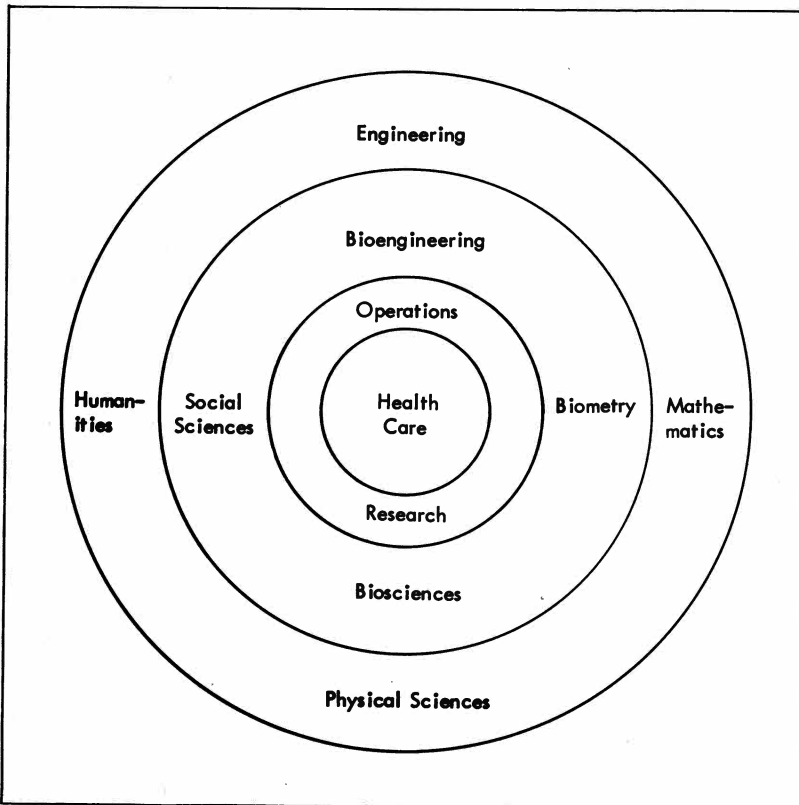

Fig. 1—Focus of various academic disciplines on health care research.

cations of the O.R. approach to problems of the city. Some references to various uses of O.R. in education are: Koenig et al. (1966), McKee and Ripley (1966), and Johnson and Wolfenden (1968).

Conclusion

In the 1968 Annual Report of the Medical College of Virginia (*Bulletin*, 1968, pp8,18) the shortage of trained medical personnel is stressed as a serious problem in the care of the sick. As a result of this personnel shortage, approximately 100 beds have recently been closed in the University Hospital. This underlies the need for large medical centers to use O.R. techniques in developing more efficient use of existing medical personnel and in seeking cost reductions while increasing the quality and coverage of medical care. When the medical center is a component of an urban university, both urban and medical problems amenable to the O.R. approach are best tackled by an academic department of the university.

References

ARROW, K. J., S. KARLIN AND H. SCARF. *Studies in the Mathematical Theory of Inventory and Production*. Stanford: Stanford University Press, 1958.

ASHBY, W. R. *An Introduction to Cybernetics*. New York: Wiley, 1956.

BALINTFY, J. L. Linear programming models for menu planning. In *Hospital Industrial Engineering*. H. E. Smalley and J. R. Freeman (eds.). New York: Reinhold, 1966, pp. 402–408.

BATTERSBY, A. *Network Analysis for Planning and Scheduling*. New York: St. Martin's, 1964.

BELLMAN, R. *Some Vistas of Modern Mathematics*. Lexington: University of Kentucky Press, 1968.

Box, G. E. P. Evolutionary operation: A method for increasing industrial productivity. *Appl. Stat.* 6:81, 1957.

Bulletin—Medical College of Virginia, Health Sciences Division Virginia Commonwealth University (Annual Report) 66:8, 18, 1968.

CHUANG, Y. H., N. R. BELL AND R. W. STACY. An automation analysis approach to the study of neural nets. *Computers Biomed. Res.* 1:185, 1967.

CHURCHMAN, C. W., R. L. ACKOFF AND E. L. ARNOFF. *Introduction to Operations Research*. New York: Wiley, 1957.

CONNOR, R. J. How to study nursing activities in a patient unit. U.S. Dept. H.E.W., P.H.S. Pub. 370, 1964.

COX, D. R. AND W. L. SMITH. *Queues*. London: Methuen, 1961.

The Documentation of Steps to Establish a Technical College and the Evaluation of PERT as a Planning Tool for Educators, Phase 1. (Submitted by R. L. McKee, president; reported by K. J. Ripley, research assistant). Bailey's Crossroads: North Virginia Community College, 1966.

DOIG, A. A bibliography on the theory of queues. *Biometrika* 44: 490–514, 1967.

DUCKWORTH, W. E. *A Guide to Operational Research*. London: Methuen, 1965.

ELSTON, R. C. AND J. C. PICKREL. A statistical approach to ordering and usage policies for a hospital blood bank. *Transfusion* 3: 41–47, 1963.
———. Guides to inventory levels for a hospital blood bank determined by electronic computer simulation. *Transfusion* 5: 465–470, 1965.

EVANS, G. W., G. WALLACE AND G. L. SUTHERLAND. *Simulation Using Digital Computers*. Englewood Cliffs: Prentice-Hall, 1967.

FETTER, R. B. AND J. D. THOMPSON. The simulation of hospital systems. *Operations Res.* 13: 689–711, 1965.

FEURZEIG, W., P. MUNTER, J. SWETS AND M. BREEN. Computer aided teaching in medical diagnosis. *J. Med. Educ.* 39: 746–754, 1964.

FLAGLE, C. D., W. H. HUGGINS AND R. H. ROY. *Operations Research and Systems Engineering*. Baltimore: Johns Hopkins Press, 1960.

