INTER-UNIVERSITY DIPLOMA

TEACHING CLINICAL RESEARCH METHODOLOGY

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YEAR 2022-2023

SUMMARY

INTRODUCTION

The methodology in clinical research underlying the movement of clinical epidemiology, then evidence-based medicine, was presented by its promoters as a new science, as a new way of approaching clinical medicine, to study and practice it. At the same time, the methodology, of an epidemiological type, ended up becoming synonymous with clinical research. Before laying the foundations of clinical research teaching, it is appropriate to briefly define its outlines.

Of course, clinical research was not born at the end of the twentieth century, and no one can deny the fundamental contributions to clinical medicine of the great semeiologists of the last century: current nosology is still for the most part based on the description that they have made various diseases or syndromes, and it is always within this nosological framework that very often current medical research takes place, in its clinical or more fundamental aspects. It was high-level clinical research based on careful observation of patients, and the durability of its results still speaks for its quality.

If the idea is not new, perhaps the methodology is? The techniques of course have benefited from the contribution of modern concepts in epidemiology and statistics. However, Jean le Rond D'Alembert in the eighteenth century already exposed in an almost visionary way the most adequate method of evaluation, according to him, to appreciate the impact of the anti-smallpox vaccination both on the population and on the individual, taking into account the natural variation in the risk of death, and the risk of contracting smallpox as a function of age (1,2). This type of reasoning represents the very basis of the current of evidence based medicine, which we will not distinguish from the current concept of clinical epidemiology which immediately preceded it, as the two concepts are superimposable both in substance and in the methods used.

Neither clinical research nor its tools are ultimately very new, and one is almost surprised at the current passion generated by their rediscovery. This movement is rather, after years of significant progress in the basic sciences, the professionalization of research and the separation of professions, a return to the sources of the last century, when clinician and researcher were one, moving from hospital ward in the laboratory, and tried, in one or the other function, to observe the pathological phenomenon as best and as precisely as possible.

Back to tradition, so... most certainly. Any feedback, however, can be innovative, at least in the topics covered, and in the development of tools based on older concepts. The aim of this first-level seminar is to provide the basics of certain methods by illustrating them with clinical situations commonly encountered by medical practitioners: contact with patients, with their illness, generates fundamental medical questions:

What is, what are, the causes of the disease?
How to best diagnose the disease?
How to best deal with it?
How can we arrive at the best possible understanding of its evolution, and, consequently, how can it best be treated according to the foreseeable evolution?

There is no universal method to answer all of these questions, and it is difficult not to see a continuum between the most fundamental research and the most applied research: if all fundamental research does not always lead to quickly recognized practical applications, all applied research is based on prior knowledge fundamental research, and we could not measure cholesterol as a risk factor for cardiovascular disease if it had not been recognized and then synthesized, a molecule whose role initially remained mysterious.

We will call clinical research in this thesis, the research directly applied to the needs of the patient. We will only develop the aspects related to the methods of clinical epidemiology, knowing that these methods alone are often not enough to establish a fact and that proof, often, is only provided with an acceptable certainty that by the conjunction of several lines of research, biological in the broad sense of the term, clinical, epidemiological...

We will approach after the presentation of the methods, the difficulties of interpretation and will make a quick overview of the epistemological questions raised by the use of these methods during the development of a work, and during the clinical application of the results obtained: the appearance of rigor is not enough to certify the reality of an observation.

Some analyzes may seem personal, and in fact are not shared by all methodologists. However, a few rare voices are heard (3). The methodology of clinical research is a tool for apprehending the living which, like other tools, has strengths and weaknesses: the appreciation of these is no longer a matter of method strictly speaking, but depends on the distance between what the method can offer and what we want it to do.

IDENTIFICATION OF NEEDS. POPULATION TARGET BY EDUCATION. BASIC CONCEPTS

It is interesting to note that clinical research methods have not been used to precisely identify the needs of their potential users: there is no audit measuring the needs of medical practitioners in terms of knowledge of the methods used by clinical epidemiology or evidence based medicine. These needs, on the other hand, have been underlined by a number of editorials or general reviews: the lack of documented studies, and the abundance of general articles is one of the paradoxes of a current going against so-called medicine. ... of opinion. The university environment, in particular, did not seek to know the precise needs of its actors and assumed that, in all likelihood, everything had to be provided or taught.

The attitude of English GPs towards evidence-based medicine has, however, been explored: the majority of them consider the evolution towards medicine based on measured facts as positive and understand the concepts. Only a minority (only less than 20%) has access to bibliographic databases allowing them to acquire knowledge developed from clinical studies. The majority of them do not have the time to use them, and believe that establishing recommendations based on the studies carried out would be the best way to promote evidence-based medicine in their clinical practice (4). It is possible that the opinion of GPs in the Wessex region reflects that of the majority of their European colleagues. Research in general medicine, however, can only be carried out effectively if the general practitioners themselves can participate in the construction of protocols, identify the biases, interpret the results according to their own clinical practice: it may therefore seem important that a teaching of methodology in clinical research can at least be offered to general practitioner (5), and that students destined for general medicine can be exposed to it during their university course.

The needs in a liberal specialized environment and in a hospital environment have not been measured, and we must content ourselves with an assessment based on daily experience: empiricism replaces evaluation. However, it seems that methodologists are more often consulted than in the past, and this right from the construction stage of a study; that the courses offered do not suffer from a lack of applications; that the interns, at the time of their thesis, are particularly aware of the flaws in the method and will often seek advice enabling them to remedy them as far as possible; that more and more clinicians feel the need, in their daily practice, to be able to read, understand and, if necessary, criticize the reports of major clinical studies whose conclusions are quickly reported by the media and made available to the general public.

Senior physicians in teaching hospitals value evidence-based medical journals the most, followed by interns, and lastly only by students (6), while graduate students acquire medical knowledge. evidence is associated with the optimal improvement of the level of medical knowledge in general (7). The non-biological medical journals with the highest impact factor are also those that publish the most work using evidence-based medicine methods, and whose results are directly useful to the patient (8). Finally, several studies have shown that teaching clinical research methodology or the results of studies using these methods modifies clinical practice habits in different cultures: in Canada (9), the United States (10), Australia (11), but also in Italy (12) or France (13). For all these reasons, the teaching of clinical research

methods to medical practitioners, but also to medical students, seems to be justified at the present time.

The program that we propose in this work is aimed primarily at medical practitioners, with a certain clinical experience and aware of the daily uncertainties relating to the establishment of a diagnosis, in the choice of a strategy of complementary examinations , in the proposal of a therapy. Its goal is not necessarily to remove uncertainty, because that is not always (not often?) possible, but rather to provide the doctor with the elements that will allow him to confirm his choice or decision with the most relevant arguments, as strong as possible.

In the absence of a precise survey of needs, the content of this program was developed on different bases: the experience of the teachers who were the first to establish teaching in research methodology of clinical research at their university has been a great contribution, and their works constitute the framework of the reference system that we used. Mention should be made, for the presentation of the basic notions, of Charles Hennekens, professor at Harvard Medical School (14), Stephen Hulley and Steven Cummings, professors at the University of California at San Francisco (15), Robert and Suzanne Fletcher, professors at the University of North Carolina at Chapel Hill, then Harvard Medical School (16), and MacMaster University Professor David Sackett (17). The reading of Kenneth Rothman (University of Massachusetts, Worcester) was particularly useful for understanding and teaching more advanced concepts (18), that of David Kleinbaum (University of North Carolina at Chapel Hill), for understanding the methods of analysis (19), and that of James Schlesselman (University of Bethesda, Maryland), for a better approach to more specialized concepts specific to certain types of study (20). The collective work of the RECIF (Réseau d'Epidémiologie Clinique International Francophone) represents the French synthesis of the concepts of clinical epidemiology, more particularly adapted to the courses of our universities, which we use in our teachings (21).

