The Exercise Physiology Paradigm in Contemporary Biology:
To Molbiol or Not to Molbiol—That is the Question

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Two perspectives on exercise physiology in contemporary biomedical research are presented. First, exercise represents a powerful tool for understanding physiology. The magnitude and gradation in physiological responses to exercise afford an opportunity for studying the range and control mechanisms in physiological systems under the diverse circumstances. Moreover, the exercise stimulus of training offers a means to study processes of physiological adaptation. Second, the science of physiology represents a powerful means for understanding the limits of human performance. The concepts, tools, and techniques of physiology allow performance-based exercise physiologists to contribute significantly to understanding and improving the limits of human performance. In contemporary biomedical science, there is a pronounced emphasis in the burgeoning area of molecular biology (molbiol). Molecular biologists have developed powerful tools for studying the regulation of essential cellular processes, such as gene expression. Consequently, within biomedical research there has been a deemphasis on classic organ-systems physiology. However, even in this milieu exercise physiologists will continue to contribute, for they are uniquely prepared to address important contemporary problems related to adaptation to environmental stressors, resistance to degenerative diseases, and expansion of the limits to human performance.

The “New,” Molecular Biology

Check the job listings in Science Magazine and notice the preponderance of job listings in molecular biology (molbiol). In addition to departments properly titled “molecular biology,” departments of anatomy, biochemistry, biology, botany, genetics, endocrinology, medicine, pharmacology, physiology, zoology, and even kinesiology are advertising for faculty with expertise in the “new,” molecular biology. Molecular biology is sweeping through the biological sciences.

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at an amazing rate that parallels, in effect, the revolution brought by relativity theory in modern physics. In major universities, departments and even whole colleges in the biological sciences are being organized around the new biology. Recently also, the major English language journal for exercise physiology was evaluated, in part, to determine if it is current in molecular biology. Because the new technology offers opportunities to pose and answer questions unfathomed only a decade ago, the thrust of the new, molecular biology is inevitable, necessary, and welcomed.

Will molecular biology, then, come to dominate exercise physiology as it has other branches of the biological sciences? The answer is, yes and no. Yes, because to remain relevant in contemporary biology, exercise physiologists must comply with the overriding thrust operant in contemporary biological sciences. The answer is yes also because exercise physiologists have already gone to molecular biology for answers to classical as well as contemporary problems. The answer is also no, because exercise physiologists as a group are too smart and too broadly educated to be swept over by the wave of scientific fashion. Just as we do today, we will in the future require scientists who are competent in tissue, organ, and system physiology, scientists who understand the effects of environment on human physiology, and scientists who understand the factors that limit the performance of both healthy and unhealthy people engaged in a variety of physical activities. Molecular biology will become an important tool in the repertoire of the exercise physiologist, but exercise physiology is not likely to become a subset of molbiol.

Exercise Physiology

Exercise physiology is a most peculiar field, for it is neither an academic discipline nor a defined subdiscipline of a larger field (Henry, 1954). There are no departments of exercise physiology and there are no journals that go by the term. As we progress through this essay, it will become clear that exercise physiology is an approach to understanding physiological phenomena. Consequently, while it has its roots in classic, organ, and systems medical physiology, today exercise physiology is an important subarea (or subspecialization) of the physical education discipline. The use of exercise stress also provides an important adjunct to studies in departments of endocrinology, medicine, physiology, cardiology, and nutrition.

My perspective is that exercise physiology, and therefore exercise biochemistry as well as exercise molecular biology, are tools for understanding biological phenomena. At one extreme, practitioners of exercise physiology utilize the techniques of physiology to maximize the performances of athletes or of patients with various medical conditions. On the other hand, the physiology scientist can use exercise as a tool to probe the control mechanisms operating in physiological systems. Thus, exercise physiology attracts a wide range of practitioners and scientists who are unified only in that they have a common interest either in using exercise to understand physiology or using physiology to understand exercise.

I also feel that exercise physiologists are scientists whose actions are governed broadly by the overall trends in biological science, but specifically by their
own perspectives, goals, and values. No departmental constraints or affiliations are appropriate, though the departmental affiliation may reflect the investigator’s perspectives. Exercise physiology is nothing more than another paradigm of contemporary biological science.