FRAMBES, cited by Battersby, A.: *Network Analysis for Planning and Scheduling*. New York: St. Martin's, 1964, p. 10.

GASS, S. I. *Linear Programming*. New York: McGraw-Hill, 1958.

GODDARD, L. S. *Mathematical Techniques of Operations Research*. Reading, Mass.: Addison Wesley, 1963, pp. 64–87.

GOOD, I. J. Rational decisions. *J. Roy. Statist. Soc.* 14: 107–114, 1952.

GREENE, J. R. AND R. L. SISSON. *Dynamic Management Decision Games*. New York: Wiley, 1959.

Hospital or Regional Stores. (Report 8). Oxford: Oxford Regional Hospital Board, 1966.

HUNTER, W. G. AND R. KITTRELL, JR. Evolutionary operation: A review. *Technometrics* 8: 389–397, 1966.

JOHNSON, H. C. AND K. WOLFENDEN. "Computer Aided Construction of School Time Tables," read before the International Federation for Information Processing Congress, Edinburgh, August 10, 1968.

KATZ, J. H. Simulation of outpatient appointment systems. *Communications of the A.C.M.* 12: 215, 1969.

KATZ, L. "Statistical Decision: Theory Versus Application, Exemplified in Smoking-Health Controversy," read before the 36th Session of the International Statistical Institute, Sydney, Australia, August 28–September 7, 1967.

KHINTCHINE, A. Y. *Mathematical Methods in the Theory of Queueing*. London: Griffin, 1960.

KOENIG, H. E., M. G. KEENEY, M. J. KING, P. GINDRE, J. E. GRIGGS, M. B. SCHERBA AND L. H. PELTIER. A systems approach to higher education. National Science Foundation Report No. 3, 1966.

LEDLEY, R. S. *Use of Computers in Biology and Medicine*. New York: McGraw-Hill, 1965, pp. 451–464.

LEE, A. M. *Applied Queuing Theory*. New York: St. Martin's, 1966.

LEVY, R. P. AND M. R. CAMMARN. Information systems applications in medicine. *Ann. Rev. Inform. Sci. Technol.* 3: 397–428, 1968.

LUCE, R. AND H. RAIFFA. *Games and Decisions*. New York: Wiley, 1957.

LUSTED, L. B. *Introduction to Medical Decision Making*. Springfield, Ill.: Thomas, 1968.

MAGEE, J. F. *Production Planning and Inventory Control.* New York: McGraw-Hill, 1958.

MEYER, H. A. *Symposium on Monte Carlo Methods.* New York: Wiley, 1956.

MILLER, R. W. How to plan and control with PERT. *Harvard Bus. Rev.* 40(2): 93–104, 1962.

MORAN, P. A. P. *Theory of Storage.* London: Methuen, 1960.

MORSE, P. M. AND L. W. BACON. *Operations Research for Public Systems.* Cambridge: Massachusetts Institute of Technology, 1967.

Optimum Purchasing Policy. (Report 4). Oxford: Oxford Regional Hospital Board, 1962.

PRAEGER, W. On the caterer problem. *Management Sci.* 3: 15, 1956.

RAISBECK, G. *Information Theory.* Cambridge: Massachusetts Institute of Technology, 1963.

RAWLE, L. J. The right order of things —network analysis progress. *Unilever Quart.* 50: 128–137, 281, 1964.

REALE, A., G. A. MACCACARO, E. ROCCA, S. D'INTINO, P. A. GIOFFRE, A. VESTRI AND M. MOTOLESE. Computer diagnosis of congenital heart disease. *Computers Biomed. Res.* 1: 533–549, 1968.

RILEY, V. AND S. I. GASS. *Bibliography on Linear Programming— Related Techniques.* Baltimore: Johns Hopkins Press, 1958.

ROCKWELL, T. H., R. A. BARNUM AND W. C. GRIFFIN, Inventory analysis as applied to hospital whole blood supply and demand. *J. Ind. Eng.* 13: 109–114, 1962.

RUSTAGI, J. S. Dynamic programming model of patient care. *Mathemat. Biosci.* 3: 141–149, 1968.

THOMPSON, J. B., O. B. AVANT AND E. D. SPIKER. How queuing theory works for the hospital. *Mod. Hosp.* 94: 75–78, 1960.

VIRGINIA. Commission to Plan for the Establishment of a Proposed State-Supported University in the Richmond Metropolitan Area. Report. Richmond, Department of Purchases and Supply, Commonwealth of Virginia, 1967. (Virginia. General Assembly, 1967. Senate Document no. 14). E. A. Wayne, Chairman.

WALD, A. *Statistical Decision Functions.* New York: Wiley, 1950.

WHITE, M. J. B. AND M. C. PIKE. Appointment systems in outpatient clinics and the effect of patients' unpunctuality. *Med. Care (Lond.)* 2: 133, 1964.

WIENER, N. *Cybernetics: or Control and Communication in the Animal and the Machine.* Cambridge: Massachusetts Institute of Technology, 1948.

WOOLF, C. R., W. CASS AND J. McELROY. The use of program evaluation and review technique (PERT) in the design and control of a medical research project. *Computers Biomed. Res.* 2: 176, 1968.

Unilateral Aphakia and Contact Lenses[*]

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Introduction

The size of the retinal image in the corrected aphakic eye is some 24% larger than the image before removal of the crystalline lens. This large differential makes binocular vision impossible in individuals with unilateral aphakia corrected by spectacle lenses. A similar calculation, but with a contact lens correction, reduces this figure to about 8% (Dawson, 1962).

Theoretically, intraocular lenses represent a nearly ideal approach to correcting unilateral aphakia. However, in practice the procedure is fraught with so many long-term complications that today this approach has all but been abandoned as a feasible way of achieving binocularity in unilateral aphakia (Lieb and Guerry, 1957; Guerry and Geeraets, 1962).

