How should we deal with a health crisis stemming from the collective realisation, in a matter of days, that a drug marketed as Mediator® (International Common Denomination: benfluorex), discovered more than 40 years ago, sometimes has serious, even fatal, adverse effects, which were not noticed earlier? We all worry about the possible adverse effects of drugs, but the beneficial results of their use are sufficiently evident to overcome this fear. In a context in which previous experience and the nature of the situation generally lead to us seeing more benefit than risk from medication, why were we unable to prevent these iatrogenic problems? How was a “health industry business” able to discover and study this drug and to distribute millions of tablets? How did we end up in a situation in which doctors were able to prescribe this drug to thousands of people after its market approval by public authorities and agreements for reimbursement by health insurers? How was it possible that people with cardiovascular risk factors, but not clinical cardiovascular disease, were able to buy this drug in pharmacies, in some cases after having requested it from their doctor, without anyone knowing that cardiac and pulmonary diseases are not generally prevented by this medicine, but are instead actually caused by it? How did a whole country manage to get so worked up about Mediator®, and how did an iatrogenic accident become a Public Health crisis?

1. Physician perceptions

Diabetes specialists, to an even greater extent than family doctors, are directly concerned by the Mediator® crisis, because they frequently prescribe drugs to facilitate weight loss, decrease glycaemia and HbA1c concentration and normalise lipid levels. They are currently nurturing a vague feeling of personal or collective guilt. They are racking their brains to try to remember whether they have prescribed Mediator® (benfluorex), Isomeride or Ponderal once, twice or many times. When they did prescribe these drugs, what was the indication, what had the patient asked of them and what had they heard about Mediator®? For those who were involved in medical education during this period, did they talk about this drug? If so, in what terms? In an emotional context, memory becomes selective: we tend to remember what we want to remember and forget what we can. With the passing weeks, the noise is growing louder and we are being swayed by certainties emanating from one person or another. This is resulting in the complete reconstruction of events and a tendency for individuals, little by little, to identify themselves with either the camp of the victims, or with that of the guilty. We need to understand, hence the decision of the leaders of the Société francophone du diabète (SFD) to request that I assess these events, and, more difficult from my point of view, write it up: spoken words are ephemeral but the written text remains.

2. Analysis of public health crises

Far from being flattered by this request, I must express the absolute need for humility required to carry out the essential analysis of any health crisis. Approaching the analysis of a crisis with the idea of demonstrating “THE” mechanism is a dangerous notion, because it is much too simplistic. Such an approach could aggravate the crisis itself, adding to suffering and could cause the protagonists to close up because they feel threatened. Above all, it could take us even further away from the only valid objective: to analyse and to reflect, to find means of preventing such a crisis from recurring. A plane crash is terrible, both in terms of its brutality and in terms of the numbers of people concerned. If we still travel by air flights, we consider the air crash risk acceptable, but we consider it intolerable when the accident finally happens. Even if society now demands enquiries and...
seeks those responsible under emotional influences, the most important aspect of the activity associated with plane crashes is that they contribute to increasing the safety of air travel even further.

It is the memory of past crises, of the painful experiences that we may have gone through ourselves, that enable us to propose analyses, to be useful. This is not to have certainties, as if the accident does not concern us directly and could not happen to us; nor as if a group, or skill in dialectics, authorises some of us to express in the media an opinion about everything, including things they have never experienced, which induces an amplification of the public debate. Pains-taking analysis of past crises provides us with a body of knowledge that enriches the discussion, and which can be refined if we take the effort to analyse every failure and every success [1,2]. Arterial hypertension, like diabetes, is a chronic disease in which the analysis of the benefit/risk ratio for drugs must be considered very seriously. The treatment of affected individuals, who are at risk of vascular disease, macro- or microangiopathy, entails specific difficulties. Treatments are long-term, often “for life”. How can we use this term when a drug has been known for less than 10 years and we are advising the patient to take it for almost 50 years? The probabilistic vision guiding prescription is that the complications we wish to avoid are likely to occur in a few months (the situation of arterial hypertension and diabetes in the 1960s and 1970s). So what happens if the probability of the complication occurring extends over decades (the situation of less immediately severe forms of diabetes or arterial hypertension of the 2000s)? To understand what has happened with Mediator® (benfluorex), we require the critical analyses of all the other examples, not only the contaminated blood “affair” or the growth hormone “drama”. They are numerous and include the links between reserpine and possible breast cancer, phenformin and acidosis, diethylstilbestrol in high-risk pregnancy and the two generations of girls and boys who subsequently presented genital abnormalities, practolol and induced immunological diseases, tienilic acid and renal and hepatic complications, mibebradil and heart rate problems, cerivastatin and myopathies, rofecoxib and coronary. The work of a healthcare professional is littered with these problems, which may one day transport any one of us into torment, whether as a patient or as a doctor. In a simplistic view of the world, the analysis of these cases and of the resulting suffering can be reduced to a simple scheme in which “bad” irresponsible people hurt “weak” poorly defended and ill-informed people. In this view of the world, everything repeats itself, continually, in a narrow framework of assumptions and dogmas that form the stock-in-trade of those who hold these assumptions rather than the solutions awaited by those subjected to them or wishing to escape them. Progress is made in an entirely different way: through the meticulous analysis of the profound differences between these accidents, increasing the chances of us being able to avoid the same events [3], provided that their causes have been dissected and remembered. Then, when the next crisis arises, in another form, unpredictable and puzzling, we will be better prepared and able to react.

