Progress in Biomedical Engineering: How Can We Proceed?

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Summary

The physician's duty and purpose is to provide patients with successful therapy. Biomedical engineering supports the physician in this mission by developing diagnostic and therapeutic tools that the physician can use in his or her practice. In order to continually improve the physician's means of ensuring the patient's wellbeing, it is fundamentally necessary to make steady progress in both medical therapy and the tools that it uses. This article attempts to better illuminate the ways and means by which this progress can be actively pursued. Progress is achieved in a number of ways, and its character can range from the occurrence of a spectacular event to the modest collection of detailed information. Thus, many different methods can be followed, each with its own characteristic strengths and weaknesses, and these methods are complementary to each other. However, all knowledge, which ultimately forms the basis for any progress, is dependent on categories of superordinate nature. In order to provide examples, the article will include discussions on applicability of methods, the framework of observation determined by the selection of terms and concepts, the significance of results, and time considerations. Communication between all parties involved has continually shown itself to be of central importance, and is beneficial in a number of ways. In particular, the extremely interdisciplinary zone at the intersection of clinical therapy, medical research, and medical technology places high demands on communication among all parties. However, these diverse points of view on the shared problem also offer new chances to understand its nature. When everything is viewed as a whole, the available information can be used more completely, and thus more responsibly, in order to accomplish the shared goal of developing a more successful therapy.

Key Words

Biomedical engineering, methods, progress

Introduction

Successful treatment of patients is dependent on the expertise and the skills of the physician. Compared to earlier times, the abilities of the physician have been greatly expanded due to our ever-increasing insight into the pathophysiology of diseases, and due to the support provided by increasingly elaborate diagnostic and therapeutic devices. However, each successful step in this development always reveals new challenges, which become apparent only due to the new situations and perspectives brought about by previous successes, and which must now be contended with. Continuously assuring the wellbeing of the patient by the best means possible requires steady progress in the physician's knowledge and experience, in medical diagnostics and therapy, and in the tools that are used.

Among the indicators for medical progress are certainly criteria like morbidity, mortality, incidence and prevalence of diseases, as well as the patient's quality of life. Based on the general goal of providing the best possible therapy for a patient's disease, progress should be defined as every insight that contributes to an improvement in the success of therapy. This may take the form of a purely empirical rule that has proven itself in clinical practice. This definition of progress

also includes the recognition of the relationships that lie behind these rules, so that their limits can be better defined or even expanded. Finally, this definition likewise includes functional or adaptive improvements in the capabilities of the diagnostic and therapeutic tools that biomedical engineering makes available to the physician.

Progress in biomedical engineering is a part of medical progress, and as such it is also inextricably linked with the requirements of clinical practice regarding the tasks that must be fulfilled and the methods and criteria for evaluation. The question of what ways and means are necessary to achieve progress in biomedical engineering can thus only be asked within the context of the larger question regarding medical progress in general. In both cases, "How can we make progress?" means the same thing as "How can we learn more?" The means by which progress can be pursued in the field intersecting clinical therapy, medical research, and medical engineering is the subject of this article. In accordance with the main focus of this issue of "Progress in Biomedical Research", the examples used are predominantly taken from the field of interventional cardiology, but this should not in any way limit the applicability of the considerations made here.

Ways to Progress

Medical Milestones

Events that are commonly recognized as milestones in medical progress can certainly offer an initial aid to orientation in the search for ways to achieve progress. The list below, which was chosen subjectively, offers a few possibly enlightening and inspirational examples from medical history:

- The introduction of the smallpox vaccine by Edward Jenner in 1796. From empirical observations, Jenner discovered a relationship between previous survival of cowpox and an immunity against smallpox; he then saw the possibility of immunization against smallpox by means of intentional infection with cowpox [1].
- The first heart catheterization by Werner Forssmann in 1929. Forssmann's confidence in his ideas that vascular catheters would be ideal for access to the heart was so strong that he experimented on himself to demonstrate the method [2].
- The introduction of coronary angiography by Mason Sones in 1958. Having unintentionally delivered a contrast-medium bolus into the right coronary artery of a patient during aortographic examination, Sones recognized the potential of this type of procedure in the depiction of vessels [3].
- The introduction of coronary angioplasty by Andreas Grüntzig in 1977. While peripheral angioplasties had already been successfully performed using catheters with fixed diameters (as per Dotter) since the 1960s, and the idea of cardiovascular balloon dilatation already been proposed (Porstmann), Grüntzig concentrated his energies on finding an appropriate technological implementation for the balloon catheter that, while maintaining a given maximum diameter, could deliver the high pressure necessary for dilatation, and continued to develop this technology further until it could be applied in the coronary vessel system [4].

