BIOMEDICAL ENGINEERING

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An International Symposium

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Preface

The Second International Symposium on Biomedical Engineering was held June 17–20, 1987, in Taipei, Taiwan, Republic of China.

The symposium was hosted by the Biomedical Engineering Society of R.O.C. and Chung Yuan Christian University. Delegates from Japan, R.O.C. and the United States of American participated.

This volume, the edited version of the proceedings, begins with an introduction to the role of biomechanics which is to predict physiological events with mathematical accuracy, using the respiratory system for illustration. The major thrust of the volume lies in three important areas in biomedical engineering:

1. Musculoskeletal mechanics, including mechanics of tissues, muscles, bones and joints, orthopedics, and spinal mechanics.

Joint and bone forces and body segment motion in healthy persons are determined by approximation or measurement. The knowledge thus obtained is used to design the prosthetic devices for replacement of diseased bone and joints after tumor resection. In the field of the spinal cord, the poroelastic theory is applied to predict the long-time creep and transient responses of spinal motion segments under axisymmetric and antisymmetric loadings using mixed finite element methods. For clinical treatments in human trauma, the biorheological properties and deformation of spinal cord injuries are studied by animal experiments. Like the spinal cord injury, head injury is commonly induced in vehicular and athletic accidents. The mechanisms and tolerance criterion for subdural hematoma, a special type of head injury, are disclosed by finite element analysis.

2. The heart and circulation, including cardiac mechanics, cardiovascular flow, renal hemodynamics, pulse feeling, and artificial organs.

In cardiac mechanics, the left ventricular function is assessed by gineangiocardiology, regional myocardial function is analyzed by a new method, and the mechanical restitution of atrial myocardium in health and disease is evaluated over a wide range of test pulses. In cardiovascular mechanics, pathophysiology of turbulent blood flow indicates possible clinical implications of flow disturbances, such as cardiac murmurs, post stenotic dilation and aneurysms, hymolysis, etc. The use of Doppler echocardiography in cardiovascular flow dynamics and the employment of laser Doppler velocimetry in coronary hemodynamics provide accurate quantitative assessment of cardiac functions. The techniques are promising for diagnostic and clinical applications. The advent of space flight necessitates knowledge on the effects of weightlessness on human cardiovascular functions. A comprehensive review of the literature pertinent

to cardiovascular responses, mechanisms, and tolerance under reduced gravity is presented. The development of biomaterials is vital to blood contacting artificial organs whose surfaces tend to encourage the formation of mural thrombi. Flow effects on the concentrations of some of the most important platelet-active substances are disclosed. Another study investigates the rheological abnormalities present in some Jarvik-7 total artificial heart patients. The study correlates the clinical outcome of these patients to blood rheology.

One unique subject in the volume deals with science in pulse feeling, a part of traditional Chinese medicine. The fundamental concept of Chinese medicine states that pulse feeling is the resonance of internal organs with the heart. Experimental evidence is disclosed to bridge the 3000 year-old pulse-feeling with hemodynamics of the Western medicine: The relation between pulse feeling and organ specific resonance waves is established. That is, the amplitudes of pulse feeling at different parts of the human body can be correlated with the resonance conditions of different organs in health and in disease.

For the renal system, a patient model and its control scheme are developed for improved hemodialysis therapy, which is free from the disequilibrium syndrome.

3. Bioheat and mass transport.

The influence of angiotensin II, a modulator of the feedback mechanism, on the regulation of glomerular filtration is investigated for better understanding of renal autoregulation.

The final chapter examines hyperthermia for tumor treatment. Electromagnetic and ultrasonic diathermy are included together with some invasive hyperthermia. The concept for the use of heat pipes in tumor treatment is introduced.

We would like to express our sincere gratitude to the National Research Council, R.O.C., for partial financial aid to the meeting. Our thanks are also extended to all the participants for their individual contributions and especially to the organizing committee members for their hard work. We also greatly appreciate the effort and devotion of Professor Walter H. Chang of Chung Yuan Christian University.