I agree with Welsh (1961) that, for the patient with unilateral aphakia, a contact lens affords the only reasonably safe method of correcting the aphakic refractive error to allow a balanced normal or near normal type of binocular vision unattainable with a cataract spectacle lens. A search of the literature of the last ten years, however, fails to uncover sufficient data about the type and degree of binocularity obtained by contact lens correction of

unilateral aphakes. Sorsby (1964) states that in two-thirds of such cases full binocular vision is regained. He states that the time elapsed between loss of the crystalline lens and restoration of binocularity is an important factor in obtaining full binocular vision.

This study was undertaken (in part) in a series of 60 successive patients with contact lens-corrected unilateral aphakia in order to shed additional light on the type and range of binocularity obtainable.

Methods and Materials

According to Parks (1968) bifixation, synonymously known as binocular fixation or central fusion, signifies bilaterally functioning macular areas. Absences of bifixation can be detected by the macular suppression scotoma that can be plotted by stereocampimetry. This type of testing is both cumbersome and extremely time-consuming. An equally reliable test for bifixation is the "stereoacuity test." Stereoscopic acuity is determined by the smallest discernible difference in binocular parallax. Therefore, as Parks (1968) has pointed out, the ability to discern small degrees of image disparity is directly proportional to the resolving power of the stimulated retinas. Only in bifoveal fixation will an individual be able to perceive stereopsis from very small degrees of angle. When only the low resolving extramacular areas are used, the quality of stere-

opsis becomes appreciably poorer.

A simple and accurate test for stereoacuity is the polaroid vectograph overlay by Wirt (copyright, 1947) or any of its variations. For this study the Titmus stereo test, manufactured by Titmus Optical Company of Petersburg, Virginia, was used. The Titmus test is a printed stereoscopic test which utilizes polarized light to allow the presentation of separate pictures to the two eyes. While the picture as a whole is fused, dissimilarities of certain parts stimulate disparate retinal points and, thus, give rise to three-dimensional perception. The test pictures are arranged in order of decreasing disparity so that stereoacuity can be graded. The range of average stereoacuity is variously reported in the literature to fluctuate from 14 to 60 sec/arc, with some trained observers able to make correct judgments to the two-second level. The Titmus test only measures acuity between 800 and 40 sec/arc but is, to my knowledge, the only presently commercially available test of its kind.

In addition to being tested with the Titmus stereo test, all patients were also tested with the Worth 4-dot test for extramacular fusion. The Worth test consists of four lighted dots—one red, two green and one white—arranged in a diamond-shaped configuration. The patient wears complementary red and green-colored spectacle lenses. If the two eyes are being used together, the patient focusses the

white light, which is the only one common to both eyes, and sees four lights. Since the size of the test is such that parafoveal areas are simulated, it is considered a reliable test for simultaneous extrafoveal binocular vision.

A group of 60 patients with unilateral aphakia—consecutively and successfully fitted with a contact lens on the cataract-operated eye—was chosen for this study. All patients had a minimal corrected visual acuity of 20/30 or better in each eye and no ophthalmoscopically discernible macular pathology. All tests were done utilizing the patient's best obtainable visual acuity at the test distance.

Results

Table 1 summarizes the results of the Worth 4-dot tests. Fifty-four of the 60 individuals gave a normal response, while six individuals exhibited suppression of one eye. Of these six, two patients showed suppression of the aphakic eye; in both instances the cataract had been present for over ten years and was of traumatic nature. Two patients showed suppression of the non-dominant phakic eye but a marked anisometropia in the history indicating possible lack of binocularity prior to surgery. The remaining two individuals showed suppression of their non-dominant aphakic eye with no demonstrable evidence of lack of binocularity prior to lens extraction. Results from this group indicated a high percentage of extramacular fusion (90%) which should provide considerable physiological benefits to the individual patient.

The results are quite different when viewed from the standpoint of bifixation. Only nine of 60 patients fell in the category considered normal by Parks (1968), while another 21 patients demonstrated acceptable levels of stereoacuity. Eighteen patients did not appreciate any stereopsis in the Titmus test, while 12 patients showed low stereoacuity ranges from 800 to 200 sec/arc (Table 2).

While the attainment of some degree of fusion is ideal for the corrected unilateral aphake, Sorsby's (1964) figure of two-thirds restoration of binocularity can only be accepted when paramacular fusion rather than true bifixation is tested. However, to the patient with unilateral aphakia, the increase in peripheral field alone, even in the absence of fusion, is highly desirable. Even Adler (1965) states that stereopsis, for instance, is not a

TABLE 1
Results of Worth 4-dot Test

Normal	54
Suppression	6
Diplopia	0
Total number of patients	60

TABLE 2
Results of Titmus Stereoacuity Test

Less than 800 sec/arc	18
800–200 sec/arc	12
140–80 sec/arc	21
60–40 sec/arc	9
Total Number of Patients	60

TABLE 3
Relationship of Time Between Loss and Restoration of Binocularity

Patients with no demonstrable stereopsis	Under 1 yr	6
	1–3 yr	3
	3 yr or longer	4
	Could not be ascertained	5
	Total	18
Patients with 800–200 sec/arc	Under 1 yr	3
	1–3 yr	5
	3 yr or longer	4
	Total	12
Patients with 140–80 sec/arc	Under 1 yr	6
	1–3 yr	11
	3 yr or longer	2
	Could not be ascertained	2
	Total	21
Patients with 60–40 sec/arc	Under 1 yr	4
	12–18 mo	3
	3 yr or longer (8 and 10 yr)	2
	Total	9

necessary prerequisite for the safe operation of motor vehicles, one of the most frequent reasons for the contact lens correction of unilateral aphakes.