Exercise Physiology at the Forefront of Physiology

The 1920s and 1930s were a time when muscle and exercise physiology were synonymous with physiology and biochemistry. The work of Hill and Lupton (1924), Meyerhof (1920), Dill and associates (Margaria, Edwards, & Dill, 1933), and Cori and Cori (1928) did then receive widespread and profound acknowledgment. Throughout the 1930s and into the 1940s, the Harvard Fatigue Laboratory was not only a major site for exercise physiology research but also served as a springboard for the establishment of physiology laboratories around the United States and in other countries (Dill, 1967).

Since the time when exercise physiology was at the heart of biomedical science, its status has probably declined. The reasons for this decline are several, but the general impetus toward a more cellular, and now a more molecular, approach to solving problems in physiology is implicated. Because prestige in the biological sciences is often measured in terms of the number of Nobel and other prizes awarded, biochemists, biophysicists, and molecular biologists are coming to dominate faculties in colleges of biology and medicine. These are the people who are hired, promoted, and advanced to administrative positions. Seeking a molecular answer to longstanding questions in biology and medicine has become a reality in both major research institutions and in granting agencies.

Because of the gradual erosion of interest by physiologists in understanding both classical and applied questions of physiology related to cardiovascular, ventilatory, and muscular performance, such studies are often left to departments of physical education. By default then, departments of physical education are likely to reemerge in prominence, at least as assessed by the public at large, as sites of research in physiology.

Problems of Classic Interest in Exercise Physiology

Two areas have predominated in classic exercise physiology: they are cardiovascular limitations to oxygen utilization, and exercise metabolism. More recently other areas of interest, “cardiac rehabilitation” and “exercise biochemistry,” have been spawned (Brooks & Fahey, 1984).

Cardiovascular Limitations to $O_2$ Utilization

The realization that $O_2$ utilization in large measure determines performance in exercises lasting a minute or more has led to primary concerns with factors limiting maximum oxygen consumption ($VO_2_{max}$). As defined by the Fick relationship, $VO_2_{max}$ is limited by the ability to expand cardiac output ($Q$) and the arterial-venous $O_2$ difference ([a-v]$O_2$); ($VO_2=Q[a-v]O_2$). With inception of the field of exercise biochemistry, there was a resurgence of interest in evaluating the relative roles of cardiac output and peripheral $O_2$ utilization in limiting
After concerted and sophisticated efforts, it has been fairly well resolved that $\dot{V}O_2\text{max}$ is essentially a cardiovascular parameter that largely depends upon cardiac output (Brooks & Fahey, 1984). However, it is now fairly certain also that the ability to sustain a submaximal exercise task is dependent upon peripheral (to the vasculature) adaptations (Davies, Packer, & Brooks, 1981; Fitts, Booth, Winder, & Holloszy, 1975). These cellular adaptations determine the ability to utilize fatty and amino acids as fuels (thereby sparing glycogen) and to maintain blood glucose homeostasis by increased capacity to make glucose (gluconeogenesis) (Brooks & Donovan, 1983; Donovan & Brooks, 1983).

**Exercise Metabolism**

Quite early in the history of modern 20th-century physiology, it was recognized that nonoxidative (anaerobic) as well as oxidative (aerobic) processes in large measure determined performance lasting a minute or less. The classic work of Hill and Lupton (1924), and Margaria, Edwards, and Dill (1933) on $O_2$ deficit–$O_2$ debt relationships formed a foundation upon which generations of scientists, coaches, and clinicians assessed the balance of aerobic versus anaerobic metabolism under a variety of conditions. In contemporary exercise physiology there is a major, continued interest in metabolic responses to exercise and training. This interest has engendered a separate field that is sometimes termed "exercise biochemistry."

**Cardiac Rehabilitation and Exercise Biochemistry**

Overriding concerns in cardiovascular exercise physiology and exercise metabolism have led to two specializations that are sufficiently evolved to justify separate terminology. The distinctive characters of specialization are evidenced by the existence of professional and scholarly organizations, publications, and meetings.