These examples illustrate how diverse the origins of progress can be. In the first case it was – in modern language – an inductive conclusion drawn from purely descriptive statistics, while the second example was essentially a deductive translation from known principles into a new field of application. Aside from this, coincidences, accidents, or even setbacks can lead to new and unexpected better methods, as long as the significance beyond the current case is kept in view which may be used to show the way to new positive application. The example of Grüntzig shows the decisive importance of interdisciplinary research and communication in attaining progress, especially in medical engineering: It took the formulation of the medical task, the proposal of a material by a chemist, and the appropriate technological realization in order to engineer a balloon catheter that was applicable in practice and thus to allow the idea of percutaneous coronary angioplasty to become a reality; the catheter then entered into competition with other therapies, and is still proving itself to be a successful therapy today. It is thus worth the effort to also stay aware of activity at the borders of one's own field. Communication, especially interdisciplinary communication, is beneficial in multiple respects, because it leads to clarification of the concepts in one's own field, and can (through conversation and cooperation with a partner) lead to completely new perspectives. Patience, careful observation and interpretation, an active vision toward the future, courage, endurance, and often also the necessary bit of luck – these are the characteristics that characterize many of the unique individuals that contributed to the milestones listed above, and to other similar milestones.

However, progress does not occur only in individual, spectacular steps, but also in conjunction with many individual, often inconspicuous contributions of detailed information, which continually add to the state of knowledge, and even gradually change existing conceptions. This process involves diverse approaches, which we categorize roughly using the key words "synthetic", "descriptive", and "analytic", and which we will characterize more completely in the following sections.

"Synthetic" approach

Typical examples of this approach are laboratory tests using cell cultures that are performed under well-defined conditions with targeted variations of isolated parameters. Analogous to an experiment in the inanimate physical sciences, one begins with building blocks that are each well defined and have widely known characteristics, and then combines these to make a model of a certain aspect of an organism. The objects of study are the known or suspected active in vivo mechanisms, control systems, reaction paths, etc. that are affected by a therapy. On the basis of a complete-as-possible understanding of the relevant processes and relationships, therapeutic interventions can then be developed and molded so that the expected changes are as beneficial as possible. The insights gained here are then proposed for application in vivo.

An example of successful progress in vascular intervention that was achieved using this approach is the development of a hemocompatible silicon-carbide coating for stents [5]. Here, physical tests of the influence of foreign bodies (implants) on blood clotting had shown that even at the precellular level (blood plasma), an electronic mechanism existed that could trigger blood clotting. More detailed research revealed that this mechanism consists in an electron transfer from fibrinogen molecules to the metallic implant, by means of which the fibrinogen – as otherwise occurs only through the coagulation cascade – transforms into fibrin and coagulates. Once this process was explained, a way to prevent it was immediately apparent, namely through the application of a semi-conducting coating that, because of its electronic bandgap, cannot accept an electron offered by the protein. Stents with a semiconducting a-SiC:H coating actually show no clotting activation in blood plasma in vitro, and show much less activation in full blood than do uncoated steel stents [6]. In the meantime, a-SiC:H-coated stents have also proven themselves many times over in clinical application [7-9].

Advantages of this bottom-up approach are that it allows relationships and causal mechanisms to be isolated and – at least in principle – explained in detail. There are no ethical limitations on the parameters or processes to be tested. On the other hand, the main problem of this approach is the question of whether it can be translated to the entire system in vivo; in other words, the question of how good the model is. By definition, a model cannot include all physiologically relevant effects and control systems, and thus in vitro one must always be prepared for the fact that compensatory or amplifying effects may not have been not considered. An extreme example of this (one that has been used positively in clinical diagnostics for quite some time) is the reaction of smooth muscle cells (SMC) to acetylcholine (ACh). ACh causes a strong reaction upon coming into direct contact with SMC; however, if the SMC are covered by a layer of endothelial cells, ACh has a relaxing effect [10,11]. In this example, it would be possible, in principle, to better approximate a real cell wall by augmenting the model, but even if a complete piece of an artery were used, the nerval and humoral (endocrine) interactions would still be lacking, as would be the characteristic mechanical stimuli. In addition, as the number of model components increases, so too do the degrees of freedom in their mutual interplay, so that the model becomes less comprehensible, and thus less able to provide insights. Since even individual cells can react to stimuli both linearly (e.g., adaptive hypertrophy) and nonlinearly (e.g., thresholds), even an agglomeration of cells cannot be described simply as the sum or product of its constituents. On the other hand, there are also collective phenomena – such as rotors in excitation propagation on the cardiac muscle – for which a sufficiently large agglomeration of cells must be present to form the necessary substrate for its existence, such that this type of phenomenon can never be studied in "small" cell cultures. The situation becomes even more complicated due to the fact that, as a rule, questions of therapeutical interest are concerned not with physiological but with pathological conditions of the organism which may be highly individual in nature.