Finally, the current content has considerably benefited from our personal experience, acquired during the holding of intensive seminars in France or abroad (Romania more particularly): during these seminars in small groups, it was necessary to meet the expectations of participants from various clinical or biological specialties, and to their many questions. Some studies have also shown that interactive teaching of methodology is more effective in terms of acquiring new knowledge and modifying clinical practices than passive teaching (22).

This has gradually, year after year, brought changes in form and content, and the feedback from the participants has played an essential role in the evolution of this teaching. The program that we propose is the result of these various influences, and will call, in the future, a more precise evaluation not only in terms of satisfaction of the taught participants, but also in term of practical repercussions: the use made of the notions in the construction of effectively implemented projects, and the completion of studies accepted in peer-reviewed journals with a high impact factor, will undoubtedly be key elements of this evaluation.

It must be recognized, however, that few studies todate have focused on the purpose of this type of teaching, and in particular its consequences on improving the patient's prognosis. This type of study undoubtedly goes beyond the framework of the evaluation of teaching, but it is difficult to ignore them in the teaching of methods entirely centered on evaluation, and whose highly proclaimed aim is, precisely, improving the health of individuals and populations. Some studies carried out suggest that this goal would be less easily achieved than

the primary goal of teaching, namely the improvement of the practitioner's knowledge and the modification of his practice...(23,24,25).

SUMMARY PROGRAM

The methodological tools necessary for the study of the risk factors or the causes of a disease, for the establishment of its diagnosis, the evaluation of its prognosis, and the choice of its treatment will be successively approached. The notion of nosology, and the realities it covers, must however be explored beforehand.

I- Medical nosology:

Beyond the very notion of normal and pathological, which varies according to eras, and within the same era, according to mentalities and cultures (alcoholism can be considered as a disease, a deviance, even as a delinquency according to the circumstances), diseases once recognized as such are classified, separated, into entities that are supposed to be distinct. The very act of classification, however, does not confer on all diseases an equivalent status of uniqueness or originality, and the criteria used to isolate a pathological entity differ according to the entity considered. We can consider that the classification of diseases is essentially based on four main axes of reasoning: diseases can be differentiated by:

a- recognition of the etiological agent
c- the epidemiological particularities
d- the association of symptoms: the syndromes.

The recognition of the etiological agent, or agents, undoubtedly represents the best criterion for differentiating a disease, especially when the etiological agent is specific to the disease described: Koch's bacillus and tuberculosis, HIV virus and AIDS. Even when the etiological agent is not a sufficient cause to cause the disease, there remains a necessary cause and is then sufficient to define the disease: there is no tuberculosis without Koch's Bacillus, even if the notion of predisposing terrain is once again becoming increasingly important with progress in immunology, genetics and the study of favorable environmental conditions.

The recognition of the immediate cause of the disease also often makes it possible to define fairly precise contours. The immediate cause may be the disturbance of a physiological mechanism (insulin deficiency, excess or deficiency of thyroid hormone, vitamin B 12 deficiency, etc.), the appearance of an abnormal mass, of abnormal location (cancers ...), disturbance of the functioning of an organ (obliteration of a vessel, epileptogenic foci...).

However, the primary cause or causes of the disease will not be known, even if risk factors have been isolated, and this will be decisive for the type of research to be carried out: one can indeed imagine that the immediate cause recognized for the disorder observed (cancerization of normal cells for example) is due to a single factor, reflects the expression of several factors acting simultaneously or successively, is only the non-specific result of very diverse factors, expressed in a variable way depending on the host. The Epstein-Barr virus can thus be the cause of a benign disease or malignant lymphoma, but the same type of malignant lymphoma in other latitudes is not associated with the virus... A research project focusing on risk factors or causes potential of a disease with a recognized immediate cause will therefore be constructed taking into account the various possible possibilities, the existence of possible confounding factors, and the adequacy to the case group of a control group, if necessary, takes on all its importance here.

In an area of high viral endemic, the viral cause of a malignant disease may not be recognized because the controls may be carriers of the virus, without expressing the disease. In such a case, the virus will not be a sufficient cause, but may be a necessary cause of the disease, on which it will be possible to act. Ignoring it because of the constitution of a control group in an apparently well-constructed study will in fact reflect the acquisition of false knowledge using a methodology that appears to be rigorous. One can imagine that such active acquisitions of false knowledge are not rare, and are the consequence of the too great success of the Pasteurian model in infectious diseases, and of its engraving in our thought patterns: to a disease, a specific cause. Nothing in fact proves that the pathophysiological processes leading to an identical lesion on the histo-pathological level are similar in two different patients.

Common epidemiological particularities have been able to classify diseases of different appearance together: Horton's disease and polymyalgia rheumatica are associated in 40% of cases, which is very much higher than the expected association rate, if the association was linked only to chance. Horton's disease and polymyalgia rheumatica are thus part of the same nosological framework. Nothing makes it possible to say, however, whether the association is linked to a common etiological factor, to the action of various etiological factors on a common ground, genetic for example, to geographical or environmental particularities that we do not know how to appreciate. ... The degree of uncertainty, or ignorance, may seem even greater in this type of pathology than in diseases defined by a known immediate cause, and here again clinical research projects must take this into account and consider additional assumptions. However, there is some evidence that a link exists between the two expressions of pathology.

The maximum degree of uncertainty, however, is reached in syndromes: the association of symptoms may, or may very well not, correspond to a precise pathological entity. Some syndromes have seen their reality confirmed over time (Brown-Sequard syndrome for example, identified as such before the nature of the lesion is understood), and have joined the pathologies of the first, second or third group . Other syndromes have been completely dismantled, and no one today is diagnosing girl's chlorosis anymore... a research project on such a subject would probably not have been able to come to any solid conclusions in the state of the knowledge of the 19th century, and would have resulted in the disappearance of the syndrome more quickly as soon as the concepts of anemia, hypothyroidism, depression, psycho-somatic disorder, various deficiencies, would have been integrated into medical knowledge and available to the clinical or biological investigation.

It is quite possible that at the present time, a certain number of syndromes, in inflammatory, dermatological, psychiatric, even neoplastic pathology, fall within this uncertain framework: here again, any research project must take this into account, and the hypothesis of a significant heterogeneity of the nosological framework must be considered first.

II- Study of risk factors, or causes, of a disease:

This is the most classic part of the course, and probably the one that has borrowed the most from classical epidemiology techniques. However, this is the most complex part, because it is the most subject to potential biases, which will be studied in detail: knowing

them is essential for the proper construction of a research project. The hierarchy of the different types of studies will first be explained:

II.1- Reported cases:

They represent the most common form of medical publication, and seem to be irrelevant to clinical epidemiology: many reported cases probably describe clinical situations linked to chance, especially when the author is looking for a rare presentation or manifestation. The future of a case reported in the history of medical knowledge is thus very uncertain, and most will be forgotten (sometimes wrongly? but often rightly) after their publication. Reported cases, however, constitute the most frequent form of identification of a new pathology, and should not be neglected in a structured research approach: the analytical approach can only follow an initial descriptive stage. The association of pulmonary embolism and taking estrogen-progestogens reported in 1961 in the Lancet has been at the origin of numerous analytical studies, which have made it possible to authenticate the association, to measure its incidence, to estimate its the risk and the co-factors, and to propose in clinical practice the contraindications to the administration of estrogen-progestogens in people at risk.