**Cardiac Rehabilitation**

Recognition that endurance exercise training helps retard the advance of atherosclerosis, and helps restore vitality of the cardiovascular and musculoskeletal systems from disuse atrophy, has led to the incorporation of exercise physiology into the clinical setting. Today exercise physiologists are working with physicians performing a variety of tasks such as pulmonary function assessment, treadmill testing, electrocardiography, and blood pressure determination. Additionally, they are writing exercise prescriptions in terms of mode, frequency, intensity, and duration. Further, they are coordinating or leading exercise classes with the intent of preventing coronary disease or rehabilitating patients being treated for the disease. In the main, departments of physical education prepare professionals to work as exercise physiologists in clinical settings. As such, the training of clinically oriented exercise physiologists is unique in contemporary medical education. Usually the training programs are allied with departments of medicine and cardiology, but the primary responsibility and support of this one group of practitioners rest within physical education. Support of exercise stress testing
and cardiac rehabilitation programs by departments of physical education represents a contemporary expression of the longstanding links between physical education and medicine (Buskirk, 1981; Park, 1981).

**Exercise Biochemistry**

The development and use of the muscle biopsy needle (Hultman, 1967) during the late 1960s in Scandinavia, and simultaneously in the United States the development of animal models to study metabolic response to exercise (Gollnick & King, 1969; Holloszy, 1967), resulted in a new field, the importance of which rapidly rivaled classical interests in classical cardiovascular exercise physiology. Compared to the established field, the new field (exercise biochemistry) was much more cellular in its orientation. Great emphasis was placed on elaborating and understanding the mechanisms that controlled metabolic responses during acute and chronic exercise. Factors such as those regulating the balance of glucose, glycogen, and fatty and amino acids during exercise continue to hold the interest of exercise biochemists. In particular, those factors that influence glucose metabolism are of interest because they have significant potential for understanding and controlling obesity and diabetes. Exercise biochemistry evolved simultaneously in departments of medicine, physiology, and physical education. Today, physical education-based or trained exercise biochemists are prominent in the field.

The increased cellular and metabolic orientation of exercise biochemistry heralded the advent of exercise molecular biology. Many investigators, previously identified with exercise biochemistry, are now applying the techniques and experimental approaches of molecular biology to the study of biological adaptation and metabolic regulation.

**Problems the New Biology Could Address**

As a result of productive work in the area of exercise biochemistry, we have become aware of many adaptations to training. With the tools and techniques of molecular biology, we are now on the threshold of learning why the adaptations occur. For example, if we knew the specific signals that affect gene expression in tissues of trained individuals, then there would be innumerable opportunities for practical application. Not only could we create stronger athletes with better endurance, but we could also reverse or slow degenerative processes operant in various myopathies; we could reverse or retard obesity, manage diabetes better, and slow the aging process.

**Gene Expression**

As members of a species, we all have certain characteristics in common. Within the scope of these characteristics, however, there are qualitative as well as quantitative differences among us that give us uniqueness as individuals. Today it is well known that the synthesis of each body protein is under strict genetic control. Thus we differ as individuals not only because of subtle but powerful differences in our genetic codes, but also because of the way in which each code is expressed in the synthesis of body components and structures.
That exercise training induces very specific adaptations in organisms, organ systems, tissues, and cells has been known for a long time (Selye, 1976). For instance, it is known that in response to heavy resistance training, muscle cells hypertrophy because of increased deposition of contractile proteins (actin, myosin, troponin, tropomyosin). Similarly, it is known that endurance training causes a proliferation of the mitochondrial reticulum in active skeletal muscles without muscle hypertrophy (Kirkwood, Munn, & Brooks, 1986). The regulation of mitochondrial adaptation is particularly interesting because usually training results in the assemblage of more, identical mitochondrial material (Davies et al., 1981; Holloszy, 1967), but the genes that regulate mitochondrial synthesis exist not only in the nucleus (mainly) but also in the mitochondria themselves. Thus we need to understand not only how exercise affects gene expression but also how the expression of genes in different cellular compartments is coordinated.