For all these reasons, humility in this work, which is entirely analogous to that of those piecing together the wreckage of the TWA, Swissair and Air France planes after crashes, must be a dominant feature of my analyses of the Mediator® crisis. This humility must take into account the major difference between arriving after the accident and recognising a danger at a given moment and having to cope with the risk “live”, without being aware of it or understanding it. What we have already heard leads us all to believe that we, in the same circumstances, would have behaved in a particular way, and believing this of ourselves is dangerously facilitated by the reconstruction of a past that has been transformed even at the very instant of its being reported. I was almost certainly asked to carry out this analysis because I have been included among those who now know that we cannot understand and treat arterial hypertension without understanding diabetes, and vice versa. However, as far as Mediator® is concerned, my only access to information has been through what can be found in PubMed and in the general press. To help find the responses that we must all find for ourselves, because any one of us may be caught up in a health crisis one day, I will use both what I have learnt from patients when I was a clinician, and what I have learnt as a Chief Medical Officer. I have in my memory, with the detail of the irrational and of the rational associated with drugs, new-variant Creutzfeldt-Jakob disease, hepatitis B vaccination and multiple sclerosis, dioxin in farmed chickens and incinerator emissions, lead in the lettuces grown in the gardens of miners in the North of France and many other threats to health. These crises form an intricate part of life in the 21st century. However, we now detect them much more rapidly, with the transmission of information more rapidly than we can think. This only serves to amplify these crises and to aggravate our perception of them.

3. Public health crises and public health organisation

A public health crisis is defined by the surge in stereotypical reactions in society in the face of the consequences for human health of exposure to an environmental, social, economic, political or, as in this case, medical risk [1,2]. Mediator® is currently at the centre of a public health crisis: we need to find the actors and the scenario, which will come together before our eyes, as in any crisis. A simultaneous search for features specific to this crisis is also required, because such features may enable us to prevent other crises when we add them to the body of knowledge already acquired. We need to define health safety: it has been elevated to the same level as internal or external safety and describes all the technical, organisational and economic conditions ensuring the safety and confidence to which people aspire concerning risks to their health. Health safety applies to the risks linked to care systems. This concept therefore relates to blood, transplants, anaesthesia, hospital-acquired infections, legionnaire’s disease, antibiotic resistance, medical devices, waste and, of course, drugs. In health safety, the aim is also to minimise risks due to food: listeriosis, salmonellosis, prion diseases and the content of food in terms of salt, sugar and fat. It lastly deals with risks linked to the environment: global warming, water, air, soils, noise, electromagnetic radiation, radioactivity, habitat, waste, vectors of infectious disease and work.
3.1. General principles

General principles are applied to the definition of dangers to humans and to the risks of human exposure to these dangers. The emergence of multiple crises in the 1985–1995 period has been analysed and attributed to confusion between the three major functions of health safety.

The first of these functions is the neutral, scientific function of risk evaluation, aiming to identify risks leading to dangers and to estimate risk exposure. In the case of a drug like Mediator®, those exposed were in danger of destroying their cardiac valves or of developing pulmonary hypertension. We need to measure the presence and force of the association with the prescription of Mediator® (benfluorex), and of Mediator® alone, determining, as always, the risk function of risk evaluation, aiming to identify risks leading to dangers and to estimate risk exposure. In the case of a drug like Mediator®, those exposed were in danger of destroying their cardiac valves or of developing pulmonary hypertension. We need to measure the presence and force of the association with the prescription of Mediator® (benfluorex), and of Mediator® alone, determining, as always, the risk.