Overall, the "synthetic" approach offers the possibility of obtaining a detailed picture of individual causal chains that are active in vivo; however, only under certain conditions is it suitable for estimating the relative significance of these effects for the entire system in vivo.

"Descriptive" Approach

In this section, we wish to describe attempts to obtain information about, for example, the effectiveness of an applied therapy, that are based on observations in patients. Since the purpose and measure of a therapy is the successful treatment of a patient, the patient is ultimately the only "sufficiently complete model system" for a test. However, there are complications both regarding the method of description, since a complete organism is far too complicated to describe as a whole (see above), and regarding the performance of the test, since the patient, as a human being, cannot be subjected to any number and kind of tests that one desires.

The description starts from the (essentially tautological) statement that there is variation between individuals. Also, each individual is an open and changeable system, so that individual observations are only conditionally transferable both between individuals and between different times for the same individual. The reasons for these differences may include genetic predisposition, environmental conditions (nutrition, sleep, stress), or life history (previous diseases, immunization, obesity); it should also not be assumed that all relevant influences are known in their effects and their relative importance to each other. Each individual case is therefore dependent on a number of partly unknown, partly indeterminable factors.

On the other hand, there are also great similarities which can be found on the cellular and organizational level throughout all animals, and all the more within single species. Biology shows that many of the elementary processes (which are understood increasingly better, or at least to more detail) operate in much the same way for different individuals. With this in view, it would be a reasonable approach to consider the existing similarities to be "standard behavior" with a certain "distribution" contributed to by the incidental or unknown systematic influences. If one considers this (subjective or objective) lack of knowledge as statistical uncertainty, one can apply statistical methods to come to (probability-) statements about a "standard" or "expected" behavior and a "dispersion spread". This stochastic description does not primarily serve toward the modeling of chance or randomness, but rather toward the modeling of complexity. The many influencing factors that were not or could not be recorded, whether they be systematic or incidental in nature, are thus – with remarkable success – regarded to be essentially stochastic.

A characteristic procedure for this approach is to perform studies with a large number of patients. For this, it is necessary to classify the patients according to various categories; the results that are achieved can then be used to characterize (with a certain probability) all patients of the same "type". For such probabilistic conclusions based on the epistemological "method of similarity", there is generally some kind of "uncertainty relation" between the translatability of statements and their certainty or predictive ability. For example, predictions regarding life expectancy that are only determined for the collective type "human" have wide validity, but due to the high variability only low quantitative certainty or predictive ability can be attained. However, if this type is limited to a small, very rigorously classified group, a much more precise conclusion is possible, but this is hardly relevant anymore for anyone outside of this group. To strike a balance between these extremes, a classification into a few general risk characteristics is used in order to attain a certain level of external applicability with middling predictive ability. Classification, however, always means a certain loss of information, since observations made on patients are not assigned to the risk combination concretely present in that patient, but rather to the risk profile for the group. The principle of classification is both the strength and weakness of this approach, since it allows the results to be externally applicable, but also leads to a loss of information in the individual case.

The greatest strength of this approach is that it allows to take advantage of the powerful, largely perfected tool of mathematical statistics. This makes available a formalized procedure that can use the recorded data not only to answer a specific question, but also to evaluate the certainty of this answer (up to the point of undecidability). The formalism necessarily always leads to a single result, so that it seems to provide a "default" path for further insight in cases of doubt; "if in doubt, randomize" is the advice that Grüntzig often offered [3]. However, even a carefully randomized study is of only limited value in the population beyond the randomized group. Also, for ethical reasons, not all interesting questions can be answered in this way. The ethical responsibility that has increased significantly since Jenner's time is currently expressed by the Declaration of Helsinki, which the scientific community is obligated to uphold [12]. This can, for example, require that more than one parameter be varied between different therapy groups in a study in order to ensure the best-

possible care, even when this makes the evaluation of the results more difficult. In extreme cases, in the interests of the patients, it may also be necessary to terminate an ongoing study even before the question that was posed could be answered.

The formal procedure in studies carries with it an additional special characteristic; it allows the study plan for a given point of inquiry to be tailored regarding classification and scope so that the question can be resolved to a certain degree of prospective significance. This is of extreme practical importance, since it makes the required expenditure possible to predict, and allows responsible procedures in recruiting patients. On the other hand, such studies are no longer "open-result" in the sense that an answer to the question outside the predetermined horizon of inquiry could be found; the results could not serve toward gaining qualitatively new information. However, this concept is very suitable for estimating the practical relevance of known or suspected correlations (even quantitatively). In this regard, the "descriptive" and the above-described "synthetic" approaches are complementary to each other.

"Analytic" Approach

In the effort to achieve medicine's goal of improving therapy, there is another helpful approach which starts searching for areas of improvement from the cases in which previous therapy has not achieved the desired success. The main idea is to use detailed analysis of these cases to reveal the processes that may be correlated with this failure, or even to explain individual mechanisms that were responsible for the (total or partial) failure of the best available therapies. Based on a deeper understanding of the relationships involved, it is then possible to submit these obviously insufficient therapies with appropriate expansion, adaptation, or modification.