Glucose Transport

Of major physiological priorities, one is the maintenance of constant blood glucose levels (glucose homeostasis). The extraction and use of glucose by cells must be balanced by the entry of new glucose into the blood to maintain a constant level. In Type I diabetes, the transport of glucose into cells is limited by the inability to secrete insulin by the pancreas. Type I diabetics must receive insulin replacement therapy. In Type II diabetes, cells lose sensitivity to insulin and fail to take up glucose despite an apparently adequate supply of insulin. Exercise is important to diabetics for a number of reasons. Skeletal muscle has an insulin-independent glucose transport mechanism that is active when the muscle contracts. Therefore, Type I diabetics who exercise require less insulin. Also, exercise training increases sensitivity of Type II diabetics to circulating insulin. Moreover, exercise training lowers blood lipids and retards the advance of atherosclerosis, a major complication of diabetes.

The point is, exercise offers a means not only for helping to manage a major disease in the human population but also a powerful means for understanding the cellular basis for the disease. This is because investigations of the effects of exercise on glucose transport offer a probe to understanding and controlling diabetes. Further, similar opportunities exist for using exercise as a probe for the cause of obesity.

Obesity

There are several causes for obesity, some of which are mainly behavioral. However, the extreme difficulty that some individuals have in losing adipose, even if stringent exercise and dietary interventions are applied, suggests a cellular defect, at least in some cases. The presence of obesity predisposes persons to a number of degenerative diseases including heart disease and diabetes. Further, it is known that most Type II diabetics are obese. Therefore it is logical to suspect there might be some association between the defects that cause Type II diabetes and obesity. Exercise is known to increase insulin sensitivity in Type II diabetics by decreasing fat cell (adipocyte) size, and as such, exercise may
not only represent a means to defend against the disease but it may also represent a paradigm for identifying the cellular defects that cause the disease.

**Aging**

Although part of the new biology involves understanding gene expression, it also involves studies of the interactions of various molecules, atoms, and ions in biological systems. Usually these interactions are under strict enzymatic control; however, given enough time and the existence of predisposing factors, nonenzymatically mediated reactions occur. One contemporary theory of the aging process involves the generation of free radicals (highly reactive atoms or molecules possessing unpaired electrons in the outer orbital) that damage structural constituents in their immediate proximity. For instance, it is known that the turnover (synthesis and degradation rates) of proteins decreases in aging individuals. This is due to a slowing in the transcription and translation of the genetic code. Moreover, not only does the rate of tissue formation and repair slow in aged individuals, but also many tissues (e.g., connective tissues) change qualitatively. This latter, stiffening process may result from nonenzymatically mediated molecular interactions that result in the cross-linking of molecules in the tissue. The accumulation of this cross-linked “biological junk” is inevitable in systems that turn over slowly, such as in aging systems.

The Free Radical Theory of Aging holds that free radicals result in tissue damage. Ironically, oxygen, the substance that allows life as we know it, is hypothesized by some to be implicated in the aging process. This is because atomic oxygen \((\text{O}^=)\), as opposed to molecular oxygen \((\text{O}_2)\), is actually used as the final electron acceptor in cellular respiration. Consequently it is inevitable that the process of oxygen utilization results in oxygen radical \((\text{O}_2^=)\) formation. The \(\text{O}_2^=\) can react directly to damage cellular structures, or it can give rise to other, even more damaging, radical species. Fortunately, we usually have sufficient radical scavenger enzymes (e.g., superoxide dismutase) as well as scavenger substances in both cytosol (e.g., glutathione) and cell membranes (e.g., vitamin E) to quench radicals that are formed. The generation of free radicals from molecular oxygen during cell respiration likely explains several well-known effects of high pressure \(\text{O}_2\). These include \(\text{O}_2\) poisoning and neural damage (particularly in infants), decreased work capacity in high pressure \(\text{O}_2\), and damage to underperfused tissues when impediments to blood flow are removed.

If free radicals are implicated in the aging process, then physical exercise could possibly negatively affect life span. Potentially, higher rates of oxygen consumption could increase rates of free radical formation and accelerate the aging process. Despite the possibility that increased \(\text{O}_2\) utilization during exercise could accelerate the aging process, obviously exercise training does not. This is likely because training induces the formation and deposition of enzymes and scavenger substances that protect against free radical formation during exercise. These scavengers are then able to operate not only during exercise but also during the remainder of the day, providing residual protection against environmental toxins that generate free radicals. Therefore we conclude that exercise is a powerful tool for studying the aging process, and hence, expertise in exercise molecular biology could be most beneficial.
Problems the New Biology Could Not Address

The classic, organ-systems approach to physiology will remain essential in answering longstanding questions in exercise physiology. Among these are questions such as these:

- The regulation of exercise hyperpnea (breathing during exercise);
- The regulation of systemic blood flow during exercise;
- The regulation of regional blood flow during exercise;
- The nature of the adaptive response to exercise in the heat;
- The nature of the adaptive response to exercise at very high altitudes;
- The quality and quantity of exercise for optimal somatic development in children.