II.2- The cases series:

They too remain within the framework of descriptive studies and may therefore seem out of place in a presentation of medical research methods. Here again, it is necessary to recognize their strengths and their weaknesses: the probability of the existence of a pathology increases when several cases have been recognized, and the series of cases show here a very clear advantage compared to the reported ones. We know the subsequent developments of the description by Hodgkin in 1832, of 7 patients suffering from an unknown lymph node pathology even though the Sternberg cell was not described until 70 years later. Similarly, the publication in 1978 by the Center of Disease Control in Atlanta of 5 cases of pneumocystosis in young, male subjects with no particular history and living in the Los Angeles area gave rise to the most rapid advances in the history of medicine, concerning the identification of a new disease, the recognition of its etiological agent, the conditions of its pathogenicity, and, less than 20 years later, the appearance of therapies making it possible to modify at least immediate prognosis.

Case series, however, can always reflect only the vision of their author (does Cogan's syndrome exist?), give rise to misleading developments on the multiple clinical variants of the syndrome, to groupings by analogy without physiopathological reality underlying, to false knowledge on the existence of such or such risk factor, on the effectiveness of such or such therapy. The absence of a comparison group in fact renders any attempt at a precise definition (where does the syndrome begin and where does it end?), explanation of the phenomenon, interpretation of its evolution without or under treatment, and this leads without any doubt to the extreme variability in the frequency of symptoms encountered in the various series of cases of different origins. It is very likely that the syndrome, although recognized, does not always cover the same pathological reality.

II.3- Ecological studies:

They must be cited because they constitute the entry stage in the analytical process. However, they are not part of the studies commonly carried out in clinical practice, and rather fall within the means used in public health. An ecological study consists of linking, on purely

statistical bases and with no relation to the healthy or sick individual, a supposed risk factor and the incidence or prevalence of a given pathology in the population.

It can thus be shown that the incidence of lung cancer in various countries is proportional to the number of packets of cigarettes sold, that the incidence of lymphoma seems to be proportional to the quantity of insecticides dumped in rural areas, etc.

This time, there is one or more comparison groups, which are the areas, regions or countries with a lower incidence or prevalence for the pathology considered. However, the ecological study, which only relates rates observed in various populations, is not interested in the individual: we will not know whether the subject with lung cancer is precisely the subject who had smoked. These studies, quickly carried out when the registers of incidence or prevalence are well kept, therefore serve as generators of hypotheses, and these hypotheses must then be tested in more detailed structural studies.

From a pedagogical point of view, they serve to introduce the difficult notion of the confounding element. It is easier to understand from an ecological study that the true, unmeasured risk factor for disease may cause an actually measured association to appear significant if the putative, measured risk factor is statistically related to the true risk factor: it is thus easily shown that the incidence of breast cancer in various countries is proportional to the number of telephone poles, or the number of ballpoint pens sold... it would be risky to conclude from this the influence of electro- weak magnetic fields or the composition of the ink on the cancerization process, and it is more likely that the factors measured are the markers of certain living conditions of which other factors, co-present, will promote the appearance of cancer. This notion of confounding element, relatively obvious in the context of ecological studies, will then be extended to analytical studies based on the individual.

II.4- Prevalence studies:

At the crossroads between analytics and description, they are also more often used for public health objectives than in proper clinical research. But here again, it is difficult to introduce the following study structures without explaining the prevalence studies, the use that can be made of them, and explaining the abuses of use often encountered in the literature.

The structure of a prevalence study allows it to answer the simple question of: “How many patients with disease X are there, in such a population, at such a time? ”.

Often, the prevalence study will ask a double question, and to the first defined above will be added one or more questions on the possible association between the disease (present or absent) and a risk factor (present or absent).

In fact, the prevalence study provides its own control group, made up of subjects questioned who do not present with the disease. It therefore allows, beyond its purely descriptive character, an analytical study.

The advantage, compared to an ecological study, lies in the fact that the questions will be put directly to an individual and that, if the association exists, it will be the result of a 'sum' of individual associations actually verified: it is no longer a simple juxtaposition of rates. The possibility of a confounding element always exists, because several factors can be linked in the same individual, and measuring the prevalence of one can be equivalent to measuring the prevalence of the other, and of the real risk factor in particular: a biological, clinical, physiological association, or a simple co-existence of several factors can therefore reveal, in studies based on the individual, a statistically significant association, but biologically or physio-pathologically ineffective, between a given factor and the disease studied in the same way as in ecological studies.

Moreover, a prevalence study measuring the risk factors at the same time as the disease that has already appeared cannot, in essence, establish a temporal relationship between the action of the risk factor and the appearance of the disease. A particularly dangerous risk factor may have produced a rapidly fatal disease, and the most seriously affected patients may have disappeared before the prevalence study was carried out. However, there are a number of conditions, rarely encountered in clinical practice, which allow a prevalence study to reliably assess a relative risk: the course will emphasize these conditions and the need to take them into account. when developing a study, or when reading a published work.

II.5- Case-control studies:

Properly analytical, these are the studies that are most accessible in practice to clinicians. These are also the most difficult studies to construct and the most subject to biases, and the course will describe the construction of a case-control study on the framework of potential biases: avoiding them will indeed represent the most important part of the study design.

A case-control study is based on the arbitrary juxtaposition of two groups, one of patients, the other of healthy subjects. These two groups are made up separately, and, although they must come from the same population, a difference independent of the disease studied may arise to separate them and make them not comparable. Similarly, the control group may be too close to the case group, and the expected difference between the two may thus disappear.

The relative position of the two groups in relation to each other is therefore essential for the accuracy of the results, and cannot be, once all the methodological precautions for the choice of the group of cases and the choice of the group of controls have been taken, only 'guessed', estimated, before launching the study: it is necessary to estimate the best way to make the group of cases as representative as possible of all the cases, and the group of controls as representative as possible of the subjects healthy in the general population.

This 'estimate' represents the major difficulty of this type of study, and is very well illustrated by the long history of case-control studies related to the association between post-menopausal estrogen intake and the occurrence of endometrial cancer: more than 20 studies have been carried out, each seeking to compensate for the biases of the previous one. The odds ratio found varied between 0.5 and 20, and the prospective cohort study carried out in the face of this uncertainty revealed a relative risk of 3… equivalent to the odds ratio of the first case-control study carried out.

The course will therefore emphasize all the precautions to be observed in the construction or interpretation of a case-control study: delicate on the methodological level, they are, however, the only feasible ones for pathologies whose incidence would make any cohort study illusory. The majority of diseases encountered in daily practice are sufficiently rare in the general population, or have a sufficiently long latency period, for a cohort study to be unable to include a sufficiently large number of cases. The case-control study, despite the fragility of its mechanism, remains the only possible recourse. The course will explain the notion of odds ratio, establish its relationship with relative risk, introduce the notion of confidence interval, and study the notion of bias using practical examples of selection bias, of detection bias, of measurement bias, of memory, to return to the notion of confounding element and then to introduce the concept of effect modifier by differentiating it from the confounding element.