If one looks at this group of patients from the standpoint of the time that elapsed between the loss of binocularity and the restoration of vision in the aphakic eye by a contact lens, the results are not what one would expect from statements in the literature (Welsh, 1961; Sorsby, 1964). It is evident from these findings (Table 3) that the time factor does not have a significant bearing on the prognosis for binocularity. In the 60 to 40 sec/arc group there were two patients with a time lag of eight and ten years, respectively, between loss and restoration of binocularity, while the group with no demonstrable stereopsis on the Titmus test included six patients who had less than one year of uniocularity.

Discussion

The results of binocular testing of this group of patients would indicate that the amount of stereopsis to be gained by fitting a patient having unilateral aphakia with a contact lens cannot be prognosticated but that such a procedure is worthwhile even when many years have passed since cataract extraction.

In order to eliminate potential failures, disappointing both to the patient and the contact lens fitter, a careful screening of all patients is advisable. While age alone is not a contraindication, the degree of manual dexterity of some older patients, especially when afflicted with arthritis, tremor and similar conditions, has to be taken into careful consideration. The integrity of the corneal epithelium, the possible presence of inadvertent filtering blebs, chronic conjunctivitis or dacryocystitis all have to be carefully weighed before making the decision to fit a patient with a unilateral contact lens. One of the most frequent causes of failure has been mild keratitis sicca; for this reason a Schirmer test should be performed on every elderly aphakic patient before lens fitting. Another condition causing a high rate of failure is the Cogan-Guerry (Guerry, 1966) microcystic epithelial dystrophy. The dystrophic change of the corneal epithelium is occasionally overlooked and, when fitted with a contact lens, a cornea thus affected will usually react with rather marked epithelial staining and breakdown. High degrees of postoperative astigmatism have not been a particular problem in fitting since the availability of toric base curve lenses. And lastly, as in all contact lens wearers, the emotional stability and attitude of the patient is a major factor in the ultimate outcome of the individual case.

Summary

The binocular functions of a group of 60 patients with unilateral aphakia were tested after fitting with a contact lens. Results showed a high degree of extramacular fusion in the group. However, only 50% of these patients obtained satisfactory stereoacuity levels. There was no relation between the time elapsed from cataract extraction to contact lens fitting and the amount of ultimate stereoacuity obtained. Some factors presenting common obstacles to successful fitting of aphakic contact lenses are discussed.

References

ADLER, F. Physiology of the Eye, Clinical Application. St. Louis: Mosby, 1965, p. 7114.

DAWSON, H. (ed.). The Eye. Vol. 4. Visual Optics and Optical Space Sense. New York/London: Academic, 1962, p. 179.

GUERRY, D., III. Observations on Cogan's microcystic dystrophy of the corneal epithelium. Am. J. Ophthalmol. 62:65–73, 1966.

GUERRY, D., III AND W. J. GEERAETS. Complications of anterior chamber lenses. Am. J. Ophthalmol. 54:229–232, 1962.

LIEB, W. A. AND D. GUERRY, III. Anterior chamber lenses for refractive correction of unilateral aphakia. Am. J. Ophthalmol. 44:579–598, 1957.

PARKS, M. M. Stereoacuity as an indicator of bifixation. In International Strabismus Symposium, Giessen, 1966. An Evaluation of the Present Status of Orthoptics, Pleoptics and Related Diagnostic and Treatment Regimes. A. Aruga (ed.). Basel: Karger, 1968, pp. 258–260.

SORSBY, A. (ed.). Trends in Modern Ophthalmology. Vol. 4. Topical Aspects. Washington, D. C.: Butterworths, 1964, pp. 627–628.

WELSH, R. C. Contact lenses in aphakia. Internat. Ophthalmol. Clin. 1: 401–440, 1961.

Days, Old and New*

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Shortly after I arrived at the Medical College of Virginia on July 1, 1925, I came upon a student newspaper, *Skull and Bones*. In that issue, I found a digest of a speech by Dr. Stuart McGuire— the President of the College from 1919 to 1925. That speech to the students outlined the desired characteristics and qualifications of the College President, who was being sought. I was a little startled, because they were looking for a man who was an educator (I thought I might qualify in that regard), a beggar, a politician, and an administrator. I wasn't much of a politician, and I hadn't yet learned how to beg. That came later.

From July 1 to September 1, 1925, I was dividing my time between the College and my old job. A new executive coming to replace another man has to find out what the components of the job are and what the problems are. Since I was a new president and the second full-time president in nearly 90 years, everybody came to me to offer advice as to what ought to be done. That was a lot of fun, but the fun really began in trying to do the things proposed.

When I accepted the post, I had no knowledge of the fact that there was a floating debt to two of our local banks, the notes of which had been endorsed by members of the Board. I had no knowledge of a

mortgage debt on Memorial Hospital, held by the Life Insurance Company of Virginia. I did not know there was a damage suit against the College by a dental student who was not awarded his diploma. He not only asked for his diploma in that suit, but also for $2,500 damages. He didn't win, but more will be said about that suit later.

There were problems other than financial. An inspection by the members of the Council on Medical Education and Hospitals in 1919 had revealed that the College was delinquent in preclinical and clinical personnel, in laboratories, hospital beds and finances. Could there be any more than that? I hadn't even heard of the Flexner report.

Right after Commencement, 1925, I was ushered off to Atlantic City with the Chairman of the Board, Mr. Eppa Hunton, Jr.; Dr. Stuart McGuire; Mr. J. R. McCauley; and Mr. Thomas L. Moore to face the Council on Medical Education and Hospitals in their annual session. "The main points to be made," said Dr. McGuire, "are we have a new President, and we are going to get things started. Moreover, we have made a lot of repairs and additions and put on much paint since you were our visitors in 1919, and now we are ready to move forward to fulfill our needs."