In particular cases, the techniques of the new biology may augment investigations in these areas, but the above problems are central to the concerns in exercise physiology, and essentially they are to be approached from the classic organ-systems perspective.

Physical Education in Exercise Physiology

Being out of the mainstream presents many difficulties and, perhaps, a few opportunities. Because classic organ and system physiology is falling from the mainstream of emphasis in biomedical research, exercise physiology (being a subset of classic physiology) is also out of the mainstream. Moreover, physical education-based efforts in exercise physiology must be seen as even further removed from the mainstream in biomedical research. This is classic organ-systems physiology. This trend has far-reaching implications for physical education-based exercise physiology because limited access to research funds restricts both research and educational opportunities in the field.

In contemporary Western countries, governmental agencies in large measure determine the direction of biomedical science. In the United States the agency is the National Institutes of Health (NIH); in the United Kingdom and Canada the responsible agency is termed the Medical Research Council (MRC). As implied in the titles of these organizations, protecting and improving the biological research with implications for contemporary health issues is favored by the NIH and MRCs. The function of the NIH (as opposed to an MRC) will be described here for it is better known to me.

The relationship between the NIH and research and education in the biological sciences must be understood by anyone who wishes to work in this field. The reality within the NIH is that the administrators who determine the areas of research to be funded, as well as the assignments and constituencies of the committees (study sections) to evaluate research proposals, carry an overriding concern for fostering medically relevant research. Mainly, members of study sections are MDs and PhDs who are on faculties of schools of medicine. The research proposals likely to be funded are those that are viewed as important from the perspectives of contemporary medicine.

In addition to defining the relevant research areas and the constituency of study sections, the role of the NIH in supporting medical research and education
in the United States can also be evaluated from another perspective, that of overhead and indirect costs on NIH grants. In addition to its administrative wing, the NIH has a significant, in-house research program. However, because the research interests at NIH are far greater than those it can address directly, the NIH sponsors an extensive extramural research effort. Beyond providing funds to purchase supplies and to hire technical support (direct costs) for principal investigators, the NIH will also provide overhead (indirect costs) to grantee institutions. These overhead costs, negotiated between the NIH and grantee institutions on an individual basis, are provided to support the facilities at the grantee institution. The range of indirect costs is great, with private institutions often commanding a rate significantly greater than 50% of the direct costs, whereas public institutions often receive less than 50% of the direct costs. In any case, many schools of medicine survive not only because the NIH directly funds the research program (often including principal investigator, faculty salaries) but also because the overhead on research grants supports the essential facilities of the funded institutions. Given this system, it is no accident that the administrators and faculties of schools of medicine, as well as their congressional representatives, act to preserve the NIH system of research support.

The above comments were made with a deliberate attempt to avoid any characterization or judgment. However, one result for exercise physiologists is that the classic physiological questions that often interest them are frequently inconsistent with NIH priorities. Therefore, a result is that the major source of funding for biomedical research in the United States is inaccessible to many exercise physiologists. Those in departments of physical education in particular are reliant upon institutional and other forms of extramural support for their activities. These avenues include support from both governmental (NASA, DOD) and private organizations (e.g., American Heart Association and pharmaceutical companies). These forms of support, however, are far less in magnitude than those available through NIH.

Despite these difficulties in obtaining outside funds to support research and instructional programs, an expanded role of physical education-based exercise physiology may emerge from the revolution in biology. This is because the revolution possesses inconsistent, paradoxical implications for classic physiology. A reasonable definition of physiology is, "the science dealing with the functions of living organisms or their parts" (Random House Dictionary, 1969). The question for physiology as a discipline then is, how can it function as a discipline if no recognition is provided for those fulfilling the specified roles of studying organisms or their parts? Moreover, how can the discipline survive if graduate students are not trained in organ and systems physiology? In my view, such a discipline cannot survive. During the time of tyranny of molbiol, if classic physiology is to survive, it will have to persist outside departments of medical physiology. In the future, departments of physical education and zoology will likely provide many scientists trained in the classic physiologist mold who will instruct medical students.