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Chun-Jean Lee

Contents

The Role of Biomechanics: Predicting Physiological Events with Mathematical Accuracy

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ABSTRACT

The best role for engineering science to play in the biomedical field is to improve our understanding of the biological process to such a degree that it is possible to predict physiological events with mathematical accuracy. We say mathematical to mean "specified", "probabilistically defined", or "quantitatively understood". This, plus a drive to bring the new understanding to be used by people in the form of products in the market place, is the essence of engineering. Examples are many. I shall use the lung to illustrate the building of a theory from experiments and the comparison between theoretical predictions and physiological observations.

INTRODUCTION

Biomedical engineering research has many objectives. Some researchers aim at design and manufacturing of products for profit, some aim at relief of human suffering; some focus on making life more fun, some try to understand the mysteries of life. All must understand physiology. The better one understands physiology, the greater is the chance of success in achieving the set objectives. Engineering science has much to offer in this endeavor. If we can understand physiology as well as we understand fluid and solid mechanics, then medicine and medical treatment can be designed as precisely as we design a space ship to the moon. If we want to master biotechnology to let living cells manufacture protein and drugs for us, then we must understand cells in as much detail as we understand automobiles. The required level of understanding is very clear to the engineer: We must be able to predict physiological events with mathematical precision when the parameters and boundary conditions are varied.

It is easy to illustrate the point. In the past two decades, biomechanics has brought improved understanding of normal and pathological physiology of organisms at molecular, cellular, organ, and integrated levels; it has helped developing medical, diagnostic, and treatment procedures; it has guided the design and manufacturing of prosthesis and instruments; it has suggested the means for improving human performance in the work place, sports, and space; it has made

us understand trauma in war and peace. Whenever it has succeeded, it arrived at the level of engineering understanding named above. If we can model, compute, and predict, then we can design, and likely to succeed.

In the future, we may look toward biomedical engineering to find ways to reduce heart disease and atherosclerosis, to provide us with improved vascular assist and replacement devices, to enhance oxygen transport in the lung, to control growth and change, to understand the mechanics of neuromuscular control and robotics, to prevent joint degeneration, to replace diseased organs, to avoid low back pain, to make the blind see, and the deaf hear. In every case we must be able to model, to control, to modify: in short, to engineer.

The papers of this Conference will illustrate the path taken by each individual in his or her approach to biomedical engineering. The style and experience may be different, but there is one thing in common: every hypothesis, every theory, every solution must be validated. Without validation, the endeavor is mere speculation.

The process of validation is usually very long, and sometimes tedious; but not unrewarding, because along the way one learns new things and makes new discoveries. In the following, I would like to mention one example: my own experience on validating a theory of blood flow in the lung.

A THEORY OF BLOOD FLOW IN THE LUNG

Blood flow in the lung is of course important. If the blood flow does not match the ventilation, the blood may become insufficiently oxygenated or have too much CO_2 left in it. If the pulmonary blood pressure gets too high, diseases of the lung and heart will follow. Emphysema, edema, asthma, cancer, and shock are common lung diseases that affect pulmonary blood flow. Any flow is driven by the pressure gradient along the stream line. But pulmonary blood flow is affected not only by the pressure of the blood, but also by two other pressures: that in the airway (bronchi, bronchioles, ducts, alveoli) and that in the pleura (outside the lung, inside the chest wall, above the diaphragm). The diameter and length of the blood vessels depend on these pressures. If we use the standard notations with subscripts "A" denoting airway, "PL" denoting pleura, "a" denoting artery, "v" denoting veins, "art" for arterioles, "ven" for venules; whereas local blood pressure be denoted by p without a subscript, then the local blood flow rate (volume of blood passing through the lumen of the blood vessel per unit time) is a function of the gradient of p, and p_A, p_{PL}. The flow through a capillary bed is a function of p_{art}, p_{ven}, p_A, and p_{PL}. The flow through the whole lung is a function of p_a, p_v, p_A, and p_{PL}. A clear understanding of pulmonary blood flow requires a complete knowledge of these pressure-flow relations.

To establish a theory of blood flow in the lung we must know the

anatomy and rheology of the lung: the dimensions and mechanical properties of every blood vessel in the lung. In the 1960's, Weibel [1], Cumming et al [2] published monumental morphometric data of human lung, but the required data on the capillary bed were still missing, and rheological data were essentially unknown. Hence our first theory of pulmonary blood flow ([3], [4], Fung and Sobin, 1967, 1969) was very tentative, built on many hypotheses about geometry and elasticity of the blood vessels. Most of our hypothetical constitutive equations were proven to be true later, but that is part of the story of validation.