The second function of health safety includes a risk management function, in which the results of the evaluation and the interests at stake are weighed up. These interests are those of the patient, through the search for and quantification of a possible benefits to health, together with social, professional, economic, political, local, regional and international interests. This process results in interventions by the health “police” and policy decisions concerning regulatory measures, accompanied by appropriate controls.

The third key set of health safety functions concern communication. These functions respond to strong demand from citizens for greater transparency (in France, the general reference for this is the radioactive cloud from Chernobyl, which was described as having stopped at the eastern borders of France, giving the impression of a conspiracy of silence).

None of these three functions is simple, but this last function is both the most explosive and the most complex. All the individuals and groups caught up in a health crisis have their own vision of the problems, a mixture of subjectivity and objectivity. These individuals and groups also have their own languages, which may not be the same as that of the other individuals or groups concerned or of the theoretical entity known as “the average Frenchman.”

Communication activities are therefore increasingly delegated to professionals in the domain of communication, the very involvement of whom raises suspicion concerning the possible truth and reality of the proposed interpretations. Indeed, the communications expert reworks the words and figures: rather than inform they fashion a vision of the problem, taking into account the impact of words, photographs and figures!

There are thus three main functions of health safety that were initially designed to act in synergy but which may, at any time, diverge. Scientists understand the relative nature of knowledge and its tendency to change with time. They use figures to look for a confidence interval and, beneath the figures, they search for a methodology. They doubt. Decision-makers apply what they understand or feel about a truth that they want to be absolute, because their decisions are absolute. These actors express themselves with different vocabularies and see things differently. The theorisation of health safety has not been and will not be sufficient to prevent new problems. The excess mortality observed after the heat-wave in August 2003 and the poor take-up of flu vaccination in the crisis of 2009 highlight the fragility of responses to health crises, despite the creation or continual redevelopment of systems.

3.2. A complex public health system

With the support of a few talented administrators and motivated parliamentarians, France, through the laws of July 1st 1998 and March 4th 2002, established an institutional organisation designed to overcome deficiencies in theoretical support and to replace the institutions held responsible for the contaminated blood and growth hormone crises. The many acronyms covering the state agencies attracting new, high-quality staff, reflect the complexity of the system; this complexity makes it difficult for agencies to work together effectively. To the board of the Administration Centrale, which helps to define the strategic orientation of the agencies, we must add Afssaps (drug and device agency), ANSES (food and environment), which was formed by the fusion of Afssa (food) and Afisset (environment and labour), l’Agence de la biomédecine, which has replaced l’Établissement français des greffes, INVS (surveillance), INPES (health education) and IRSN (radiations), which has replaced OPRI.

The various agencies are co-ordinated, at the Direction générale de la Santé, by a comité d’animation du système d’agences (CASA), a body that meets weekly, the members of which include representatives of Inserm (health research), Civil Safety and, frequently, the Direction générale de l’Alimentation. In the overall system, for drugs, we also need to include an independent institution, the Haute Autorité de santé, which is responsible for evaluating the utility of drugs and medical devices, evaluated by other bodies, and the Comité économique des produits de santé, which depends on the minister for decisions relating to whether or not these items should be reimbursed and for fixing of the rate of reimbursement. The mechanisms of the social security system and price setting must be kept separate from the evaluation and control of drugs and devices: they do not depend on the same institutions whose responsibilities overlap in some situations and gap in others. The complexity of the system, with its successive strata, is obvious, as are the risks inherent to the complexity of communication between the various bodies dealing with the same subjects, but from different angles.

Any analysis of internal function in Drug Companies would also provide evidence of complexities and in the structures and methods of functioning of such organisations. There may also be breaks in information transmission pathways. Analyses of the functioning of the private and public systems can be carried out in parallel if we have experience of both. The memory
of decision-making mechanisms over decades and the risks of breaks in the communication between research and development units and pharmacovigilance units in industry and between different agencies and the ministry in public administration could clearly result in dysfunction. The late detection of such dysfunctions is worrying, but remains possible, in ways that always have the capacity to surprise.

