Editorial corner
The fundamental role of clinical research

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Attilio Maseri

The explosion of knowledge in the fields of cellular and molecular biology provides the intellectual and technical background for studying in much greater depth the mechanisms of disease that, on the basis of existing knowledge, are considered fundamental. However, only the potential mechanisms of disease already identified can be studied in depth. New mechanisms of disease can only be identified by innovative clinical research.

As stated by Kuhn[1], research has a natural tendency to focus on details of accepted paradigms. Indeed Scientific Communities are built around accepted paradigms that determine major lines of research, influence the chances of obtaining grant support or publishing results and establish standards of therapy. Once a paradigm becomes established, it is very difficult to change, just like criminal cases are hard to re-open once a culprit has been blamed and jailed. When a criminal case is considered closed , there is no longer an incentive to pursue the investigation and there is strong resistance to accept newly discovered discrepant evidence. In the same way established paradigms have a tendency to monopolize research and to disregard discrepant results.

In the past, by providing compelling new evidence, clinical research has occasionally succeeded in changing established paradigms and has opened innovative lines of research.

Lessons from the past

In the 1950 s and 1960 s an established paradigm stated that angina pectoris could only be caused by a critical reduction in coronary flow reserve and that myocardial infarction occurred when this reserve persistently dropped below resting needs. The coronary circulation was assumed to be of the terminal type, thus there was no role for collaterals. This paradigm had major negative influences on clinical practice, on pharmacological and research developments which have persisted for decades and have not yet completely waned from the back of the mind of many clinicians and investigators.

i) Until the mid 1960 s patients with acute myocardial infarction were confined to strict bed rest for 3 weeks in order to minimize their myocardial oxygen consumption.

ii) In the 1950 s it was thought that nitroglycerin acted by increasing coronary blood flow based on its effect in animal models. Thus dipyridamole and carbochromene were developed and marketed as anti-anginal drugs just because they markedly increased coronary blood flow in animals, although their anti-anginal effect could never be proved. It was a clinical study that disproved this universal belief by showing that, at doses effective in relieving angina, nitroglycerin did not increase coronary blood flow[2]. Up to 20 years later, among the positive features of some calcium antagonists, their capacity to increase myocardial blood flow was still stressed, although nowadays this feature would be considered a theoretical disadvantage because it could cause transumural coronary blood flow steal in the presence of coronary flow limiting stenoses.

iii) Research was hindered by dogmatic statements by established authorities. Pickering[3] in the *Lancet* claimed that there was no need to postulate coronary vasoconstriction in angina, given the very obvious presence of coronary stenoses at autopsy. Friedberg[4] in his classic textbook stated that the ischemic origin of angina occurring at rest should be questioned unless it occurred also on exertion. As a consequence, until the late 1970 s angina occurring as a result of a primary reduction in coronary blood flow[5] was considered so rare as to be defined Pisa angina as McGregor[6] recalled in a review article a decade later.

Yet, although the evidence of the role of coronary spasm[7] and of coronary stenosis constriction[8] provided a rationale for the use of calcium antagonists and nitrates for the relief and prevention of epicardial coronary artery constriction, the notion that coronary atherosclerosis may play an essential role in causing ischemia is still conditioning research. For example, although the possible role of microvascular dysfunction in patients with atherosclerotic coronary disease was revealed by clinical studies[9,10], the isolated existence of coronary microvascular dysfunction in patients with angiographically normal coronary arteries is still considered with scepticism. Indeed, in some major institutions, patients with angina and completely normal coronary arteries are not even submitted to stress tests and, accordingly, in patients with normal coronary angiograms a positive stress test is considered a false positive test , totally disregarding the possibility of a coronary microvascular dysfunction[11,12].

Until the late 1970 s, the cause of myocardial infarction was still speculative and thrombolytic therapy, although available, had not been clinically used in acute myocardial infarction. Coronary arteriographic studies, daringly performed in the very early hours after the onset of chest pain, demonstrated convincingly the presence of coronary thrombosis[13], dispelling widespread previous scepticism, and led to the general use of thrombolytic drugs in acute myocardial infarction.

Compelling angiographic evidence, disproving widely held beliefs, demonstrated that at the end of intracoronary thrombolysis the residual culprit coronary stenosis was often only mild or moderate[14]. Accordingly pre-infarction angiograms showed that the infarct-related artery had only a minimal or a mild stenosis in about 70% of the cases[15-18]. Yet often also coronary stenoses that do not cause a transtenotic pressure gradient are still dilated or bypassed under the assumption that this will improve the symptoms and prognosis.

I have chosen these classic paradigms as examples because over the past 40 years they have been a significant component of my own research experience and because they show how clinical research has been crucial for challenging them and thus has given way to the development of new treatments and novel avenues for pharmacological and basic research.

These cardiovascular paradigms may not be the only ones that should be challenged. At present for evidence-based medicine treatments and for pathogenetic research broad clinical syndromes such as sudden coronary death , dilated cardiomyopathy , essential hypertension , myocardial infarction , coronary restenosis are still considered as if they were single disease entities. At the beginning of the new millennium clinical research will have a fundamental role in the identification of individual disease entities within each of these broad cardiovascular syndromes and for personalizing therapy and prevention.