And what were our needs? Memorial Hospital, St. Philip Hospital and Dooley Hospital provided a total of 300 teaching beds, 420

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total beds. We had an open staff, which meant that local practitioners were using both teaching beds and private beds. In some instances we received very little return in time or teaching for the instruction of students and resident staff. We had a total resident staff of 16. We needed hospital beds, but more urgent than hospital beds were the appeals of the senior staff for a teaching building.

One of the most lamentable aspects of the new undertaking was that very few people in Richmond knew anything about the Medical College of Virginia. What was a man like me going to do? What would you do to find out whether it was true that the people of Richmond, much less the people of Virginia, knew little about the Medical College of Virginia? Two students were asked to stand at Seventh and Broad Streets one morning and ask everybody who paused during the rush hour, "Where is the Medical College of Virginia, please?" You may be surprised to hear that very few could give directions to these "lost students."

The most persistent pressure from the students involved the failure of the faculty in meeting classes. Mrs. Sanger and I had sessions at our house at night with the officers of each of the classes in Medicine, Dentistry, Pharmacy and Nursing to find out the extent of the problem, and we found it was considerable.

We had a campaign to raise funds to build a nurses' residence on Broad Street. It was once named Cabaniss Hall but is now the Nursing Education Building. We met some opposition from our colleagues on the staff who felt a teaching building should have priority. What does one do? There is just one thing to do. One can say, and that's what was said, "We have to set a standard for the care of our women here, equivalent to what we would expect our own daughters to live under, and we

are going to construct this building." We raised the money and built Cabaniss Hall. A few years later, we raised funds and built St. Philip Hall, later named MacFarland Hall.

We had those things out of the way, but we desperately needed a building to house an adequate library. The square footage in the old library in McGuire Hall was no more than is in this room. We learned that Dr. Joseph L. Miller had given to the Richmond Academy his very valuable library, with the understanding that it would be properly housed. That appeared to open an opportunity for the new president; so he began to talk to Dr. Stuart McGuire, Dr. Shelton Horsley and other leaders in the medical community, asking them whether we could join with the Academy of Medicine to help build for them a home and for us a library. The idea stemmed from a tour I had made in 1927. Here is my diary, and it is interesting reading.

I started in Richmond and went from coast to coast, stopping at about 20 medical centers altogether. Every night, what was heard and seen during the day was written in this diary. It is one of the most useful books I have ever acquired. I can't tell you all about that journey, but I can tell you one little funny thing about it. I found we didn't have much money, so I paid part of my expenses. If I bought a Pullman ticket with so many hours' stay at every stop, generally a day or two days, then I could save a lot of money. I understand you can't do that now. I went to Detroit, Chicago, Milwaukee, Minneapolis, Rochester (Minnesota), then up through the Canadian provinces as far north as Edmonton in Alberta, on to Seattle, Portland, San Francisco, Los Angeles, and then home by Salt Lake City. The diary grew out of that long trip.

What had we been looking for? Ideas with respect to two fundamental things: (1) physical plant;

and (2) personnel, particularly hiring and keeping satisfied clinicians on a full-time basis. At that time, we had only two clinicians with college offices in Memorial Hospital. They were Dr. Claude Coleman, neurosurgeon, a very loyal and able worker, and Dr. Paul La Roque in general surgery, an excellent teacher.

I wanted to find out, for example, how the University of Michigan kept happy clinicians on a paid basis but restricted as to private practice. That was one of the questions posed along the way. Where do you find these academic people, and what kind of folks are they?

At the end of that trip we began to make things happen. In 1928 we found our first full-time professor of medicine in Dr. William Branch Porter. I don't believe this college will ever adequately define the contribution he made here. His devotion and his competence were perfectly wonderful. He didn't always agree with his colleagues, but he was certainly levelheaded in most instances. He used to come to my office and sit and say, "Mr. President, we've got to do this, and we've got to do that," keeping up my spirit and talking about the things to be done. He was a good clinician, and I'd like to say a few words of tribute. My wife went into his office for professional care one day, and he said, "Sylvia, you are anemic." She said, "How do you know?" He replied, "I can tell from your tongue and lips." He put her in the hospital. Her hemoglobin proved to be dangerously low. This incident in itself is not spectacular but serves to show that he was one of the keenest observers I have ever seen, not only of things clinical, but of the cleanliness of the institution and the attire of the students and other personnel.

Following the adoption of the whole-time plan for clinicians, some confusion and unpleasantness ensued, a case of "town and gowns," and it set the clock back.

In 1930 I made my report on the five-year accomplishments of the institution. I think this is a valuable historical document. It showed growth in the student body of 66% and similar growth in such areas as finances and hospital intake of patients. It is a rather remarkable record, and it was made possible by a wonderful Board of Visitors and a faculty loyal even in the midst of strife. We had built two dormitories, but we hadn't built the Education Building yet. The State had appropriated the money for the library by 1930, and it was to go under construction at an early date. If you don't think it's a job to unite the local medical society sufficiently with an educational institution to accomplish the kind of thing we did, try it! The way we went about it was to have so many members of the Academy to dinner and explain to each group why, where, and how we were going to get an Academy of Medicine Building and an MCV library. It worked but was a demanding job.

Dr. Bigger had arrived in 1930 as Professor of Surgery—a superb appointment. He was a real teammate for Dr. Porter, beloved by all his patients, a most loyal faculty member and a surgeon of rare ability.

We were almost always unanimous in our decisions in the Board or in the Executive Committee. One reason for this phenomenon was that, in advocating action by the Board, I found that time should be allowed for complete understanding of the action involved. If the resistance to taking affirmative action was sufficient to imperil the vote, I would say quietly, "Well, that's fine; we'll just think it over and bring it up again if it seems appropriate." There were a lot of things never brought up again.