In 1970, we published our analysis of the anatomy of the pulmonary capillaries ([5], Sobin et al, 1970). In 1972, we published the following results [6, 7, 8]: the capillaries in the lung form a very closely knit network in the alveolar walls. In each alveolar wall the space between the capillaries (called "posts") is filled with connective tissues. In the direction perpendicular to the wall the capillaries are enclosed in a membrane of about one micron thick which consists of three layers: an endothelium, an interstitium, and an epithelium. Beyond the membrane there is only gas. This structure implies that the pulmonary capillaries will receive full support from the posts in the plane of the alveolar wall, and no support from the gas in the direction perpendicular to the wall. The capillaries are thus expected to be distensible in the direction perpendicular to the alveolar wall, but rather indistensible in the plane of the alveolar wall when blood pressure is varied. Experimental this was found to be the case [8]. When the alveolar wall expands with increasing transpulmonary pressure, the pulmonary capillaries expands with it with the same strain in the plane of the wall, whereas in the perpendicular direction the caliber is reduced, [4]. Thus the mechanical behavior of the pulmonary capillaries is entirely different from that of a circular tube. Their distensibility is directional. To communicate this feature, we named the vascular network in the alveolar wall a sheet (short for the pulmonary alveolar vascular sheet). The sheet thickness varies with the blood pressure as shown in Fig. 1, whereas the sheet area is unaffected by the blood pressure [8]. The blood flow theory based on these geometric and rheologic properties is called the sheet-flow theory [4,6].

In 1972, Fung and Sobin published a theoretical analysis of the expected deformation of the alveolar sheet based on its structure and material properties, and showed that the theoretical results agree well with the experimental observation [7]. The sheet flow theory was extended and put into a more complete form [6]. Then we began a lengthy process of validation.

VALIDATION OF SHEET FLOW THEORY

Since the capillary vascular bed in the lung is large and multiply connected, it is not possible to make pressure-flow experiments on individual capillary sheets. The only opportunity available to an experimenter is to use a lobe or a whole lung. Therefore, only when the experimental pressure-flow relationship of the whole lung is worked out in detail; when the flow in all the blood vessels, large

and small, is included in the theory; when the theory is so tightened that the effects of different parameters are clearly identified; then, and only then can the individual parts of the theory said to be validated.

The road of validation is long. As one travels along the way, one cannot help revising his old thoughts. The final theory can rarely be expected to be identical with the original one. In the present case, the original sheet flow theory of zone 3 (where the arterial and venous blood pressures are both larger than the alveolar gas pressure) survived without any need for modification, but the original theory for zone 2 (where the arterial pressure is greater than the airway pressure, but the airway pressure is greater than the venous pressure) was too primitive, and needed the addition of several new elements. The facts learned along the way and the new addition to the theory are outlined below.

Morphometric Data

Yen et al [9, 10] measured the bifurcation pattern, the number of vessels in each generation, and the dimensions of vessels in each generation in the cat lung. Strahler system was found to describe the anatomy well.

