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Acculturating Human Experimentation: An Empirical Survey in France

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Preliminary results of an empirical study of human experimentation practices are presented and contrasted with those of a survey conducted a hundred years ago when clinical research, although tolerated, was culturally deviant. Now that biomedical research is both authorized and controlled, its actors (sponsors, committees, investigators, subjects) come out with heterogeneous rationalities, and they appear to be engaged in a transactional process of negotiating their rationales with one another. In the European context “protective” of subjects, surprisingly the subjects we interviewed (and especially patient-subjects) were creative and revealed an aptitude for integrating experimental medicine into common culture.

I. HUMAN EXPERIMENTATION IN THE EUROPEAN CONTEXT

A. AN EARLY 20TH-CENTURY EUROPEAN SURVEY: BONGRAND’S THESIS (1905)

At the beginning of the 20th century, for his graduation as a medical doctor, Pierre-Charles Bongrand (1882–1926) at the University of Bordeaux defended a dissertation entitled “On human experimentation – its scientific value and its moral legitimacy.” Bongrand had extensively reviewed the European medical literature to establish the facts. His discussion of the scientific value of current medical trials was based on his own training (he had worked for the Pasteur Institute). His reflections on the moral legitimacy of such trials were illustrated with a kind of opinion survey: he had consulted lawyers, theologians, philosophers, medical practitioners, and novelists who wrote about medical investigators.¹

Bongrand argued that ever since Claude Bernard had promoted the image of an “experimental medicine,” and Pasteur had imported into medical practice “the experimental rigor of the chemist,” medical experiments had gained respectability, although with a favor of avant-gardist deviance. Indeed, medical doctors did not always feel comfortable with experiments, and they tended to cover them under a “therapeutic pretense” or conceal their actual aims from their patients. But medical trials were in no way conducted underground: they were published and discussed openly in medical journals. Bongrand found such large numbers of published reports of experiments that he had to give himself criteria of selection. He restricted his study to experiments performed “out of sheer scientific curiosity” and aimed at discovering the cause of some infectious disease. What did he find? Some examples (Bongrand, 1905, Chap. 1):

1. The plague: “Desgenettes inoculated himself with no result. White also inoculated himself: he died. [...] Two convicts were inoculated on the occasion of the Cairo epidemics in 1835: positive results.”
2. Measles: “Home, at Monro’s instigation, inoculated successfully blood collected from a morbillous macula. [...] Themmen, at Tuessing’s instigation, inoculated without success to children the tears, blood, nasal mucus, sweat, epidermic squama, of the ill.”
3. Syphilis: “Padova inoculated without success the milk of a syphilitic woman to four healthy nurses. [...] Voss, at the hospital in Kalinkine, conducted a similar experiment on four consenting prostitutes (aged 13, 15 and 16 years): only one positive result.”

4. Malaria: “Grassi, Bignani and Bastianelli had healthy subjects bitten by anopheles mosquitos, after infecting the mosquitos through having them bite people suffering from malaria. The subjects did contract the disease, but the experiment was conducted in the countryside around Roma, an area infested with malaria anyway.”

5. Yellow fever: “Domingo-Fereire in 1883 thought he had found the germ responsible for yellow fever. He inoculated an attenuated solution of a culture of this microbe to 60 individuals; 30 were infected, 13 died. [...] Finally, around the same time, already suspected that yellow fever might be transmitted by mosquitos. To test his theory he performed the following experiment on Aug 18, 1883. Father U, a Jesuit newly arrived in a community’s farm where no case of yellow fever had arisen for seven years, offered himself as a subject. He had him bitten by a culex mosquito which, two days earlier, had bitten two persons affected with severe yellow fever on their sixth day of illness. After an incubation period of eight days, a mild yellow fever appeared, which lasted six days.”

Bongrand enumerated over a hundred similar examples. When examining them, he said, he balanced between horror and admiration. He wondered whether he was confronted with crimes that should be punished, or with audacious attempts at acquiring new knowledge that should be encouraged. He forcefully argued that, if human experimentation had to take place at all, then it must be of the highest possible scientific quality, which meant that there should be no trial devoid of an explicit rationale and scientific strategy, and that no experimental strategy should be the idea of an isolated researcher (he wanted a ‘scientific commission’ behind each trial). He pointed out many defects in the strategy of the experiments he reported. But, he asked, should scientific experiments on humans be performed at all? At the beginning of the 20th century, nowhere in Europe was there any law or official regulation permitting or prohibiting such enterprises. The lawyers consulted by Bongrand answered that medical experiments came under the common law, and if dangerous for the subjects, they could be prosecuted and punished under the charge of “aggravated assault,” or even “homicide.” Indeed, some physicians had been publicly accused by their colleagues, or by journalists, of abusing their patients for the sake of science, such as the physician in Reims who had supposedly inoculated his patients with cancerous tissues while they were asleep (to find out whether cancer was contagious) (Bongrand, 1905, p. 64). However, no lawsuit was mentioned by Bongrand. In spite of being described by novelists with a thrill of cynical horror, and reported in the medical press with ingenuity, human experimentation by the medical profession was apparently well tolerated socially (society “closes its eyes,” said Bongrand (1905, p. 87)).