What is likely to happen in a decade or so, when the hysteria for molbiol has died down and the Nobel fashions have changed, is that molecular biology will be recognized as just another cornerstone of biological science. It will also be realized that there is a shortage of organ and system physiologists to evaluate the results of molecular biologists, to initiate novel studies in organ and system
physiology, and to train clinicians. If they survive this, classic organ-systems and exercise physiologists may reemerge in prominence for they will have to assume additional burdens of responsibilities associated with rescuing work in fields left fallow during the molbiol drought.

Exercise physiologists understand that for an individual to function at or near peak power output for extended periods, the integrated participation of all systems is required. Classical physiologists also realize that evaluating peak capacity is one of the most useful ways for describing functional capacity of an organ or system. In physical education-based exercise physiology, emphases have been placed on muscular, cardiovascular, and ventilatory responses to exercise. Considerable though lesser emphasis has been placed on responses of the endocrine, digestive, and skeletal systems to exercise, but efforts in these areas have been no less important. Because of the underlying interest of physical education-oriented physiologists in understanding factors that limit human exercise performance, interest in the muscular and cardiovascular and pulmonary systems is likely to remain central to their efforts. When the scientific world again realizes the need for competent physiologists in the classic mold, departments of physical education will provide many of the personnel to fill the need. By providing a safe haven for classic physiology, departments of physical education will be instrumental in serving biological science.

Playing the Molbiol Game

It is a given in science that if funding is not available for scientists to work on the problems of primary interest, they will work in allied areas to remain productive and keep the laboratory organization together until funding becomes available to support the work of primary interest. Experienced scientists accept this requirement of occasionally working in related areas for it not only keeps mind and body together but also provides the opportunity to learn something interesting. This is the Darwinian perspective of adapting to survive. In the near future, some areas of interest to exercise physiologists might be more fundable than others. Below are listed some research areas that might be fundable within the molbiol perspective and might also be of interest to performance-oriented physiologists.

- Exercise and aging: the use of exercise to probe mechanisms of the aging process and the elaboration of exercise and dietary regimens to retard aging;
- Exercise and environment: the use of exercise to probe the immunological system and the development of exercise to improve immunological resistance to environmental toxins;
- Exercise and gene expression: the use of exercise to probe the expression of genes that regulate muscular hypertrophy, assembly of the mitochondrial reticulum, and receptor and transport proteins;
- Exercise and metabolite transport: the use of exercise to study the regulation and induction of membrane receptors of hormones and transporters for glucose and other metabolites.
- Exercise and atherogenesis: the use of exercise to modify the formation and degradation of lipoproteins and triglycerides in arterial smooth muscle and other tissues;
Exercise and osteoporosis: the use of exercise to induce bone deposition in children and young adults as well as postmenopausal women.

This list is by no means comprehensive but it does serve to illustrate that performance-oriented physiologists can work in areas that are relevant to molbiol, and that are therefore fundable over the short run. For example, if an investigator were interested in factors limiting glucose metabolism in exhausting exercise, then a study on the effects of aging on carbohydrate metabolism would necessarily include control observations on young trained and untrained subjects during prolonged exercise.

**Conclusion**

By virtue of its tradition and emphasis on understanding factors limiting performance, exercise physiology will retain its basic interest in classic, organ-systems physiology. However, to survive and remain relevant to contemporary biology, exercise physiologists must adapt to the changing times. There are many challenges to be faced in making this adaptation, but exercise remains a powerful tool for studying the molecular biology of adaptation and metabolic regulation. By taking advantage of the tools of the new molecular biology, exercise physiologists will continue to contribute to the advancement of biological science. In all probability, exercise physiology research, conducted in departments of physical education, will retain as its perspective understanding the factors that limit human performance. In practical terms, however, this perspective may make little difference on how the research is conducted once the problem of investigation is identified. This is because the scientific method, tools, and techniques of contemporary biological science will provide the means and ultimate context in which the work is performed (Brooks, 1981a; 1981b).

**References**