Useful contributions are offered primarily by pathologic studies during dissections or also tissue samples resulting, e.g., from atherectomies or bypass operations. Regardless of their potentially great significance, pathological analyses of human coronary arteries, for example, occur very rarely in the clinical literature [13,14]. Even when the number of reported cases is small and the results are "unspectacular", since they usually confirm mechanisms that were suspected due to insights from animal models, this type of confirmation alone is already one further step of insight that has not been there before. Moreover, in contrast to the artificially created stenoses in animal models, the analysis here is based on typical stenosis formations with "natural" pathogenesis and the environment of a human organism, so that in addition to showing the limits of the animal model (e.g., time scales), new insights into the relevant relationships can also be gained.

Likewise, expanded in vivo diagnostics too can make essential contributions toward explaining pathological mechanisms, as shown by the example of an examination of typical restenosis mechanisms for patients with and without a history of diabetes who underwent interventional treatment [15]. Here, an IVUS analysis of the wall structure of a restenotic lesion helped find two different active mechanisms (intimal proliferation and arterial remodeling) that were dominant in the different patient groups, but which led to the same angiographic findings. On the basis of this type of observation, therapy that is better adapted to these individual subgroups can now be developed instead of searching for "the" therapy for treating restenosis, which under such circumstances may not even exist.

The largest advantage of this type of "analysis" lies in the fact that it provides, in principle, a view into the causal chains that are actually relevant to the success as well as to the failure of the "best available therapy", and also allows one to assess the mutual importance of these factors. In this way, even the still-remaining weak points in an already mature therapy could be improved in a targeted fashion. Especially with respect to implants such as stents, one can not only establish relationships between the implant and the organism response, but also further explore the type of interaction involved (e.g., predominantly chemical or mechanical), so that criteria for technological improvements can already be formulated in the language of the technology. The primary disadvantage of this approach is that pathological studies can hardly be planned systematically, and this is even more so the case for relatively young, very successful therapies such as percutaneous interventions. Also, the time delay until therapeutic innovations can be submitted to this type of examination is very long (which it should be, for the sake of the patients); even an extremely detailed evaluation of the few cases that occur early on can hardly offset this fact. Finally, it should also be noted that the results come mostly from the examination of static preparations; these allow direct statements on dynamic processes in vivo only in so far as these processes have evolved up to the point at which they are examined. Of

course, this is not true for in vivo diagnostics, but these only allow access to a much smaller (but again, complementary) amount of information.

Discussion

None of the approaches described above for pursuing progress are ideal in and of themselves, but each provides indispensable information that helps fill in the gaps left by the other approaches. The targeted analysis of the weak points of a therapy, the macroscopic evaluation of effects, and the explanation of the elementary microscopic relationships each contributes in its own characteristic way to the continual improvement of the best therapies that are currently available. In particular, progress in the recognition of correlations often occurs in areas where different approaches can work together and provide stimuli to each other. Open-mindedness to all possibilities for attaining progress is one of the most essential prerequisites for it to actually occur. For example, Edward Jenner made his contribution to progress in cardiology through his pathological-anatomical studies, in that he was the first to identify a "malorganization" of the coronary arteries as the morphological correlate of angina pectoris [1].

In the following sections, we wish to discuss a few general considerations regarding the acquisition of knowledge, which we view to be an essential characteristic for progress. These considerations are not organized according to the methodological approaches defined above because many of the aspects discussed are relevant to multiple approaches. For example, the statistical methods discussed above are generally used today extensively beyond the pure "descriptive" approach, and are applied generally in order to quantify the conclusions made from observations, as well as their reliability. The goal of this discussion is thus not to introduce a ranking among these approaches, but to offer a critique of some important aspects they have in common in order to improve their utility as tools in practice.

Correct Application of Methods

Work that is methodically correct is a basic, "self-evident" prerequisite for obtaining new knowledge. This includes not only competent use of a method, but also the testing of whether the prerequisites of the method itself are fulfilled. This is then no longer self-evident when the method is taken from a field other than the one in question, as is the case when mathematical statistics is applied. In this particular example, the prerequisites are defined exactly, so that rigorous testing is actually possible; the method actually even makes such tests available.

The fact that even a test of this type can help one obtain knowledge is shown by an example from the literature [16]: In a study on the size of angiographic restenoses, the authors determined that the measured values did not follow a normal distribution. Instead of tacitly assuming this important presupposition of many statistical theories – as a gross approximation, if necessary – they used this observation to show the existence of two classes of patients with average restenoses of 30 % and of 70 %. The identification of such groups is an elementary precondition for determining different risk-correlations or even different dominant restenosis mechanisms between the groups, and for developing appropriate therapies for each case. In addition, the authors found that the closeness of their separation criterion (53 % restenosis) to the standard criterion of "≥ 50 % diameter stenosis at follow-up", which had previously been justified more through historical use [17] than physiological proof, offered a theoretical basis for the largely successful application of that criterion in practice.