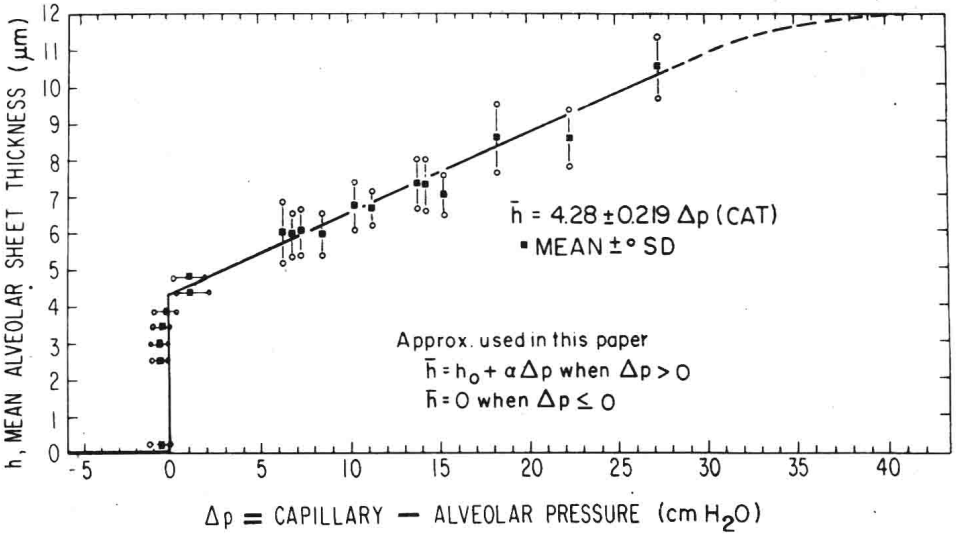

FIGURE 1. Pulmonary alveolar wall sheet thickness (vascular space) versus the transmural pressure (difference of capillary blood pressure and alveolar gas pressure). Cat lung.

A surprising finding is that the arterioles and venules occupy different parts of space. The arteriolar regions are like "islands" embedded in a venular "ocean",([11], Sobin et al, 1980). The ratio of the number of alveoli in a unit volume to the number of arterioles in the same volume is 24.5, whereas the ratio of the number of alveoli to the number of venules is 17.8, ([12], Zhuang et al, 1985). Adjusted with regard to the volumes of islands and ocean in which arterioles and venules lie separately, we found that each arteriole supplies 10.5 alveoli, whereas each venule drains 10.1 alveoli, ([13], Fung, 1987). Until our work, it was believed that the ratios of the numbers of arterioles, venules, and alveoli are 1:1:1, [14].

Rheological Data

The distensibility of blood vessels of all generations was also measured by Yen et al. [15, 16]. A pleasant surprise is that the pressure-diameter relationship is linear

$$D = D_o + \alpha\,(p - p_A) = D_o\,[1 + \beta\,(p - p_A)] \tag{1}$$

where D is the diameter, p is the blood pressure, p_A is the airway pressure. D_o, α , and β are constants which depend on the generation number and the transpulmonary pressure, $(p_A - p_{PL})$. This equation holds for pulmonary arteries and veins of all generations, including the smallest arterioles and venules, ([17], pp 212-214, 302-306), for p varying in the range of -10 to +10 cm H_2O. That Eq. (1) holds for negative p from 0 to -10 cm H_2O is extremely important for our theory.

Stability of Blood Vessels Under Negative Pressure

Unsupported peripheral arteries and veins become collapsed when the transmural pressure (blood pressure minus external pressure) becomes negative. Yet pulmonary arteries and veins would not collapse in this negative pressure range [18]. The reason for the patency of these vessels is the tethering of interalveolar septa to the outside of their wall [17, 18]. The blood vessels are embedded in the lung tissue which is composed of the interalveolar septa. The interalveolar septa have tension when the lung is inflated. The consequence is that the flow limitation mechanism (the so-called Starling resistor mechanism) cannot be located in pulmonary arteries and veins. Only the capillaries can collapse in the lung under negative transmural pressure (blood pressure smaller than the alveolar gas pressure). Hence the sluicing gates, if any, must be located at the end of the capillaries, where the blood is drained into the pulmonary venules.

Pressure-Flow Relationship in Individual Vessels

For steady flow of blood in a vessel obeying Eq (1), the volume flow rate Q is given by the equation ([17], p. 91-94, 334)

$$\frac{640\ \mu\alpha L}{\pi}\ \dot{Q} = [D_o + \alpha p_{entry}]^5 - [D_o + \alpha p_{exit}]^5. \tag{2}$$

Here D_o is the tube diameter when p is zero, p is the transmural pressure, α is the compliance constant, L is the length of the tube, μ is the coefficient of viscosity of the blood, and the subscripts "entry" and "exit" refer to the ends of the tube. Equation (2) is nonlinear with respect to $p_{entry} - p_{exit}$; thus differ fundamentally from Poiseuille's law. It can be corrected for loss due to turbulence and bifurcation by replacing μ with an "apparent" viscosity which depends on Reynolds number.