I once made the mistake of saying in a meeting downtown that our Board always voted affirmatively. It was true that our Board was almost always unanimous on

actions taken, but the statement got out in the community and made the Board sound ineffective. I explained to the Board that if the action of the Board was not likely to be unanimous or virtually unanimous, I just didn't push it. I reasoned that either more educational work was needed or that, perhaps, the President was wrong.

In order better to clear things for Board action, the very first thing done in 1925 was to reorganize our fundamental administrative structure. We had three deans and soon had a fourth—the Dean of Nursing. We organized the present Administrative Council, which was, and is, responsible for gathering the data for budget making and formulating policies and procedures to be recommended to the Board. As a consequence, when the President made recommendations to the Board, it was almost always with full backing of the executives of the institution. We met weekly, because there were so many problems to be considered. Almost every night of the week I would meet with some departmental committee. I went everywhere to see everything that I could possibly see that would be helpful to us. I must admit that I was a very poor husband and parent in those days, because I wasn't home enough.

One of the things I have always been proud of, ladies and gentlemen, is the November, 1932 College bulletin. We sent this bulletin to the medical profession of Virginia, inviting them to use our library, on the basis that we would pay the postage to send them books and journals if they would return postage. The bulletin listed all of our journals, over 200 complete sets. *The Boston Medical Journal*, I remember, went back to the very first issue and was a very difficult set to complete. We were then receiving 500 journals, and we offered these as well as the use of our books. We were trying to be useful to the State.

We asked the State for student

scholarships granted on the promise that after graduation the recipients would practice medicine in rural areas of the State. We also took steps to find out where our patients came from. One year when we totaled the count, we found we had patients from every county and city except one. I said, "For goodness sake, go over there and bring back a patient who needs hospitalization." We took care to let our legislators know that we were taking care of their sick people on a routine basis. This service went up and up, until we finally had to get out a bulletin entitled *Where Ends Don't Meet*. We got money from the Community Fund and every Tom, Dick, and Harry we could reach, but there was still insufficient money to pay hospital and outpatient clinic costs. We even had pictures framed of the Egyptian Building in color and asked the lawyers of Richmond to hang these up in their offices with a nice, little legend below, inviting anybody making a will to think about us. Every kind of device you ever heard of was used. We talked to anybody that would hear the story. Well, what happened was that by the time we got going pretty well in the 30's, I found myself involved in all kinds of local and national activities. People still sometimes come to my office and ask, "Where did you get all these citations?" Well, I just say, "If you live a long time, work a little bit, and don't run off with anybody's wife, this just happens." I didn't work for those things. The College had to be involved in the community and make the community become involved in the College.

Then came the blight of the depression. What were we going to do? Where were we going to get our teaching building? Where were we going to get the new hospital and the house staff dormitory?

There were two programs in the Roosevelt administration inviting applications for Federal funds to put people to work. One of them

was the Works Progress Administration, under which we had several hundred people working here, paid by the Federal Government. We were training unskilled workers, and two of them were in my office all of the time. The outpatient clinic, the hospitals and the laboratories had as many as 150 to 200 of these people on each tour of duty. I never before knew that people were in such great need of opportunities to work. I wish we could stir up a little of that interest now. We turned out a lot of good stenographers, bookkeepers, and other personnel. Then came the PWA program and the opportunity to meet our needs. We were the second institution in Virginia to get money. It was grant money, and originally 70% was to be furnished locally and 30% by the Federal Government. It was found that the localities couldn't meet this cost, so the percentage was reduced to 60-40, and then to about 55-45. We moved to get our hospital on that basis. We didn't know where our part of the money was coming from, but we hoped it would materialize; and then we found the door was closed. What does one do when the door is closed? One does something that might lead to another open door. We decided to try to build a laboratory building and outpatient clinic. We found a man and his wife who gave us the money we didn't have, and we got that building. We understand the contractor lost money, and we are, of course, sorry about that, but that was because prices were firming up.

As you would expect, there was criticism. It was said the President of MCV had no business building a clinic and teaching facility when the need was for a hospital. Even my closest friends criticized me, but one has to be thickskinned if one is going to be an executive. We had planned the clinic, the laboratory building and the hospital as one associated set of facilities. Almost as soon as the clinic doors opened, we applied for hospital

construction funds. We were told that if we wanted equipment, we had to apply for the equipment when we applied for the building. We saw no way of obtaining the resources with which to buy equipment, so we left that out for the moment.

I was on vacation in Edinburgh with my wife and son when I got a cablegram from Mr. McCauley saying the hospital grant had been approved. As a preliminary to this trip, I had been in Washington seeing a Senator and everybody else I could see about the hospital, while my wife went on to New York. I spent most of the night before sailing writing letters to follow up on getting that money. The joy of getting the cablegram was so great that, I must tell you in all honesty, I never slept a wink that night. Many things had to be done. We had a short schedule in which to put people to work, and I didn't see how we were going to meet it. We did it by having one contract for excavation, one for the steel frame, one for the building, and others for plumbing, electrical work, etc.

We opened the clinic building in 1938 and MCV Hospital in 1941. As you would expect, there were scoffers. People said, "They will never fill the new hospital." Some called it "Sanger's Folly." That didn't bother me too much. I had seen a lot of other follies like that. When we had open house—December 5, 1940, I think it was—it was a frosty, cold night. We had standing outside two lines of people— at times, as many as four abreast— extending from the hospital up to the City Hall. Fortunately, we had things organized to take care of people with dispatch. It was a wonderful experience, including gifts of flowers everywhere.

During the same period we received our Alpha Omega Alpha Chapter. We then built the heating plant, tunnel system, laundry, and Hunton Hall, and, during PWA days, added two floors to McGuire

Hall. Later we extended that building to the west. We then got the new dental building. Now we are getting another dental building, which is very important.