On the other hand, some conditions required by the statistical approach are much more difficult to verify than the normal distribution. This includes especially the statistical independence of the observed parameters (observables) that is required, e.g., for the Moivre-Laplace limit theorem, and even for the law of large numbers (in its "strong" form). If one then considers the above-mentioned reasons behind differences between individuals, genetic predisposition can constitute its own risk, but also influence sensitivity to external risk factors; the probability densities for genetic and environmental risks can therefore not be independent (at least not rigorously). In addition – especially for age-dependent research topics – the statistical character of an observable itself (here "age") must sometimes be put to question. Because environmental conditions change continually in a manner that is not just coincidental, the dependence on the age of an individual – which could be more correctly described as a dependence on prehistory – cannot simply be modeled through observations of individuals of different ages at the same time.

These examples should be sufficient to show that it is anything but "self-evident", and often even impossible

(in the strict sense) to conduct "work that is methodically correct" in the gray area between the rigorous demands placed by methodology and that which is feasible under real circumstances. It is therefore that much more important to understand the approximate nature of the results, and to correctly estimate the limits of their predictive capability.

Choice of Terms

The basic foundation for every type of description and exchange of information is the determination of a basic lexicon of terms. Choosing a level of description, as well as the terms themselves, can itself decisively promote the pursuit of progress. However, it can also significantly inhibit progress, because, for example, the inherited concepts and methods of description are not always suitable to describe new phenomena, or even to formulate the type of question that could lead to a "milestone" in medicine. Terms must be measured by whether they are appropriate to a given phenomenon; the search for better terms and, if necessary, new terms, is an integral component of the pursuit of progress.

However, every choice of terms is subjected to different and possibly conflicting requirements, for example between the (patho-)physiological relevance and the clinical-diagnostic availability. As an illustration, in the characterization of a stenosis, the "vessel diameter", as a value that is directly determinable angiographically, can be contrasted with the physiologically more important "flow resistance of stenosis", which (in approximation to a long tube) is scaled to the reciprocal of the fourth power of the diameter. A reduction in the diameter to 3/4 or 1/2 would lead to an increase in the flow resistance by 3.2- or 16-times; it thus has a much higher effect than the numerical value of the change in diameter would suggest. On the other hand, the actual decisive value is the "volume flow". This is additionally dependent on the resistance of the distal vasculature, which is thus an absolute (but not constant over time!) reference value for the evaluation of the stenosis resistance. The TIMI-categories for the flow implicitly use this physiological "internal reference".

The example above makes it clear that the choice of terms is always closely bound up with the question at hand. Terms and criteria that have proven themselves from one particular standpoint can be completely irrelevant from another standpoint. Conversely, the same circumstances can yield completely different types of information when viewed using different conceptual categories. It can only be beneficial to ask questions about given observations using different points of view, especially when interests from different fields intersect. As an illustrating application, the clinical evaluation of an interventional therapy using a new type of stent technology may serve as an example. For those on the clinical side, the main point of interest is the evaluation of the quality of therapy as a whole, which thus includes the entire time from the decision to use the therapy to at least the completion of follow-up. In accordance with the declaration of Helsinki, the best possible treatment is both the principle and the goal, so that each time the goal is not achieved, or in other words each adverse event, must be included in the evaluation. The interests of those on the technology side are concentrated on the information that can be correlated most directly with the stent (or ideally with the individual characteristics of the stent). This is quite natural because, in effect, the stent is the only component of the therapy upon which technology (and only technology) can have a direct influence. In this regard, it is not only legitimate, but also desirable, that these types of questions are posed and the corresponding information evaluated.

To gain new insight, it may not even be necessary to collect additional data, but may rather be sufficient to group the data in new ways: while, for example, the major adverse cardiac event (MACE) rate is an often-used indicator of the benefit of the entire interventional therapy, the performance of the stent would be reflected by the subgroup "MACE related to Target Lesion" with greater emphasis. The frequency of hemorrhaging complications during follow-up examinations is an indispensable value for the physician in risk assessment; however, is this more likely to provide information about the stent (which had passed these locations only within the catheter lumen, if at all), about the catheter used for the intervention, or about the catheter or the procedure employed during follow-up?

In this context, it is also conceivable to ask whether the MACE rate is then an ideal therapy criterion from the view of the patient. The complications that are counted as MACEs range from angiographic restenosis without influence on the patient's daily life to fatal acute myocardial infarction. Since many of these complications differ so drastically regarding manageability and prognosis, from the patient's standpoint they should not be weighted equally in assessing the best therapy that is currently available.