Clinical syndromes: an intermediate step in medical knowledge

A syndrome is characterized by a set of symptoms and signs, common to a group of patients, that are easily identified by physicians as a recognizable clinical entity. By definition a syndrome is the common end result of different pathogenetic mechanisms, each of which may have different etiologies. A few examples will clarify this point and the most illustrative one is not cardiological. Anemia is characterized by persisting pallor and fatigue. The reduced blood red cell count and hemoglobin content explain these symptoms, but anemia may be caused by different mechanisms. When anemia is very severe, a blood transfusion is beneficial independently of its causes. However prevention of anemia requires knowledge not only of its pathogenetic mechanisms, for example iron or vitamin B12 deficiency, but also of its etiology, for example iron or vitamin B12 deficient diet or defective intestinal absorption. Treating all cases of anemia indiscriminately with the same magic bullet would nowadays be inconceivable for hematologists.

Angina pectoris is another broad clinical syndrome, characterized by the typical pain described by Heberden, which may result from different pathogenetic mechanisms such as a flow limiting coronary stenosis when myocardial oxygen demand increases, occlusive spasm, constriction of coronary stenoses, transient thrombosis and small vessel dysfunction. However, also the etiology of flow limiting coronary stenoses, of spasm, of small vessel dysfunction and of thrombosis, may be multiple and they must be precisely identified in order to decide on a specific prevention.

For example the understanding of the pathological role of coronary vasoconstriction or of thrombosis has led to the widespread use of vasodilators and antithrombotic drugs. However these treatments, in order to correct a local coronary dysfunction, clearly alter the vasomotor tone and the hemostatic equilibrium of the whole body. A rational specific treatment requires the identification of the precise etiological mechanisms responsible for coronary vasoconstriction and for the transformation of thrombosis from a natural defense mechanism to a critical determinant of disease.

These mechanisms may not be the same in all patients. The same line of reasoning may apply to other broad clinical syndromes such as essential arterial hypertension , idiopathic dilated cardiomyopathy , sudden coronary death and myocardial infarction . Moreover the study of genetic components within a given clinical syndrome requires the identification of specific phenotypic traits, which identify patients with the same causative genetic defect or polymorphisms. For example erythrocyte phenotypic traits such as sickle cell or target cells allow hematologists to identify families with different genetic causes of anemia.

Indeed family clustering of a syndrome such as sudden death or premature myocardial infarction does not imply that the same genetic defect or polymorphism involved is the same in all families studied.

From evidence-based medicine to personalized treatment and prevention

The end of the 20th century was characterized by a long awaited transition from clinical empiricism and anarchy to evidence-based medicine[19]. Thus for broad clinical syndromes, such as cardiac failure, arterial hypertension, myocardial infarction, the choice of treatment is guided nowadays by the statistical significance of the prognostic benefits demonstrated in large clinical trials according to the principle of evidence-based medicine. However, we should consider the possibility that in these broad syndromes the average statistically beneficial effect may not necessarily apply to all patients who met the inclusion criteria of the trials[19]. For example, once more borrowing from hematology, in a randomized trial including unselected anemic patients, iron supplements are likely to cause a significantly greater average increase in hemoglobin levels than placebo. However this average increase would result only from the benefit occurring in those patients included in the trial who happened to have iron deficiency.

Whether or not the benefit observed in a given clinical syndrome applies to all patients who met the entry criteria of a therapeutic trial is becoming a critical question for two reasons.

i) New or more aggressive treatments may carry a greater risk and/or cost, therefore ideally they should be reserved for those patients who do not respond to simpler forms of therapy. For example in acute myocardial infarction, ideally tissue-type plasminogen activator should be reserved for those patients who are unlikely to respond to streptokinase and primary angioplasty should be reserved for those who are unlikely to respond to tissue-type plasminogen activator. Clinical research is essential for identifying possible individual differences in the mechanisms of coronary thrombotic occlusion in acute myocardial infarction in order to personalize myocardial reperfusion strategies.

ii) For many syndromes the number of treatments that are shown to improve prognosis is steadily increasing. For example beta-blockers, anticoagulants, aspirin, statins and ACE-inhibitors were all proven to improve prognosis in post-infarction patients. As the burden of polytherapy, the risk of side effects and the probability of low patient compliance increase with the number of drugs prescribed, are all these treatments indicated for all post-infarction patients? Indeed, the cumulative reduction in reinfarction that would be obtained by adding together the mean beneficial effect of each of these treatments, would greatly exceed 100%, which strongly suggests that at least some of these treatments are beneficial only for selected subgroups of patients.

It is mandatory that we begin to investigate which subgroup of patients actually benefits from each of these treatments in order to increase compliance and reduce side effects and costs by personalizing preventive strategies[20]. The same line of reasoning may also apply to other syndromes such as cardiac failure, congestive cardiomyopathy, sudden coronary death and restenosis following coronary angioplasty.

Conclusions

Clinical exposure to the varied presentations of individual cases provides a continuous stimulus for cardiologists with inquisitive minds, as long as they do not limit their attention only on the minimal diagnostic criteria which allow patients to be classified into one of the established broad clinical syndromes.

However the number of unusual cases observed in any single institution is likely to be limited.

Therefore, for each major cardiovascular syndrome, it is mandatory to undertake a systematic, prospective collection into common registries of detailed clinical cases with a long-term follow-up together with corresponding plasma samples and genomic DNA, stored into biological banks. When such cases are considered in detail with an open mind, occasional deviations from standard paradigms may be observed. When such deviations are considerable they may suggest a new previously unsuspected pathogenetic or etiological mechanism. This was, after all, the way that some diseases and syndromes were identified about a century ago by clinicians whose names they bear.

In the third millennium multicenter collaborative projects for the development of large, telematically connected clinical and biological data banks will set the stage for the identification of the multiple specific disease entities, presently still grouped under the same commonly recognized clinical syndrome. In order to do so clinical research may have to open new horizons of research which may be hindered by established paradigms.

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