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# Laboratory and Clinical Medicine. A Gap beyond Reduction?

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*S u m m a r y. Confronting discrepancies between laboratory results and clinical practice is a common problem in modern medicine. Using antiplatelet therapy as an example, we try to analyze why reductive approaches do not explain such gaps and show how the problems are encountered by the medical community.*

## INTRODUCTION

The development and introduction of drugs are based upon thorough and detailed laboratory studies; studies that employ first line technology and take advantage of basic science methods. However, their usage in clinical practice has often unpredictable results, results that do not keep up with the commonly used reductive model of modern medicine. In this study we intend, after explaining this reductive model, to try to present such discrepancies by using as example common antiplatelet drugs, and to comment upon the methods used by modern medicine to overcome this gap between laboratory and clinical practice.

## METHODS

The reductive model of modern medicine is approached through notions of 20$^{th}$ century philosophy of science and their attempted application to medicine. The problems arising between laboratory experiments and clinical use of antiplatelet drugs are noted: The expected beneficial effect of drugs is questioned by the results of clinical trials, while indications and dosage are constantly reevaluated; the unexpected findings of clinical use of drugs constitute the gap between laboratory results and practice we try to delineate and analyze.

## RESULTS

Modern medicine has, since the era of Claude Bernard and the theories he presented in *Introduction to the study of experimental medicine* in 19$^{th}$ century France (1), developed mainly upon the notion that molecular mechanisms are responsi-ble for clinical presentations of disease. Whatever appears as a symptom, disorder or debilitating process of the human body can be explained in terms of molecular alterations, and, through the comprehension of these alterations, doctors can understand and predict the outcome of disease. Hence, intervention with drugs, which are isolated (or well known mixtures of) chemical substances, can alter these mechanisms, change the clinical course of the disease and in that way provide cure. This reductive theory - reductive because macroscopic presentations are reduced to molecular structures - is the mainly accepted medical theory. Trying to rephrase the above in terms of philosophy of science we could interpret this theoretical scheme as the modern paradigm for medicine in Kuhnian terms (2). Thomas Kuhn, analyzing the development of science, defined a period of *normal science*, within which all scientific work is aimed towards the enhancement of the theory and application of her basic principles through experimentation. The commonly used antiplatelet drugs are aspirin, dipyridamole, ticlopidine, clopidogrel and the intravenous platelet glycoprotein IIb/IIIa receptor inhibitors (abciximab, eptifibatide and tirofiban). The introduction of platelet antagonist drugs in therapeutics is aimed to prevent thrombosis and alter the natural history of atherosclerotic vascular disease, since platelets are required for the formation of thrombi at sites of vascular injury (3). Antiplatelet drugs

are considered to act through different mechanisms: Aspirin blocks the production of thromboxane $A_2$, the major cyclooxygenase product of platelets that induces platelet aggregation and vasocon-stricton; the complete inactivation of thromboxane is achieved when at least 160 mg are taken daily, in order to produce a cumulative effect. Dipyridamole interferes with platelet function by increasing the cellular concentration of adenosine 3A, 5A-monophosphate (cyclic AMP) (3). Ticlopidi-ne blocks ADP-mediated platelet aggregation and transformation of the platelet fibrinogen receptor into a high affinity form, while clopidogrel is involved only in the latter mechanism (4). The IIb/IIIa inhibitors block the platelet glycoprotein receptor for adhesive proteins such as fibrinogen and von Willebrand factor; abciximab is a murine-human chimeric antibody, eptifibatide a synthetic peptide and tirofiban a synthetic nonpeptide (5). The prevention of thrombosis in healthy subjects is maintained through a series of counter mechanisms. However, pathological formation of thrombi can result in potentially life threatening states that involve blood vessels of any size: I. Coronary disease, includeing acute coronary syndromes (ACS: myocardial infraction with or without ST elevation, unstable angina), stable angina, and history of infraction, II. Ischemic stroke, III. Peripheral arterial disease, and IV. Atrial fibrillation, to name the most common, can lead to potential non-reversible debilitating out-comes, even death. The reductive theory that we have described suggests that since our anti-platelet drugs inhibit the formation of thrombi and since thrombi cause a series of morbid con-ditions, the use of such drugs should prevent or cure them. This theory can be viewed as a typical deductive-nomological model: There is a firm logical argument (drugs prevent morbid conditions by preventing thrombi), has empirical evidence in the explanans, and the premises are true (5) (antiplatelet drugs do prevent thrombi and thrombi do cause morbid conditions). So where can the problems of this reductive scheme be traced? Let us make some remarks upon the use of antiplatelet drugs: Since they have different sites of action in the chain of events leading to the aggregation of platelets, will their combination prove more effective? Is the maximum safe dosage the most effective one and can this be defined? Are they all effective in the morbid states mentioned above? If the reductive model of current medicine is correct then the answer to all of the above questions should be positive, but is it so in practice? And, if not, how can we explain such gaps between the predictions of theory based on laboratory results and their application in clinical practice? The answer to the third question against the theory is easy: even in the same category of antiplatelet drugs, the IIb/IIIa inhibitors, the three mentioned drugs have different indications as determined by clinical trials; abciximab proved effective in terms of clinical outcome (and not in terms of experimental antiplatelet action) only as adjunct treatment in patients undergoing percutaneous transluminal coronary angioplasty, while tirofiban and eptifibatide are indicated as primary therapy in ACS without ST elevation (5). Dipyridamole, on the other hand, is indicated only in combination with anticoagulants for prosthetic heart valves (4). The medical community is now aware that reductive generalizations of laboratory results are often dubious and deceptive and require evidence for every distinct drug indication separately. Large clinical trials are still conducted years after drugs have been introduced, and their results often contradict what was considered as truth. Antiplatelets make an excellent example of this: The first efforts to determine indications and accurate dosage date from 1994 (6-8). We shall now focus on the results of a meta-analysis published in 2002 (9). In this paper, the authors, who included only large randomized clinical trials, conclude that: I. Allocation to antiplatelet therapy reduced the outcome of any serious event, II. Aspirin is the most studied drug and the effective dose ranges between 75-150mg daily. III. Clopidogrel and ticlopidine provided 4% and 7% better results than aspirin, respectively. IV. The addition of dipyridamole to aspirin (a combination commonly used) is of no benefit. V. The addition of IIb/IIIa inhibitors to aspirin prevented a further 2% of events in patients with high risk of immediate coronary inclusion. These results, apart from their clinical significance provide crucial evidence to our subject. An obvious laboratory result does not necessarily translate into a clinical benefit and drugs producing the same effect in an experimental environment will not alter the clinical course in the same way.

## CONCLUSIONS

Classic reductive models, like the one described above, cannot predict clinical outcomes. Modern medicine however, seems to deal with the problem by trying to link randomized clinical trials to laboratory results in an *a posteriori* explanation of the actual clinical outcome. The reductive theoretical position is not refuted and

forthcoming accumulation of knowledge on physiology and pathophysiology of the human subject is hoped that some day will overcome the difficulties.

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