In summary, narrowing the field of a question to a small number of terms (indicators) does not make full use of relevant information that is available. Terms and criteria (figures of merit) should always be checked for their appropriateness to the problem and hand, and possibly be chosen based on their suitability.

Evaluation of Correlations

Correlations represent a crucial concept in the evaluation of statistical data. They serve to quantitatively determine the "consonance" between various observables – that is, to measure the extent to which changes in one observable are accompanied by changes in the other.

In order that changes are possible at all, the observables must be able to assume different values. This condition is fulfilled even by a binary classification (e.g., "Diabetes yes/no"). However, binary classifications can only be used to show linear correlations; a test of whether the assumption of linearity itself is empirically justified is not possible in these cases. Non-linear correlations, however, are common in inanimate nature, and especially so in living organisms. If the functional relationship is a priori unknown, then the method for describing a nonlinear correlation is graphic depiction, which can then be used to empirically show the relationship. As a basic principle, correlations can be determined with more certainty when the observables (are allowed to) vary more strongly. Even when the object of testing is whether suspected physiological relationships are compatible with the observed correlations, binary divisions such as "Diabetes y/n" or "Hypertension y/n" barely offer any assistance; more helpful would be a categorization of the type "treated/ not treated, with values within/ deviating from/ strongly deviating from the normal range", possibly supplemented with entries on the duration of the prehistory.

That the proof of a correlation between two parameters still does not allow the conclusion of a possible causality is a fact noted in every textbook on the fundamentals of statistics. The following comment is very incisive in that regard [18]: "When two parameters correlate, there is probably a connection, but this does not necessarily imply a direct causal relationship. For example in Mediterranean countries there is a good overall correlation between birthrates and stork density. However, neither the notion that babies evolve into storks, or that storks bring babies, seems a viable hypothesis in the light of other evidence." A correlation alone allows no differentiation between cause and effect. Even less can a correlation uncover whether the two parameters are influenced by a common cause, and are otherwise unrelated (one cause in the above example could be the level of industrialization). The search for the causal relationship that is responsible can only be performed "in the light of other evidence"; this means evidence made available from independent sources.

While it is true that knowledge regarding causal relationships is rarely obtained through proof of correlation, it is also the case that the correlations exist even when one cannot give (or approve of) a causal mechanism for them. From this fact, one can derive a useful empirical rule for clinical therapy, which in an extreme case, for example, consists in intentional use of the documented placebo effect in pain therapy. Even rules such as this contribute to (practical) progress.

In purely descriptive proofs of correlations, there is always the possibility that these correlations are the result of the systematic influence of unknown or unconsidered parameters. This type of limitation is regularly noted in the discussion of study results, and it is good common practice to do so. Possible causes that are often named are demographic peculiarities such as characteristic nutrition- and living standards, local risk factors (environmental loads) in the area in which the study is being conducted, incomplete recording of clinical parameters later suspected to be relevant, or systematic procedural differences between different clinics. Time can also have an influence, which can be caused by improvements in the therapy as well as by expansion of therapy to cases with worse prognoses due to the therapeutic improvements (precisely this compensatory effect is responsible, for example, for the fact that the reported development of the MACE rates over time does not reflect the actual improvement in the quality of interventional therapy).

It should also not be overlooked that despite sophisticated diagnostic techniques, there is always the possibility of bias due to a systematic measurement error. This danger is especially relevant when a well-established diagnostic procedure, for example, quantitative coronary angiography (QCA), is used uncritically upon the advent of a new therapeutic procedure, for example, stent implantation: in fact, it has been shown both theoretically [19] and experimentally [20] that the presence of a stent leads to a systematic artificial

widening of the luminal shadow as measured by QCA; this widening is due to the principles of X-ray depiction, and cannot be avoided. Quantitatively, the upper limit for this widening is determined by the resolution of the X-ray device, which for modern devices comes to a few tenths of a millimeter. The widening is then determined by the radiopacity of both the stent and the contrast medium in the lumen. Calculations show that the widening will only be negligible for very high concentrations of contrast medium and very low stent visibility. With lower concentrations and increasing radiopacity, the widening increases progressively to its maximum value. From the X-ray picture alone, it is generally not possible to differentiate between the shadow of the lumen and that of the stent; in particular, the QCA system has no information on the fact that such a differentiation would be necessary at this location. If this systematic error is not considered during evaluation, then it leads to the situation where stents with greater visibility are incorrectly measured as having a larger lumen, and thus a smaller restenosis. Conversely, in order to reach the same post-procedural angiographic result, less visible stents will be dilated to a systematically larger diameter than more visible stents. This could, on average, mean an increased rate of vessel injury, which would then provide a cause for a systematically higher restenosis rate.