For steady flow in the capillary sheets in which the transmural pressure is positive, the sheet thickness is given by ([19], p 289)

$$h = h_o + \alpha (p - p_A) \tag{3}$$

for $0 \leq (p - p_A) <$ an upper limit of about 25 cm H_2O (for cat) or 15 cm H_2O (for man). The flow, $\dot{Q}$, is given by ([17], p 331)

$$\frac{4\mu k f L^{-2} \alpha}{SA} \dot{Q} = [h_o + \alpha (p_{entry} - p_A)]^4 - [h_o + \alpha (p_{exit} - p_A)]^4 \tag{4}$$

Here A is the capillary sheet area, S is the vascular space/tissue space ratio, k, f, are dimensionless parameters depending on sheet geometry ([17], pp 298-300, 312, 313), L is the average length of the blood path between the inlet and outlet of the sheet.

Flow in the Whole Lung

Synthesizing the flow in all the branches, correcting the static pressure change that occur at the points of bifurcation of the tree due to sudden change of the vessel cross-sectional area and the corresponding velocity of flow, ([17], p 18), and taking into account the morphology and rheology of the branches, we obtain the flow characteristics of the whole lung. For zone 3, this is done in [20].

But more needs to be added for the analysis of flow in zone 2. First, the sluicing gates have to be identified. This is done easily because the stability study mentioned above has shown that the gate cannot exist in any vessel other than the capillaries. Since pressure decreases along the capillaries, the gates must be located at the exit ends. The detailed fluid mechanics through the sluicing gates is then analyzed ([21], Fung and Zhuang, 1986). Then it is shown that two possible states can co-exist in the lung: collapsed capillaries and patent capillaries, ([17], p. 350, and [22] p. 1641). Regions of collapsed capillary sheets embedded in non-collapsed sheets will form a picture of "patchy filling" of alveolar wall observed in 1972 by Warrell et al [23]. A detailed analysis of the partially collapsed sheets shows that if a sheet is collapsed at one spot, then the entire sheet (one wall of the alveolar) must collapse because a partially collapsed sheet is

thermodynamically unstable ([22], p. 1648). The collapse of a sheet can be stopped at the junction where two open sheets exist (See Fig. 1 of Fung and Yen [22], p. 1645). Finally, a model of the lung structure was put forward and validated ([24], Fung, 1987). With this model and the assumption that the maximum number of sheets that can collapse is the totality of all sheets directly draining into the terminal venules, we can calculate the limiting area of collapse, the factor F in Eq. (11) of Ref. [22], p. 1645. Although the model in [13] is based on the tetrakaidekahedron, a sample calculation based on dodecahedron is given in [22], p. 1646.