There is one thing that I should like to say with regard to great hurdles. We found it was easier to beg money from the State for building than it was to get money for land to build on. We have over 30 acres in Richmond now, but we had precious little when we started here. One thing we did was to get a good real estate man who would live with the job. He made drawings of every block in this area, with the name of the owner, the assessed valuation, frontage, etc. Each was to scale or relative scale, and the collection was bound into a number of books. When an owner or salesman would come in and say, "Well, I understand you want to buy property, and I've got so and so," I would say, "What do you want for your parcel?" He'd name his price, and I would look at my little book and see whether it was in line. Sometimes we bought land when we didn't know how we were going to pay for it, but we always did ultimately. In time I bought over 100 pieces of property, and others bought some, too. I could tell you real estate story after story. Once we blocked the location of a filling station from being located where Hunton Hall is by being alert to the problems involved. We continued to move in many directions.

The funds appropriated by the State when I first arrived were $25,000 for hospital care and $65,000 for teaching, which was, of course, "sound money." In 1928 I went to Governor Byrd's office at his request, and he said, "Doctor, you are not a state institution, and I think you ought to be satisfied to receive the same appropriation in the next biennium that you received in the past biennium." I said, "Governor, I am sorry to say, sir, but we *are* a state institution." He said, "How is that? I've been in the Sen-

ate all these years, and we have always thought of yours as a state-aided institution and, therefore, haven't felt too obligated." I was uncertain as to our position, but I promised to get the records.

The background which enabled us to get over that hurdle is interesting. A dental student, mentioned earlier, had sued for his diploma, and we had to retain a lawyer. The lawyer, in searching the old records, found that about 1883, when the Governor of Virginia tried to abolish our Board, although another Governor had appointed it, the Board locked themselves in the Egyptian Building and refused to surrender. The case went to court, and the court decided, in brief, that we were a state institution on this basis: The appropriations of 1844 and 1860 by the State, a total of $55,000, provided that in consideration of these appropriations, the buildings to be put up—the Egyptian Building and an infirmary, which was later called Old Dominion Hospital and located about where St. Philip Hospital now stands—constituted state property. All property acquired subsequently likewise was to belong to the State. This is known as a "future property clause."

There had been a movement in the legislature in 1922 to bring the medical school in Charlottesville to Richmond. You may have heard about that. I think it would have been a mistake. In that dispute, the question of a state-aided or state-controlled institution was also heard.

When I found the court records referred to above, we didn't have any Xerox equipment. Hence, I copied the records in longhand and took them to the Chairman of the Board, Mr. Hunton, whose office was in Broad Street Station, and told him I had discovered something important and explained it in detail. He said, "Doctor, if that's true, nobody else has ever heard about it." It was on that basis that we established the case subse-quently that we are a state institution and have a right to receive state money.

We had another battle in the General Assembly in which what we asked of the Legislature was vindicated. It was the right to borrow money, like other institutions, by issuing certificates of indebtedness. We won this right, because during the Adjustor period in the state government referred to above, we had been declared by court action a state-owned facility, and everything we acquired in the future belonged to the State. Later court decisions included the University College property with which we consolidated in 1913.

These are some of the things that represent the "Old." You know about the "New." There isn't time to talk about the new, except to praise accomplishments.

I was asked when I came here today why I accepted the presidency of MCV. In the first place, I was partly ignorant, but even if I hadn't been, I would have accepted anyway. It is not generally known that I started out to obtain a Ph.D. in the basic medical sciences to prepare for a career in clinical medicine. Later I actually applied for admission to this medical school for advanced standing—which was then permissible—in order, perhaps, to prepare for psychiatry. I had the feeling that psychiatry was a neglected subject, that it needed lots of research and that perhaps I was called to do it. I never got to it because of serious progressive nearsightedness, but if I had any capacity at all for projecting ideas and calling in recruits to help implement them, it grew out of the greatest assets in aggressive administrative work. Years ago I used to decry taking a man out of a research laboratory to put him into a deanship. I don't do this any more.

Another thing I found necessary over the years was to become somewhat expert in a number of fields. How do you treat alcoholism, for example? How do you get ready to implement a physical medicine department? If you got all the books you could from the library, stacked them up in your office, read them and became an honest-to-goodness hobbyist in that field, lived with it at home and by visits elsewhere, you could cast your whole career in a series of hobbies, and hobbies have their great merit. If I were ever to write anything about my career as an executive, it would be called *The Hobbies I Have Tried*. This is not very well analyzed here, but I have to conclude.

I can say to you, though, that no man in his day could have had more rewarding experiences than I have had right here in this community. Despite the disputes that could have been prevented if we had been a little more alert (like the one in 1941 when MCV Hospital was opened), there has been great satisfaction. When offered elsewhere twice the salary that the State was willing to pay, I would have made the greatest mistake of my life in accepting it. I believe that, by taking root and growing, one can reap maximum benefits, not so much in shekels, but in getting things done among people who respect you and love you.

BOOK REVIEW

Computers in the Service of Medicine. Essays on Current Research and Applications. Gordon McLachlan and Richard A. Shegog (eds.). *2 Vols. London: Oxford University Press, 1968. 382 p. $7.00.*

The 23 short articles presented in these two paperback volumes describe work in progress and the current thinking at a number of British medical centers on the use and installation of computers in hospitals. The majority of the authors are doctors, working in medical schools, who see medical computing as their discipline. Progress in this field is notable in the United Kingdom in spite of the use of what we in this country would consider to be small and antiquated computers (although allowance must be made for the fact that more sophisticated computing systems will have been installed since 1967). This progress is probably due to the organization of medical care through the National Health Service, to the existence in British medical schools of social medicine departments which have provided the manpower for most of these studies, and to Nuffield and N.H.S. support of operational research in hospitals in the last ten years.