The Impact Of Time

The influence of time on the significance of the MACE rate as a therapeutic criterion was already mentioned in the previous section. In the development of a new therapeutic procedure, however, there are other aspects that are dependent on the passage of time, of which two will be discussed here in more detail.

First, it can be stated that with the increasing "maturity" of a procedure, there are characteristic changes in the type of information that is exchanged in the community involved with the procedure. For the example of percutaneous transluminal coronary angioplasty, one could model how an idea first becomes a reality through close exchange between a small number of parties in medicine, the natural sciences, and technology [4]. Upon the appearance of the first case reports [21,22] increases the number of interested parties, and later the number of participants, so that the spread of the procedure leads to the accumulation of experiences from different perspectives. Expansions and variations of the method begin to appear (e.g., directional atherectomy, rotablation, laser angioplasty, etc.). First, systematic comparative studies document the acute success of the therapy; later, long-term results are added, which evaluate the permanent success of the therapy [2]. While an extensive, detailed information exchange accompanies the birth of a procedure, the time after the procedure reaches a certain maturity is characterized by the use of a relatively small number of highly abstract terms; the individual cases are subordinated to these terms, but the information that is shared has a wider validity for precisely this reason. Viewed from the standpoint of technology, the initial situation – with its wealth of detail and high flexibility in the definition of terms – offers many chances to find criteria that can be translated into the language of technology. With the progressive reduction to clinically relevant categories (or even just to easily obtainable categories), there is the danger that the "shared vocabulary" of all parties is limited or even lost. Of course, it cannot be expected that there be one shared set of terms that is equally relevant to all parties. However, a basic set of all terms that are used in the pursuit of progress (e.g., as observables in a study plan) should, in this sense, be included in the "vocabulary" of all parties involved.

A time consideration of a different sort becomes especially evident when a therapy has a very good acute success, so that the cases of failure decisive for evaluation do not occur for an extended period of time. This is becoming the situation for vascular interventions. This has consequences for the relevance of clinical studies, which must be designed with increased scope and long study times due to the number of cases necessary. On the one hand, progress in complementary therapies could decrease the failure rate over the course of the study so that the projected power of the study is no longer attained; this would limit the comparability between early and late participants in the study, or in extreme cases lead to the result that the therapy group originally targeted by the study no longer exists. On the other hand, the time span of multiple years required for the study to obtain significant results is simply too long a "reaction time" for the evaluation of technological improvements on the stent. An loophole here would be to plan studies so that they can be evaluated over shorter time scales, and have them be structured into multiple time steps after each of which the study could be terminated if desired. It would then be possible to evaluate and make use of

results or tendencies at an earlier point in time. One might anticipate, too, that the detailed analysis of the (available) cases of failure, which may even be conducted in parallel to the continuing long-term study, would also become increasingly important as a source of information.

Concluding Remarks

Progress in biomedical engineering, like progress in medicine in general, is oriented toward providing benefits for the medical therapy of a patient's disease. Clinical practice both determines the future tasks and provides the standards for measurement, which are essentially based on systematic comparative observations on patients. In collecting this type of data, high ethical requirements are placed that have as their highest principle the protection of the life, health, privacy, and dignity of the human subject [12]. Data coming from observations on humans are thus not only relevant, but also costly; in the interests of handling these data responsibly, it is only reasonable that the information that they provide should also be used optimally.

This can mean, for example, that the available data be evaluated with regard to different questions, and also using different conceptual categories. In this way, one can prevent the loss of information that unavoidably occurs when one projects observations only onto a single conceptual level. It can also mean to focus not only on the classification of distinct risk groups, but also on the concrete risk combinations in individual cases that could possibly be useful in coming up with "the right idea" regarding the circumstances behind the failure of therapy. Especially in the case of successful therapies, it can be beneficial not only to strive for the demonstration of effectiveness, but also to consider the analysis of adverse events as a main point of interest. On the one hand, this offers the opportunity to complement the existing empirical knowledge with knowledge of the underlying relationships; on the other hand, there is even the possibility that limiting analysis to a collective that consists of "100 % interesting cases" may earlier lead to significant results.

Progress can thus not sustain itself on only one or another of the methodical approaches described; progress is most successful when the complementary insights from the different approaches can be combined to support one other. This view is even more compelling when one considers the technical tools that biomedical engineering makes available to the physician for diagnosis and therapy; the cooperation required here extends outside the limits of any single academic discipline. Based on the needs of clinical practice, a physician formulates the need for a certain type of device. This need must be translated into the scientific language of the inanimate physical world so that its requirements can be converted into a set of technologically comprehensible parameters. When a technological solution is found, then it must be evaluated in vitro, in vivo, and finally in clinical application. From the insights gained here, new requirements arise that then stimulate the next pass through the cycle, so that continual improvement of a device is made possible.