3.3. Citizens and media implication in public health crises

The same ingredients of a public health crisis, regardless of the technical nature of the problem concerned, are always found, to various degrees but with considerable similarities as concerns citizens and the media. There are a dozen or so such ingredients concerning citizens (Table 1). A crisis is particularly likely to be severe, long-lasting and poorly tolerated if the risk to which the citizens consider themselves to have been exposed or to be exposed corresponds to the expressed or latent fears of society. Increases in the speed of information transmission, through newspapers, television, Internet and Facebook, are a major factor likely to deepen or escalate the crisis, because there is no longer enough time to check the validity of the information transmitted. The repetition of certain items of approximate or erroneous information may even distract attention from the main phenomenon that actually triggered the crisis. If the analysis of a health crisis is to provide a useful contribution or to help us to understand what happened, then technical and investigative work must begin immediately. The coverage of the health problem posed by the complications attributed to Mediator® (benfluorex) sensitised us to the Mediator® affair. Few people have experienced all these factors and, more frequently, each individual has his or her own factors, contributing to the situation of disequilibrium characteristic of the acute period of a crisis.

Table 2 summarises the most important axes in the transmission, by the media, of the information around which the crisis has developed. In the case of Mediator® (benfluorex), it is easy to identify incidences in which suspects have been diabolised: on the one hand the members of the industry that makes a profit from patients and uses mysterious methods to develop and to sell drugs; and, on the other, the members of an administration seen only as anonymous, incompetent and dominant. The multitude of actors concerned or feeling themselves to be concerned, leads
Fig. 1. The development of a crisis following the discovery of an unexpected or underestimated danger to health.

3.4. Victims, whistle-blower, lawyers, and judges

In a health crisis, one or several victims are usually represented by a spokesperson, often a journalist, but in this case a doctor who had written a book on the subject. This author played a key role in raising the alarm, using an appropriately catchy title indicating a certain number of deaths due to the drug. She gained additional publicity for her book from the very strong hostile reaction of the manufacturer of Mediator®, which rapidly adopted a tactic of denial in a larger strategy of seeking a legal judgement forcing a change in the title of the book. This only served to focus more public attention on who was “bad” and to award who was “good.” The performance of a “whistle-blower” is enhanced when a hostile environment is created: noone is listening to the whistle-blower even though he or she is right and everyone else is wrong, and this rejection strengthens the desire to contest the stonewalling by the other side. Not listening: in health crises a failure to listen is a powerful detonator. The commission responsible for pharmacovigilance did not listen to her, and may even be seen as contemptuous, when the whistle-blower expressed her version of the truth, whereas the facts were evident to those close to the patients and largely documented in these cases by the whistle-blower’s testimony. The next issue raised by whistle-blowers is why nobody is listening. This raises doubts about the sincerity of the opposition. All this becomes public and the truth and adhesion to professional or moral values rapidly lead everyone to recognise an error — an entity very different in nature from a fault — introducing simplicity and humanity into the debate. It is not fault that we should be looking for in the first place, but the error and its causes, and even that...
only after everyone has been allowed to express their point of view without feeling threatened. Those who believe they have rarely done anything wrong have probably done very little... Dysfunctions of the system are as important as individual error, and could have been avoided if the system functioned correctly. Is it really realistic to ask for a review of 6000 drugs in a matter of a few years? The search for scapegoats is particularly active when that search extends into the upper echelons of society; indeed, this has become an obsession for some, particularly since the contaminated blood affair and the issue of ministerial responsibility. In a very hierarchical society, whether public or private, the level of responsibility can always be questioned: depending on their ethical values, the “bosses” may or may not assume their responsibilities. When a crisis occurs, the objective search for an error is rapidly replaced by a search for scapegoats, making it increasingly difficult to find the truth, due to the hardening of attack and defence strategies [5]. Contributions by outliers poison the debate without adding any factual information. The whistle-blower, who reveals the problem to everyone, has an enormous responsibility, for good or evil, which is expressed over time according to the psychological characteristics of the person concerned or even the expression of his or her interests or personal ideals. The crisis is amplified as lawyers and judges become involved, a step that occurs all too rapidly these days. Each of the four basic protagonists, without being aware of it, follows the same pathway trod by many others in other health crises that have been just as painful or even more difficult. The amplification loop described in Fig. 1 may astonish experts in the regulation of sodium metabolism or glycaemia, because it creates a parallel between physiology and pathology on the one hand, and accidents in society on the other. We can conclude, simply, that the work of scientific societies, as Société franco-phone du diabète (SFD) is doing, is to consider this activity, the analysis of crises, among the range of relevant subjects and to introduce a form of teaching of this approach into the training of healthcare professionals.