The expression of the results in a 2X2 table will also make it possible to show that, with equal appearance, a 2X2 table in a case-control study proceeds from a meaning different from the one constructed in a cohort study.

II.6- Cohort studies:

They represent the most reliable structures for the study of risk factors, and make it possible to establish with precision the incidence of the disease in the exposed and unexposed groups, and, therefore, to calculate the relative risk. They appear to be simpler than case-control studies on a conceptual level, follow over time the normal evolution of exposure towards the appearance of the disease, and are therefore the only ones to adhere to the physio-pathological process. as it unfolds in reality.

They make it possible to introduce the essential notions of attributable risk, excess risk, proportion of cases attributable to the risk factor considered. The advantages -prospective study, initial measurement of exposure to the risk factor, diagnosis of the disease based on pre-established criteria at the time of its occurrence, independence of data collection from the patient's clinical file, not usually designed for research purposes- are numerous and will be explained.

The heaviness of these studies, the importance of the necessary resources in terms of people and time available, the required characteristics of the pathology considered in terms of incidence and frequency of exposure, however, make them difficult studies to implement, particularly in a clinical service. *Historical cohorts* can, under certain conditions, allow rapid risk assessment for diseases with long latency times, and the course will address these conditions. Likewise, we will briefly define *double cohort studies*, drawing the student's attention to their advantages - interesting when exposure is rare - and some of the biases they may share with case-control studies. We will detail in the course the various forms of expression of risk, will approach the main principles of analysis of a cohort study without going into the details of the statistical methods, sophisticated as soon as the cohort becomes a dynamic cohort.

II.7- Summary:

We will insist on the fact that epidemiological studies alone do not most often make it possible to affirm the role of an etiological factor, and that the proof of causality usually depends on the concordance of their result with data from other pathways of investigation, biological in particular. The Bradford and Hill criteria remain valid for most of them, and the plausibility of the effect of a causal agent, its action during laboratory experimentation, understanding the physio-pathological mechanism will all be additional arguments if they converge with the results of epidemiological studies.

III- Establish the diagnosis of a disease:

The question raised is that of the validity of a diagnostic test, understood in the broad sense of the term: the test can just as well be represented by an element of history taking or clinical examination, a biological test, a characterized radiological image, an anatomo-pathological reading... or a combination of several of these elements.

Several notions underlie the notion of validity:

- The accuracy of the test is the first: is the blood pressure measured externally - the cuff - a reliable reflection of the real blood pressure, measured by arteriotomy against a column of mercury?

- Intra-observer reproducibility: does the same test, applied to the same patient under the same conditions and by the same observer, give the same results?
- Inter-observer reproducibility: does the same test, applied to the same patient under the same conditions but by different observers, give the same results?

Calculation of the Kappa reproducibility coefficient, taking into account identical results linked to hazard alone, will be explained here.

- The sensitivity of the test: what percentage of real patients is the test able to diagnose as such?
- The specificity of the test: what percentage of real healthy subjects is the test able to recognize as such?

The construction of an ROC curve and its interpretation will be discussed here.

- The positive predictive value: when the test comes back positive in a patient, what is the probability that the latter will actually be affected by the disease?
- Negative predictive value: when the test comes back negative in a patient, what is the probability that the latter is actually unscathed?

The positive and negative predictive values are those that interest the clinician the most, because they are the ones that he will use in practice: a test is requested in the face of a clinical situation suggestive of such a pathology. What does the response mean? These two values, instinctively evaluated by any doctor, have particular characteristics, the most puzzling of which at first glance is that, unlike sensitivity or specificity, they depend on the prevalence of the disease in the group, or population, under consideration. The positive predictive value of micro-calcifications on a mammogram will be very different, and much higher, in a breast center where patients at risk are consulted than in a screening in the general population. This often overlooked fact leads to errors in the assessment of the results of a test, and we will particularly insist on the demonstration of its importance using specific clinical examples.

The determination of the different values stated above (reproducibility aside) can only be done when one has a gold standard. This gold standard does not exist for many pathologies, and we will briefly discuss the conditions for diagnosis in its absence: consensus, arbitrarily decided criteria (the levels of blood pressure figures defining normal pressure, moderate, severe and malignant arterial hypertension are both arbitrary and consensus).

We will also address the problem of new techniques, perhaps more sensitive, perhaps more specific, which are compared to the old reference technique: what is the gold standard then? the old technique, known and proven, or the new? How to determine it? These questions are crucial for any new radiological technique, any new serological test, which risk being poorly evaluated compared to the reference technique, particularly in the event of increased sensitivity.

In practice, this seemingly simple evaluation is often done by successive touches, difficult to quantify, depending when surgical or anatomo-pathological verification is not possible, on the increasing or decreasing conviction of the observer that such a technique must replace or not the old reference technique in the role of gold standard, and this conviction will depend on the progressively accumulated experience of the two techniques... and the experience, although unavoidable, escapes the evaluation methods implemented in clinical epidemiology.

We will then consider the interest of tests carried out in series (increase in specificity and negative predictive value) and tests carried out in parallel (increase in sensitivity and positive predictive value). The uses of these different diagnostic strategies will be detailed, particularly in the screening indications.

IV- Establishing the treatment of a disease:

Many therapies have been launched in the history of medicine, without rigorous evaluation studies. However, it was not necessary to carry out such studies to understand very quickly the interest of penicillin, or tuberculo-statics. Clinical epidemiology studies are only intended, in therapeutics, for treatments whose effectiveness cannot be observed with the 'naked eye', and they therefore serve to highlight the action of treatments… less effective than desired.

IV.1- The reference study:

The essential study at present in this field remains the randomized trial. The course will situate it in relation to other therapeutic trials (phase I, II, III, and IV trials, the randomized trial being most often a phase III trial, more rarely a phase IV trial), emphasizing the fact that phase I and II trials, which are not developed in clinical epidemiology manuals, are also part of clinical research and of course represent the essential stages before moving on to the following stages.

The comparative therapeutic trial can be non-randomized (by historical comparison, by comparison with the results obtained in other departments, etc.), and the multiple biases of these comparisons will be explained.

The trial can then be randomized without blinding (surgical treatment versus medical treatment, for example), single-blind (the patient does not know whether he is taking the standard treatment or the treatment being evaluated), double-blind (the patient and the prescribing physician do not know), or triple-blind (the patient, the physician and the statistician responsible for analyzing the data do not know).

The randomized trial is a particular form of cohort study, where the experimenter controls the exposure conditions. Randomization is supposed to eliminate any selection bias between the two groups being compared, by randomly allocating between the two groups any patient characteristics or treatment sensitivity that could influence efficacy or the occurrence of side effects.

We will insist on the fact that this certain theoretical advantage of the randomized trial is not, however, automatically obtained in practice: confounding elements may be present in a rigorously randomized trial, and it is important to identify them before the launch of the trial and collecting all relevant data. It is then important, at the time of the analysis, to ensure the comparability of the two groups with regard to these potential confounding elements.

Finally, when the groups prove to be comparable, it is important to nevertheless estimate the weight of these confounding elements in the results of the therapeutic trial: that two groups are not significantly different in their characteristics does not mean that these characteristics do not slightly influence the test result. When the risk of error in asserting a difference when it does not exist (alpha error, expressed by the 'p'), approaches the arbitrary threshold of 5%, a small influence of the distribution of the initial characteristics between the two groups on the result obtained can cause the value of p to pass above, or below, the

threshold of 5%. Many randomized trials, in cardiology in particular, are designed in such a way as to reach the limit p value, and indeed obtain it in a limit way.