Communication between all parties is of central importance here, and is beneficial in a number of respects. Even the simple act of sharing information causes one to work out the essential issues. When one is confronted with different approaches and ways of thinking about an issue, one must justify and sharpen one's own conceptualizations. At the same time, the two partners in a dialogue enrich their shared "vocabulary" with their individual conceptual universes, and this can almost effortlessly lead to new, sometimes surprising viewpoints. In the interests of the shared goal of improving therapy, there is thus no reason for hesitance in exchanging ideas or for ideological exclusivity. Since each of the partners can add his or her own specific contribution to this goal, it is also important that each person formulate his or her specific requirements and keep these in mind, for example, in initiating collaborative studies. The different perspectives from which the partners view the results are helpful in gaining a more complete picture of the information content, and in appropriately assessing the relevant conclusions. Ultimately, the search for relationships and correlations can only profit through the partners' cooperation.

So, how can we proceed? There is absolutely no single, "only" optimal way to attain progress. However, there are certainly approaches that can make their own characteristic contributions to progress. Once again, it may be helpful to look to the example of nature: Even the evolution of life simultaneously follows many different paths that, while different from one another, are also interdependent, and complement each other in the goal to explore and exploit every possible improvement.

References

[1] Baron J. The life of Edward Jenner, M.D. London: Henry Colburn. 1827.

[2] King SB. The development of interventional cardiology. J Am Coll Cardiol. 1998; 31: 64B-88B.

[3] King SB, Meier B. Interventional treatment of Coronary Heart Disease and Peripheral Vascular Disease. Circulation. 2000; 102: IV-81-IV-86.

[4] King SB. Angioplasty from bench to bedside to bench. Circulation. 1996; 93: 1621-1629.

[5] Bolz A, Schaldach M. Amorphous silicon carbide: A semiconducting coating with superior hemocompatibility. Artif Organs. 1991; 14 (Suppl 4): 151-160.

[6] Bolz A, Amon M, Özbek C, et al. Coating of cardiovascular stents with a semiconductor to improve their hemocompatibility. Texas Heart Inst J. 1996; 23: 162-166.

[7] Heublein B, Krecksch R, Pethig K, et al. Coronary stenting in cardiac allograft vasculopathy: The impact of silicon-carbide coating on luminal re-obstruction. Prog Biomed Res. 2000; 5: 215-220.

[8] Hanekamp CEE, Koolen JJ. Coated stents in small coronary vessels - A successful strategy? Prog Biomed Res. 2000; 5: 221-223.

[9] Carrie D, Khalife K, Hamon M, et al. Initial and follow-up results of the Tenax coronary stent. Prog Biomed Res. 2000; 5: 224-228.

[10] Elsner M. Methoden der funktionellen Koronardiagnostik. Herz. 1998; 23: 78-96.

[11] Zeiher AM, Drexler H, Wollschlager H, et al. Modulation of coronary vasomotor tone in humans. Progressive endothelial dysfunction with different early stages of coronary atherosclerosis. Circulation. 1991; 83: 391-401.

[12] World Medical Association Declaration of Helsinki as amended by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Available from: URL: http://www.wma.net/e/policy/17-c_e.html

[13] Komatsu R, Ueda M, Naruko T, et al. Neointimal tissue response at sites of coronary stenting in humans - Macroscopic, histological, and immunohistochemical analyses. Circulation. 1998; 98: 224-233.

[14] Farb A, Sangiorgi G, Carter AJ, et al. Pathology of acute and chronic coronary stenting in humans. Circulation. 1999; 99: 44-52.

[15] Kornowski R, Mintz GS, Kent KM, et al. Increased restenosis in diabetes mellitus after coronary interventions is due to exaggerated intimal hyperplasia - A serial intravascular ultrasound study. Circulation. 1997; 95: 1366-1369.

[16] Schömig A, Kastrati A, Elezi S, et al. Bimodal distribution of angiographic measures of restenosis six months after coronary stent placement. Circulation. 1997; 96: 3880-3887.

[17] Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation (abstract). Circ Res. 1978; 43: 242-253.

[18] Israel FP. In: Wolstencroft RD, Burton WB (editors). Millimetre and Submillimetre Astronomy. Astrophysics and Space Science Library: Current Research, Vol. 147. Dordrecht: Kluwer. 1988: 293.

[19] Schmiedl R, Schaldach M. X-ray imaging of coronary stents. Prog Biomed Res. 2000; 5: 184-196.

[20] Fish RD, Das TS. QCA overestimates stented lumens: A source of artifact in the late loss index of coronary stenting (abstract). Circulation. 1995; 92: I-600.

[21] Grüntzig A, Turina M, Schneider J. Experimental percutaneous dilatation of coronary artery stenosis (abstract). Circulation. 1976; 54: 81.

[22] Grüntzig A, Myler R, Hanna R, et al. Coronary transluminal angioplasty (abstract). Circulation. 1977; 56: 84.

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