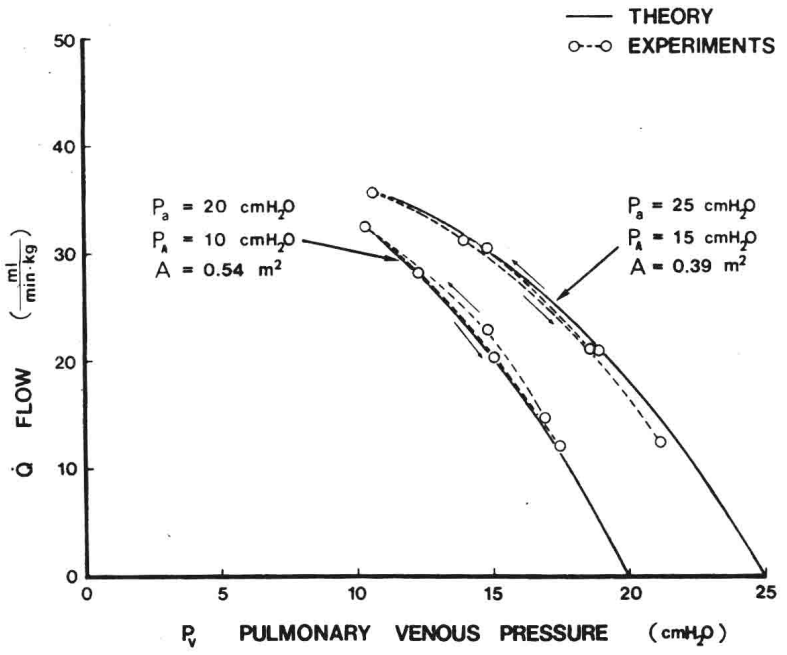

FIGURE 2. Pressure-flow relationship in 2 right lungs of cat in zone 3 condition. In the case in which P_A = 15 cm H_2O, it was found that P_v = 8.0 cm H_2O when flow (Q) reached the peak value of 48 ml/min kg. Hence, when P_v was cycled between 22 and 10 cm H_2O, flow condition was in zone 3; i.e., $P_{ven} > P_A$ throughout, although $P_v < P_A$ in part of cycle. Lower curve was from Exp. 5-25-83-1, which had a Q_{max} of 44 ml/min kg when P_v was 2.4 cm H_2O. Theoretical curves were drawn with alveolar wall surface area A (half lung) indicated in figure. Good fit is obtained by adjusting the values of A, P_a = arterial pressure.

With these factors considered, the theory of zone 2 flow was completed.

VALIDATION OF THE THEORY OF BLOOD FLOW IN THE WHOLE LUNG

Perfusion experiments of isolated cat lungs were done and the data were compared with the theoretical results. The comparison, illustrated for zone 2 in Fig. 2 and zone 3 in Fig. 3, seems satisfactory.

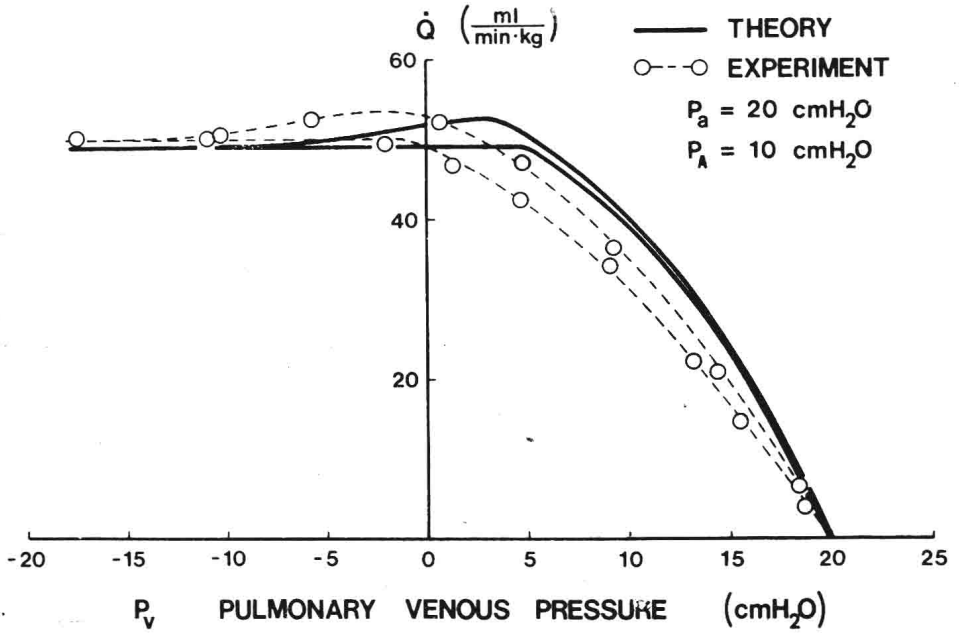

FIGURE 3. Comparison of theoretical and experimental results in pulmonary blood flow in zone 2 condition in right lung of the cat. Theoretical curves were computed with morphometric and elasticity data, and A = 0.84 m^2 for half lung. In return stroke, collapsed area is deducted from initial value of total alveolar wall surface area of right lung under assumption that collapsed alveolar sheets are not reopened until zone 3 condition is reached and the pulmonary arterial pressure is increased. Value of A was so selected that a reasonable agreement between theory and experiment is obtained.

CONCLUSION

Once a mathematical model is validated, then it can be applied to study a wide variety of problems. Currently our model is used by other physiologists in their study of the effect of various pharmacological agents on pulmonary blood flow.

Validation is a directed process, we know what we are looking for,

hence there are fewer wasted steps. Occasional surprises are often most interesting. Agreements are satisfying, disagreements offer changes of advancement.

I have presented only one example. The scope of my example is limited to the use of engineering methods to clarify a physiological phenomenon. For engineering applications, design, development, manufacturing, marketing would have to follow. A wide variety of talents are needed. In that respect biomedical engineering is not different from any other engineering. In its direct concern with the mystery and well being of man, however, bioengineering has no match.

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