We know that such a value is fragile and highly dependent on the test conditions.

The course on randomized trials will introduce the notion of study power and beta error (the risk of not being able to highlight a difference that nevertheless exists in reality). This notion applies just as well to case-control studies and to cohort studies, but is more immediately 'palpable' by students in the context of randomized trials.

Finally, we will insist on the interpretation of a randomized trial: it should not be forgotten that it was designed to highlight differences in efficacy not visible 'to the naked eye', and that it should then be looked at the numbers carefully. If it seems spectacular to announce that thrombolysis reduces myocardial infarction mortality by 20%, it is already less spectacular to say that this reduction reduces overall mortality from 11% to approximately 8% ([11 - 8]/11 = 27%), and that, based on the results of the GISSI study, 1000 patients need to be treated to globally prevent 23 deaths, but that 9 vascular accidents will be caused.

Similar examples can be given for the benefit of the treatment of moderate hypertension, and we will differentiate in the course the overall benefit, perceptible at the level of a population, from the individual benefit, which is much more difficult to measure.

IV.2- Meta-analyses:

We will briefly outline the principles of meta-analysis in this course, and the reasons that currently make it a particularly popular method. We will not go further for several reasons:

- Their realization requires statistical skills that will not be available to many clinicians, and meta-analysis remains the domain of specialized structures.
- Meta-analysis, by pooling the results of previously carried out trials, seeks on the one hand to increase the power of the trial by increasing the sample size, and on the other hand to minimize the selection biases of entry into the study including patients of various origins.

However, these ‘positive’ effects have not always been confirmed when randomized trials of a size comparable to that of the corresponding meta-analysis have been carried out. It is appropriate - but this is a personal opinion - to better analyze the potential perverse effects of meta-analysis, probably resulting from the addition of the biases of the various studies constituting them.

A meta-analysis is necessary to highlight a low-amplitude efficacy, potentially interesting at the level of a population, but whose individual benefit for the patient still remains to be estimated more precisely.

Finally, the evaluation of meta-analyses by comparison with high-powered randomized trials still remains to be done in many fields, and remains difficult, because the meta-analysis was carried out precisely to replace these trials, which are difficult to implement. … We believe that epistemological reflection must now follow the development and use of an attractive research methodology, but for which we have little perspective.

IV.3- Decision trees:

In clinical practice, there are many situations for which a satisfactory therapeutic response will not be found in a randomized trial. Should a coronary bypass be performed in a 73-year-old patient with lupus, presenting poorly controlled angina on a multistenosed anterior interventricularis, carrier of an anti-prothrombinase with a history of venous thrombosis, moderate renal insufficiency related to her lupus? formerly treated with immunosuppressants,

while it has been difficult for 4 months to go below the threshold of 15 mg of corticosteroids per day?

The purpose of the decision trees is to provide the best possible answer to the question, by combining each of the risks estimated on separate studies: risk linked to the intervention on an anterior descending device in patients over 70 years of age, operative risk in patients with anti-prothrombinase, in patients on corticosteroids, in patients with nephropathy, etc.

The principle of decision trees will be explained in class. In practice, it turns out that decision trees are not easily achievable, and that the time required for their creation is often incompatible with the workload of the clinician. The response they provide is also difficult to assess: the combination of risks implies a multiplicative effect of the weight of the biases of each study, an effect that can only with difficulty be compensated for by sensitivity analysis as it is currently conceived.

The sensitivity analysis does not address the problem of bias, but only reports on the decision tree the statistical uncertainty observed on the results of each of the studies used. Arriving at a probability of a beneficial effect of the intervention of 60%, and of a deleterious effect of 40%, remains in these conditions difficult to interpret for the patient in question and can sometimes be used to falsely reassure the doctor on the accuracy of his decision. A figure seems clean and definitive: it only reduces a reality that is much more complex, and therefore more difficult to grasp. The methodologist can then ask the heretical question in clinical epidemiology: 'What about the 'clinical impression', whose foundations are difficult to discern, compared to the figures with falsely precise contours?'.

V- Evaluate the prognosis of a disease:

This is a special question because the doctor, no more than anyone else, knows the future. Everyone in their clinical practice has been surprised by an unusually rapid evolution, an unexpected stabilization, an unexpected improvement. The evaluation of the prognosis of a disease is therefore based, as always in clinical research, on the observation of patients already presenting with the disease in order to draw lessons concerning future patients.

Here again, we are confronted with the problem of applying data collected on a population to an individual concerned with knowing his personal prognosis. There is an additional difficulty in prognosis studies: the outcome of two groups of subjects is compared, patients and healthy subjects constituting the norm, patients presenting certain characteristics and patients presenting other characteristics, and in each group we measure the number of events occurring during a given period depends on the duration of each patient's follow-up.

A prognosis is measured and compared over a period of follow-up to establish a difference on the scale of the average human lifespan. Ultimately, there is no difference in prognosis between sick subjects and healthy subjects… We will therefore compare the number of events that have already occurred in each group (certain data), knowing that a certain number of events are not occurred, either because they will not occur, either because they have not yet occurred (so-called censored data).

The so-called survival curves, which are used in prognostic studies, therefore do not simply report the occurrence of events over time: they in fact report the probability of survival as a function of the time elapsed since the diagnosis and according to the deaths that have occurred previously: at each death (at each step of the curve), the size of the population changes, and the probability of survival is recalculated according to the new sample size. In practice, this means that as the sample size decreases, each death will represent a larger

proportion, and the 'steps' on the curve will appear larger. This also means that the precision of the probability decreases with the size of the sample, and that we are often far at the end of the curve from the precision reached at the beginning: when there are only two patients left, a death means a probability of survival over this period of 50%, whose confidence interval is close to the extremes of 0 and 100%…

Understanding the construction of a survival curve according to the *Kaplan-Meier method* is essential to understanding the modes of comparison of two survival curves, and its explanation using a practical example and a construction of the curve will occupy half the time allocated to prognostic studies (i.e. approximately 45 minutes).

We will then discuss the comparison of two survival curves, first of all monofactorial by the log-rank test, by establishing the link with the chi-square test previously explained in practical work. It is easy to explain the test using two survival curves and to show that a chi-square test is carried out at each 'stair step': a comparison of proportions is carried out at each change in proportion . The sum of these tests is equivalent to a chi-2 for study in strata, that is to say the variant of chi-2 called Mantel-Haenzel.

The prognosis, however, does not usually depend on a single factor, but several co-factors may intervene: age, stage of the disease, performance status, etc. To take these factors into consideration and not to wrongly attribute an observed difference between two curves with a single factor such as treatment, a multi-factorial analysis of the survival curves is necessary.

We will therefore approach, on a qualitative level only by setting out its general principles and indications, but without going further into statistical theory, the Cox model and its parallelism with logistic regression. This course alone will not allow you to perform a survival analysis, but should allow you to understand the articles on the subject and to demystify the notions of curve and survival analysis, which are frequently confronted by clinicians.

PEDAGOGICAL MEANS AND TEACHERS

I- Teachers:

The teachers are members of the RECIF (Réseau d'Epidémiologie Clinique International Francophone), a structure created in 1988 by the University Claude Bernard, the Hospices Civils de Lyon and the Mérieux Foundation.