4. Conclusion

The lessons I have personally learned from this work of reflection and teaching about health crises concerns essentially the position of doctors in the face of human suffering, which they mostly decrease, but may sometimes increase, rarely do I hope. The benefit/risk ratio is the result of all acts of care and assistance. It is simultaneously the result of all social, administrative and financial activities. We would find it hard to live with ourselves if we were continually remembering all those pregnant women exposed to diethylstilbestrol, those infants placed on their fronts to sleep, those haemophiliacs who received contaminated blood transfusions, those children treated with growth hormone, those workers exposed to asbestos, those road-builders and factory workers exposed to toxic chemicals, and those with irradiated prostates. I have been afraid over the last 40 years that we might need to include all those hypertensive or diabetic patients treated for life, with my intervention perhaps increasing their risk when I ventured into the unknown and prescribed recently developed treatments. The morbidity and mortality statistics over the last 40 years are reassuring, but the battle is never truly won and the slightest error can cost very dear. Every death is one death too many, and public health and its crises cannot be fully represented by the figures alone. Suffering repeatedly emerges from society’s lifestyle in the form of crises: the victims feel increasingly victimised and the others, racked by doubt, are just as afraid of one day becoming victims themselves; the dead do not come back, money does not prolong life, public recognition is transitory, the punished survive through negation and the injustice that they now share with the first individuals affected, the same people who should never have been affected in the first place. So, what should we want? We should want society to refuse to be dominated by a stereotypical simultaneous search for victims and scapegoats. We should also prioritise, spread and practice more values of professional honesty and dedication: we should assume our responsibilities, at all levels, by obliging ourselves to examine — and to say — what we have and have not done, even when working and when the system designed to minimise individual error failed to ensure the protection in which its designers believed. We should also hope that crises are managed so as best to prevent subsequent crises, but without illusions. When conscious or unconscious risk-taking by some is detrimental to one person, or frequently to many people, we no longer tolerate it: this is progress. When a crisis occurs, we can all contribute to the prevention of subsequent crises, and this positive view is much more important that regret, accusation and compensation, which will, possibly for a long time, extend the acute phase of the Mediator® crisis, this crisis in society being transformed into a chronic social disease. Despite everything, the thousands of excess deaths during the heat-wave of 2003 led to the generation of billions of Euros that have proved indispensable for the funding of the Caisse nationale de solidarité pour l’autonomie (the National Autonomy Solidarity Fund). Thalidomide is now used to treat certain myelomas and Rendu-Osler disease. In the future, we will probably try to determine why some of the patients exposed to norfenfluramine suffered valve damage, others suffered pulmonary arterial hypertension and others suffered no adverse effects: exposure or target, environment or genetics, pharmacokinetic or pharmacodynamic issues?

I have carefully avoided to disclose names, and my only access to files has been through a complete scientific literature survey and the attentive monitoring of the investigative press. I cannot, however, resist the temptation to try to contribute to the prevention of future crises. A drug has three names. It is a chemical entity (in this case norfenfluramine), and it has a common, generic name used internationally (benfluorex), assigning it to a particular chemical structure and pharmacological class. However, as for almost all other drugs, there has been, in the minds of all — prescribers, dispensers and patients, and perhaps even the discoverers of the drug — only one name, a trade name, Mediator®. It seems ridiculous: we have transformed medicine, its quality and its costs, using fantasy names of drugs, instead of carrying pharmacological information indispensable for scientific treatment, in association with the daily dose and its justification from dose-response curves. This is why the ICD
has been so frequently quoted in this paper at the contact of the commercial denomination.

In the wake of this crisis, we are likely to propose more regulations, more controls and more procedures. I propose more science, more pharmacological knowledge than promotion of trade names and more attachment to professional and ethical values when developing, targeting, selling, prescribing or dispensing drugs. This would constitute a precautionary principle, even more important at the time of the indispensable generic drugs arrival, and the insufficiency of public funding for continued medical education, now included among public health safety actions. This major educational function of the State, in charge of health safety, has yet to be fulfilled and that has contributed, in my opinion, to this severe dysfunction of the private and public health system.

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