Everyone remotely interested in computers in medicine will find something of interest in these two small books, since the articles cover such topics as:

- justification and installation of hospital computers (1),* (21);
- systems analysis of medical records and the flow of information in a hospital (13) with a critique of this use of systems analysis (14);
- computer coding of clinical data—peptic ulcer outpatients (6), diagnosis (16), medical records (17);
- various computer methods of identifying patients (3), (4) and the error rate in patient identification by existing methods (15);
- storage and retrieval of medical information (2), (18), (19); and
- future role of computers in medicine (22).

The applications described are well known, viz., application of computers to EKG analysis (7), automation of clinical chemistry (8), radiation therapy planning (9), detecting side effects of drugs (10), (11), and development of admission policies resulting in greater bed usage (20).

The writers briefly describe their own studies, most of which are incomplete. They omit for the most part references to other workers or to work in the United States. (For a more comprehensive survey of computer applications to medicine in this country, see Levy and Cammarn.†) However, McLachlan and Shegog give a simple introduction to some of the problems under consideration today. Clearly the computer is not a panacea which will change the face of medicine overnight. More efficient use of the doctor's talents and an increase in the quality and quantity of the care of the sick will undoubtedly result from the increased use of computers in medical centers. This will be achieved only if the taxpayer is willing to invest in this type of research, if a significant number of the medical profession are prepared to contribute their energies to making the computer relevant to medical practice, and if the profession as a whole is willing to accept these changes.
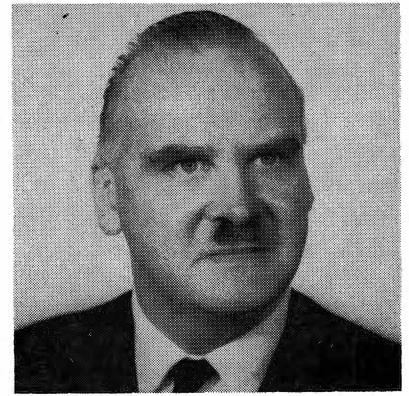
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* Refers to the numbering used in the text.

† Levy, R. P. and M. R. Cammarn. Information systems applications in medicine. *Ann. Rev. Inform. Sci. Technol.* 3: 397–428, 1968.

Contributors
to this Issue

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Arthur Keith Mant (*Carbon Monoxide Poisoning: Some Aspects of the Problem in Great Britain*), a native of England, teaches forensic medicine at a number of hospitals, including St. Mary's, Guy's, King's College, and at London University and the Police College. After graduating from Denstone College, Staffordshire, and St. Mary's Hospital Medical School, he took advanced training in pathology. His published work has dealt with the investigation of obscure deaths, poisoning, and war crimes. Dr. Mant was the 1963 A. D. Williams Distinguished Scholar for the department of legal medicine at the Medical College of Virginia.

Quentin N. Myrvik (*The Interplay of Defense Mechanisms Against Infectious Diseases*) is professor and chairman of the department of microbiology at the Bowman Gray School of Medicine of Wake Forest University. He received his M.S. and Ph.D. degrees from the University of Washington. Dr. Myrvik was formerly a member of the faculty of the University of Virginia School of Medicine. His research interests include cellular immunity, physiology of alveolar macrophages and delayed sensitivity.

William Thomas Sanger (*Days, Old and New*), chancellor emeritus of the Medical College of Virginia, was graduated from Bridgewater College and received graduate education at Indiana University (M.A.) and Clark University (Ph.D.). Before serving as president of MCV (1925 to 1956), he had taught history, philosophy, psychology and education at Bridgewater and Harrisonburg State Teachers Colleges and had been dean of both colleges. Dr. Sanger's contributions to medical education have reached far beyond the Medical College of Virginia and Richmond. He has been consultant on educational and hospital needs in many states and has been awarded honorary degrees from several colleges and universities.
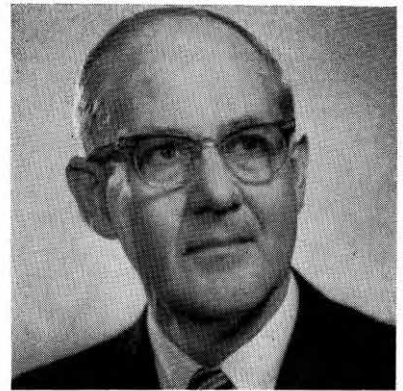
Richard W. Schayer (*Histamine and Thyroid Hormone Function*) is principal research scientist, Research Center, Rockland State Hospital, Orangeburg, New York. He received a Ph.D. in biochemistry from Columbia University and was formerly on the staffs of the Merck Institute for Therapeutic Research, Rahway, New Jersey, and the Rheumatic Fever Research Institute, Chicago, Illinois.

Roland Schmidt (*On the Antiquity of Man*) is a pediatric cardiologist and associate professor of pediatrics at West Virginia University Medical Center. A native of the state of Washington, he received his M.D. from the University of Chicago. After nine years in general practice in Louisiana and California, he took his pediatric and pediatric cardiology training at the University of North Carolina.
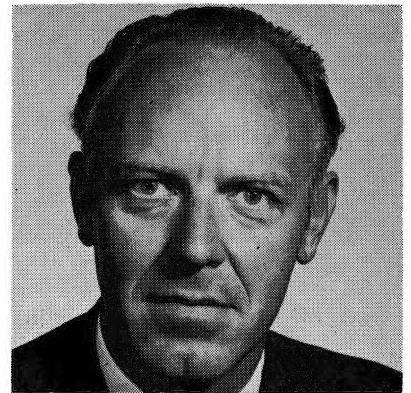
Herbert Wiesinger (*Unilateral Aphakia and Contact Lenses*) is a graduate of the University of Vienna Medical School. He took his postgraduate training at the University Eye Clinic in Vienna and the Institute of Ophthalmology of Columbia University. He has been on the staff of the department of ophthalmology at the Medical College of Virginia since 1954, presently serving in the capacity of associate professor.