The RECIF unit in Amiens was created in 2003. The teachers hold a thesis in science, epidemiology or statistics. All teachers coordinate at least one clinical research project. They also serve as a tutor for a construction research project (one to two projects per year and per tutor on average), and as an advisor for several projects each year.

II- Teaching methods:

We place ourselves from the outset in the best teaching conditions (the easiest too…), because it is an optional course, chosen by residents, assistants or hospital practitioners wishing to build a research project, and delivered in groups of no more than twenty participants (face-to-face) (or more if the teaching cycle is distancially delivered). The intensive seminar also frees participants and teachers from any other obligation for a week, thus increasing everyone's availability.

Each participant is asked to come with his/her research topic, and the seminar is focused on the construction of the project: this facilitates interactions because the questions often arise from each person's questions relating to their own project. The multidisciplinarity of the participants allows the presentation of various projects, posing various problems on the methodological level.

The answers are not necessarily unequivocal and this maintains the debate among the participants. "Free" time is reserved for individual work or in small groups each day, which allows a better assimilation of the concepts brought during the day.

The mornings are devoted to lessons, and the main medium used is the computer with projection. The paper-board or the blackboard allows, if necessary, to explain in a qualitative way the mathematical forms rules by gradually bringing each of their terms, in such a way as to make people perceive, by playing more on intuitive understanding than on a mathematical prerequisite which no longer always exists, their meaning and the role they play in the mathematical expression.

The explanation is therefore not based on a real demonstration when it is not accessible to non-mathematicians participating in the course. The courses are illustrated with examples taken from the literature or research carried out by RECIF members. The experience of teaching in diverse countries has taught us to use, for these countries, examples more suited to the pathologies encountered and to the medical means actually available to these doctors. This

pedagogical adjustment greatly benefited from the first seminar held in Algeria and Romania, and from the contacts we were able to have during these weeks with the course participants.

The afternoons are reserved for practical work: half of them relate to the knowledge acquired in the morning, and are focused on published work. The articles are chosen according to several criteria:

- Some may have recognizable biases at this stage of knowledge acquisition, and the work will consist of detecting them and seeking solutions that could have been implemented.
- Some are representative of very well-conducted studies, and thus show the 'tricks' that their authors may have used to compensate for potential biases.
- Some have obvious biases, the correction of which, however, remains difficult after reflection: they illustrate the practical and ethical difficulties, linked to the current limitations of our knowledge, in answering certain questions that are nevertheless well-founded and commonly encountered in clinical practice. A study sometimes, although imperfect, brings a 'better' than previously published studies, and our knowledge often progresses in small steps, sometimes doubtful, but eventually progresses...

The other half of the tutorials, in the second part of the afternoon, is devoted to the presentation of the research topics of each of the participants. The group then discusses the adequacy of the subject to clinical research techniques (some subjects will sometimes be better served by other investigation techniques), the best study structure, the feasibility of the project in terms of staff , measurements, time required, means, then the first stages of construction. During these practical assignments, the problems of the study schedule, the drafting of a protocol, the evaluation of the necessary budget, and the request for a subsidy are addressed.

The “free” times, at the end of the afternoon and the beginning of the evening, allow, according to the requests of the participants, a more individual “refining” of the projects.

The content of the teaching is summarized in the collective work of which a new edition, freely available to all through the RECIF website both in French et en English, is in progress:

‘Clinical Research: Think, Realize, Publish’, under the direction of RECIF (French-speaking International Clinical Epidemiology Network).

The former edition (2010) in both French and English versions, is already available on our website

https://recif-amiens.org/enseignements/le-livre-recif/

EVALUATION

The terms will be slightly different, depending on whether the teaching is carried out in Lyon or abroad.

I- Teaching in Amiens:

It constitutes a university degree of a total of 104 hours (dissertation not included), divided into two full weeks (January and May), and three days divided between the two seminars. The assessment is based on:

1- Full course assistance.
2- The main purpose of the seminar is to build a clinical research project, directly applicable in his specialty or in his practice by the course participant. This construction will be done throughout the year, with the help of the tutor chosen according to his particular clinical and methodological skills. The student will make an oral presentation of his project in front of the teachers of the diploma, and will submit his finished project at the end of the year, ready to be submitted for a grant application.

II- Education abroad:

It is more complete and its purpose is more ambitious: it serves as the basis for the construction of a RECIF Clinical Research Unit in the host university.

The teaching consists of the same 3 seminars totalizing 104 hours, as in Amiens (4 weeks spaced 3 or 6 months apart).

It is completed by a fourth week (40 hours), entirely devoted to the analysis of databases already constituted, real, brought either by the teachers or by the course participants, and these personal databases will be privileged. The seminars are carried out within the framework of collaborative programs between the Jules Verne University of Picardy and foreign faculties in a spirit of inter-university collaboration, under the aegis of RECIF. The foreign faculty delivers its diploma countersigned by the RECIF and the Jules Verne University of Picardy. Generally, graduation is based on full course attendance, and participants are encouraged to write their research project. We remain at their disposal to help them solve the problems raised during the drafting by e-mail.
In Romania, where the educational experience has been pushed the furthest so far, the RECIF has accredited 4 centers which have trained more than 400 people in the last 10 years.

Of course, this fourth week will also be proposed to the Amiens participants, although the timetable exceeds the upper limit of a University Diploma in France (< 120 hours).

FIGURES AND LETTERS... OR GENERAL REFLECTIONS ON THE CONTENT OF TEACHING

A pathological process often proceeds from a complex physio-pathology: if tuberculosis is caused by Koch's Bacillus, being in contact with the bacillus, however, is not enough to contract the disease. It is undoubtedly necessary that the bacillus undertakes through the airways a journey strewn with pitfalls, escapes ciliated elimination, manages to settle in the pulmonary parenchyma where it will be the target of a complex immune reaction involving multiple specialized cells and more mediators, interacting with each other. We do not yet know all the conditions necessary for delayed immunity to be effective and to counter bacillary multiplication; the exact role of immunity in the destruction of the pulmonary parenchyma following bacillary multiplication also remains to be detailed; the reasons for the stabilization or worsening of a lesion are also probably multiple; and finally we know that if tuberculosis is an infectious disease, the role of external factors, promiscuity, poverty, undernutrition, unfavorable social conditions, is decisive in the declaration of the disease and its transmission. The onset of the disease is in fact a story with multiple actors all interacting according to a pattern specific to each patient, which it would ultimately be easier - and more accurate - to tell in words, in the manner of a novel, if we only knew all the chapters.

Reading an epidemiological study always leaves a strange aftertaste. Telling a story does not proceed from a scientific approach, and it is necessary, to circumvent the multiple uncertainties or approximations of the imagination or the immediate vision of a phenomenon, to establish a method of observation and analysis. as rigorous as possible. To manage to measure, to quantify a phenomenon can seem the quintessence of observation, because can we find more precise than a figure or a number?

Measurement, quantification, equating and construction of mathematical models are techniques that have been proven fruitful for several centuries in the field of exact sciences. They have considerably changed our view of the world and have proven to be remarkably effective in the fields of physics, astro-physics, mechanics. They have made it possible to tell a much more complete story of the interactions between inert bodies, have broadened our perception of the universe, have made it possible to reformulate differently the big questions of why? How? 'Or' What ? when ?. They made it possible to *predict* the existence of structures long before we were able to *perceive* them.

This way of thinking has entered the field of life sciences only very recently. The mathematical models and techniques used are simpler than in physics. However, the reality described is more complex, more polymorphic, and it quickly proved difficult to describe phenomena of great variability by means of fixed laws. Statistics then aimed to quantify not only the observed phenomenon, but also the uncertainty that was necessarily associated with it. The first paradox of the method was therefore to try to surround the unknown with a visible, precise barrier, expressed in figures with defined contours. The small p, the confidence intervals, which seek to define the zone of uncertainty as closely as possible, have brought a rigor that the observation of simple figures did not allow and they thus make it possible to avoid transforming an observation into an affirmation whose reality is questionable.

Conversely, by aiming to delimit what in essence escapes direct quantification, they are inherently misleading: quantifying uncertainty does not remove uncertainty, and the sharpness of the figure provides a somewhat fallacious mask to the unknown. The number reassures, and reduces what we are unable to perceive to an illusion of perception by providing it with a known appearance: those of the limits that we have drawn around a black hole.

The null hypothesis technique, usually used in statistics, consists of asserting that two observations are similar and testing their similarity. The basic axiom, which underlies all calculations and represents the sine qua non of their validity, is similarity between observations. If the calculation succeeds in retaining the hypothesis, we conclude that there is no difference between the two observations. If the calculation results in not accepting the hypothesis, we conclude by default that there is a probable lack of similarity, and therefore that there is a probable difference between the two observations. There is a conceptual void in the logic of this default reasoning, which is to transform the absence of similarity into the assertion of a visible difference, because we have failed to demonstrate the supposed similarity in the first place.

What would happen if we knew how to start from the hypothesis of an asserted difference, to demonstrate that it does not exist? What about the reliability of a calculation based on an axiom essential to its validity, when this calculation leads to the conclusion that the axiom was not verified? A statistical test would ultimately be reliable only when it leads to the acceptance of the null hypothesis, only when its results are in favor of similarity between observations. The rejection of the null hypothesis, on the other hand, proceeds from an intellectual aerobatics whose logic we do not fully understand.

However imperfect they may be, statistics are a tool that epidemiology cannot do without. Epidemiology itself is not free from paradoxes. The first of these, for a clinician accustomed to caring for an individual, is that clinical epidemiology was born from the frequently encountered impossibility of perceiving a pathological phenomenon from individual observations. This impossibility leads to diagnostic or therapeutic uncertainties, which are numerous in daily practice. The study of a series of patients then becomes necessary, in order to be able to identify trends that have been verified, tested, validated on a large number, and the goal of acquiring this more reliable knowledge is of course to better know to diagnose the disease, to better understand its pathophysiology, to better know how to treat the individual.

The large number guarantees the reliability of the knowledge acquired. We do not know, on the other hand, how to apply in an exact way this valid knowledge at the level of a defined population, to the individual who consults us. Who knows if this patient, in his own particularities, belongs to the majority of patients for whom the treatment will be beneficial, to the minority for whom it may be detrimental, to the subgroup for which it will bring neither improvement nor aggravation? ? We would not need epidemiological studies if we were able to understand, individual by individual, the disease which affects it, its characteristics, its physiopathology, and in the best of cases, to adjust an appropriate treatment. The lack of individual understanding of the pathological phenomenon leads to epidemiological study, which, by bringing out the major trends in knowledge at the level of a population, does not provide the answers that were sought for the individual, but only the right questions to ask about him: is the risk factor isolated by the epidemiological study the one responsible for the disease in this patient? Is the diagnostic strategy recognized as optimal at the level of a population, the one that should be priority for this patient? Is the effective treatment for the majority the one that should be prescribed to this patient, who may be part of the minority?

To the statistical uncertainty of the figure, poorly framed by attempts to quantify the unknown, is therefore added epidemiological uncertainty, an unavoidable reverse of the very justification of such studies and of the inability to perceive the reality at the level of the individual. Here again there is a space that we do not know how to explore, and the numbers with which we have tried to describe knowledge do not allow us to bridge the distance between the population and the individual. The epidemiological study could be compared to the observation of a city by satellite, which would give us the main traffic trends in the agglomeration, but would not make it possible to know how and to where such an individual is heading.

It could be objected that the search for the exact mechanisms stems not from epidemiological research, but from biological research. Biological research, however, could be compared to the investigation which consists of isolating an individual in the flow of traffic, extracting him from it and questioning him, in a place sheltered from the hustle and bustle of traffic, about the reasons and the how of its displacement, then to quantify the answers or to translate them in the most precise way possible.

In both cases, the precise apprehension of the individual in the flow, of the reality of pathological phenomena in vivo escapes our means of analysis, and we do not know how to quantify the distance of the population from the individual either than that of the in vitro phenomenon to the in vivo reality.

The figures, the numbers only appear precise because they have considerably reduced the reality that they are supposed to describe. That a difference between cases and controls is significant, and that the risk of error can be estimated at 5 chances in 100,000, does not indicate how a causative agent can possibly be responsible for a disease, how a treatment can be effective or harmful, or whether the patient we have in front of us will be among those who will benefit from the treatment, or among those who will show toxic effects.

We translate reality into numbers, because numbers are easier to handle and they give the impression of a solidity that words cannot achieve. The price of their precision is, very ironically, their inability to tell the exact story of the bacillus or of the bacillary strain capable of passing the tracheal and bronchial barrier, of taking advantage of the immune alterations induced by possible malnutrition, of inducing a reaction life-saving or on the contrary toxic, to detail the factors intervening in the determinism of this reaction and the way in which they themselves were influenced by the external environment, to explain the adhesion of the bacillus to the cell wall and its penetration, to outline drug penetration, its interaction with cellular metabolism, and bacillus defense mechanisms leading to resistance...

Telling the story of a pathology like a novel would probably be the only completely scientific way to proceed. As in a novel, words alone could accurately describe the pathway from cause to effect, and the individual action of the multiple stakeholders that ultimately allow the disease to develop or the host to resist. One can no more tell the story of a disease with figures than assert that two swashbuckling novels are similar because, all things considered, there is no significant difference in the two works between the number of tournaments, knights at war or beautiful ladies at the top of the dungeons...

Is scientific reality distorted, distorted by figures, yet used to serve it best? Definitely. Should it, ideally, be expressed primarily in words, perhaps with numbers? No doubt, if we refer to the life sciences. But in practice, we imagine the story in such a way that it appears coherent with the quantified observations of epidemiology, fragmented from biology, and the problem then becomes, to test the truth expressed by the words... At the three currently

unexplored spaces, the statistical unknown, the epidemiological unknown and the distance between in vitro and in vivo in biology, unknowns that we believe we perceive because we have tried to circumscribe them, sometimes by figures!, would be added the unexplorable space that logic has tried to flee as it seemed inaccessible, that of narration, the only one capable of optimal precision, the only one capable of telling the story as it actually unfolds, irreducible to restrictive simplification figures, essential when we seek to understand or explain a phenomenon, but ultimately refractory to any verification because they go out as soon as we come into contact with the figures, the only verification tools that we know how to handle with quantified uncertainty.

These empty spaces undoubtedly translate a certain handicap, a certain infirmity, of our current mode of scientific thought. We do not really know how, by what means, to approach them in order to reduce them. We simply estimate that, when the data provided by each knowledge space converge, it is likely that the uncertainty linked to the unexplorable spaces is weakened. This estimate, purely intuitive, is neither quantitative nor “scientific”. Proof of this are the multiple truths, or perceived truths, that time has disjudged.

To affirm that the techniques of evidence-based medicine make it possible to provide the solution to all our clinical questions, or that randomized trials represent a perfect solution to the problems of therapy, is more a matter of theological affirmation or of the doctor's need for intellectual security than of observable reality... paradox for a specialty aiming to quantify, precisely, the observable.

To denigrate them because they are ignorant of the reality of the physio-pathological processes underlying the appearance of a disease, its symptoms or the action of therapeutics would be to forget that our vision of physio-pathology is only fragmentary, and that we often do not know how to tell the exact story that would allow us to predict the deleterious action of a causal agent, the possibly beneficial action of a treatment...

We are reduced to it for the moment to marry our investigation techniques and to prefer, among the results that they allow us to obtain, those which seem to us the most coherent with the maximum of knowledge that we have, and the maximum of techniques of observations employed. This choice can sometimes be arbitrary, and can make us admit, or refuse, results wrongly. The history of science is full of these controversies, which only time and new observations can sometimes resolve when they remain topical.

APPENDIX 1: OBJECTIVES

The main types of clinical study:

1- To know how to define the main types of clinical studies, position them in relation to each other.

2- To know the structure of an ecological study

3- To know the 'indications' for carrying out an ecological study

4- To know the strengths and weaknesses of an ecological study

5- To know how to precisely define the notion of confounding element

6- To know the structure of a prevalence study. To know how to define and calculate prevalence.

7- To know the usefulness, the 'indications' of a prevalence study

8- To know the strengths and weaknesses of a prevalence study

9- To know the conditions under which a prevalence ratio can approach the relative risk

10- To know how to criticize the conclusions of a prevalence study according to the conditions of selection of the target population, the measurement of the data collected, their statistical exploitation

11- To know the notion of selective survival and its consequences in the different types of study

12- To know the structure of a case-control study. Distinguish between prospective study and retrospective study

13- To know the sampling techniques for cases and controls

14- To know the conditions for selecting controls depending on the cases

15- To know the advantages and disadvantages of hospitalized controls, controls from relatives of patients, controls from the general population

16- To know how to explain the advantages or disadvantages of multiple controls for a case

17- To know how to explain the advantages or disadvantages of multiple control groups for a group of cases

18- To understand the advantages and disadvantages of matching in a case-control study, and to know how to state the differences between matching in a case-control study and in a cohort study.

19- To know how to build a 2X2 table in a case-control study, and to know how to explain the difference from a 2X2 table in a cohort study

20- To understand and know how to calculate an odds ratio

21- To understand the relationship between an odds ratio and a relative risk, and to know the conditions for using the odds ratio according to the prevalence of the pathology studied

22- To know how to position a case-control study in relation to a cohort study

23- To know the strengths and weaknesses of case-control studies, especially the biases inherent in this type of study

24- To know how to differentiate the notion of confounding element and effect modifier. To know how to differentiate them from a stratified analysis

25- To know the structure of a cohort study

26- To know how to define the incidence-density and the cumulative incidence

27- To know the conditions for carrying out a retrospective cohort study

28- To know the possible biases of a cohort study, and in particular the bias of loss to follow-up

29- To know the conditions and the advantages for carrying out a case-control study nested in a cohort study

30- To know the conditions for carrying out, the advantages and disadvantages of a double cohort study

31- To know how to define the notion of relative risk, attributable risk, excess risk, attributable proportion

32- To know the advantages and disadvantages of a cohort study

Evaluation of a diagnostic test:

1- To know how to define the notion of gold-standard, or gold standard

2- To know how to define the validity of a test: true positive, false positive, true negative, false negative

3- To know how to define and calculate the sensitivity and specificity of a test

4- To understand the factors of variability of the sensitivity and specificity rates according to the population studied

5- To know how to define and calculate the positive predictive value and the negative predictive value of a test

6- To understand the role of prevalence in positive and negative predictive value

7- To know how to build and interpret a ROC curve

8- To know the general principles for using very sensitive tests, very specific tests

9- To know how to define the notion of intra- and inter-observer reproducibility. To know how to calculate a Kappa coefficient under the simple conditions of a dichotomous response test

10- To know the principles of using series and parallel multiple tests

Therapeutic trials:

1- To know how to place randomized clinical trials within therapeutic research. To know the different phases of clinical trials (I, II, III, IV), and the specificities of the phases in oncology

2- To know how to differentiate clinical trials, field trials, and community interventions

3- To know the interest of a comparison group. To know the disadvantages of historical comparison groups, before/after comparison

4- To know how to define an open, single, double, and triple blind randomized clinical trial

5- To know the structure of a randomized trial, and its analogies with a cohort study

6- To know the randomization techniques

7- To know the advantages and disadvantages of the treatment received analysis, and of the intention-to-treat analysis, in terms of internal validity and ability to generalize the results

8- To know sampling techniques, probabilistic, non-probability, stratified

9- To know how to define inclusion criteria, exclusion criteria

10- To understand the notion of study power, and alpha error. To know how to calculate them. To know how to extend these notions to other types of clinical studies

11- To know the potential biases of randomized trials, the strategies implemented to avoid them

12- To know the test structure in factorial plan

13- To know the structure of a trial with permutation

14- To know the European legal procedures for validating a randomized trial project, the role of ethics committees, the European legislation

Prognosis study:

1- To know how to differentiate risk factor and prognostic factor, and to know the differential characteristics of these two types of factors

2- To kow how to differentiate natural history and clinical history of the disease, using examples

3- To know the importance of sampling bias inherent in studies published by major centers

4- To understand, using specific examples (multiple sclerosis, etc.), the importance of sampling bias inherent in unpublished cases

5- To know how to define the clinical or biological elements of prognosis evaluation

6- To know the importance of the zero point in the assessment of the prognosis, and the resulting biases

7- To know how to construct and interpret a survival curve according to the Kaplan-Meier method

8- To know the principle of the log-rank test

9- To know the principle of logistic regression

Limits of interpretation of an epidemiological study. Summary:

1- To know how to differentiate the notion of error linked to chance, bias, and external validity of a study

2- To understand the notion of precision of a study: beta error, alpha error, the notion of study power

3- To understand the notion of sampling chance, differentiate it from the notion of selection bias

4- To know the means to remedy the errors related to chance through the sample size

5- To know how to differentiate the main categories of bias: selection and/or detection bias, measurement bias, confounding elements

6- To know the possible origins of selection bias (inclusion/exclusion, non-response, detection, selective survival, etc.)

7- To know the possible origins of measurement biases (diagnostic tests, recall bias, data manipulation, etc.)

8- To differentiate the effects of a bi-directional and uni-directional measurement bias on the results of a study

9- To know how to correct a confusion bias through stratified analysis. To know the interest of logistic regression in this correction

10- To know the statistical possibility of significant tests by chance. To know the inherent risk of multiple comparisons

11- To know the existence of invisible biases: biases linked to unpublished studies, negative studies

12- To know how to integrate the results of an epidemiological study into the broader field of bio-medical knowledge. The Bradford and Hill criteria

The objectives of this last paragraph deliberately repeat objectives already mentioned elsewhere. This course is a synthesis of the most commonly encountered biases in clinical research methods, biases already reported, often, in previous courses. It is intended to make course participants aware that the construction of a study is more about the analysis of potential biases and the best way to remedy them, than on the simple knowledge of the study structure and the analysis methods.

APPENDIX 2: TEACHERS

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This listing will be completed after the 27th June meeting f the Pedagogic Committee

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