Was it morally acceptable? Philosophers had found little to say, according to Bongrand, while theologians were of more help. They tentatively distinguished between two kinds of risk. No one was allowed to expose his life, because that was tantamount to suicide, and no doctor was allowed to abridge the life of a patient for the sake of science. But exposing one’s health to some dangers for science could be considered a good deed, an act of devotion to society, provided the subject knew what he was doing, and he was willing to do it.

Bongrand’s conclusion was in favor of experimenting on human subjects for the sake of science, because, although “immoral” (as a “sacrifice of individual beings to the community”), it was “sometimes necessary” (to the extent that animal experimentation did not suffice). However he deplored that numerous experiments were conducted on helpless people, children, pregnant or nursing women, and poor patients at the doctors’ disposal in public hospitals. On the other hand, he approved of dangerous experiments performed on mentally retarded persons (“idiots”), on the dying, on convicts or on people sentenced to death, because it was a way that a “lost life” could be useful beyond itself. Finally, he concluded that society could not decently go on indulging in its “placid ignorance” of the problem. Human experiments should be permitted under strict conditions, the most important in his view being that there be a contract between the subject and the investigator, specifying the subject’s preliminary consent, and possibly guaranteeing him some “compensation” (such as a reduction in their sentence for convicts). But as we know (Fagot-Largeault, 1985), society’s “placid ignorance” lasted many more years.

B. EUROPEAN AND FRENCH CONTEXT AT THE END OF THE 20TH CENTURY

At the end of the 20th century, all European citizens are in principle protected against the risk of being included in medical trials against their will, or without knowing it. The Convention on Human Rights and Biomedicine (CHRB) adopted in 1997 by the Council of Europe² states explicitly:

Art. 5 – An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it.

This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks.

The person concerned may freely withdraw consent at any time.

Although the agreement between subjects and investigators can hardly be called a contract (because it can be broken “freely”), and even though the notion of “appropriate information” is highly variable, everywhere in Europe today the research subject will sign a consent form after receiving some information. All member States of the Council of Europe have agreed to “guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine” (Art. 1 of CHRB). This implies that scientific research may be carried out freely, subject to strict provisions “ensuring the protection of the human being” (Art. 15 of CHRB), especially those human beings whose free or informed consent is impossible or fragile.

In the particular case of France, legislation on the “protection of persons undergoing biomedical research” was passed in 1988, whereby biomedical research on humans, as distinct from standard medical care, is permitted under specified conditions:

Art. L. 209-1. – Clinical trials or experiments organized and conducted in man with the objective of developing medical or biological knowledge are hereby authorized under the conditions prescribed in this book and are referred to herein by the term: “biomedical research.” ...

Art. L. 209-9. – Prior to the carrying out of biomedical research on any person, free, informed and expressed consent must be obtained from such a person after the investigator or physician designated to represent him has informed the person of the following:

- the research objective, methodology and duration;
- the anticipated benefits, the limitations and risks associated, including in case of premature termination of the research;
- the opinion of the Committee mentioned in article L. 209–12 of this code.

Art. L. 209-12. – Before conducting research in human subjects, all investigators are required to submit the research project to a consultative committee for the protection of persons in biomedical research located in the region where they exercise their activity.

We have been interested in finding out how the various actors of biomedical research, as identified by the law (“consultative committee,” “human subject,” “investigator,” “sponsor”³), have by now appropriated the law and positioned themselves in the context induced by official regulations. Note that “consultative committees for the protection of persons in biomedical research,” in short CCPPRBs, are the French equivalent of the American IRBs, or of what are called Research Ethics Committees in other countries.

II. INFORMATION AND CONSENT: A SYSTEMATIC EMPIRICAL SURVEY

Bongrand tried to document a variety of points of view regarding human experimentation. Beyond the facts and arguments he exposed, what interested us – and what we share with him – is the concern for differences. The survey from which we present here preliminary findings was conducted among real actors of human experimentation: sponsors, investigators, CCPPRB members, and subjects. The main objective of this survey was to describe the specific rationality of each type of actor while participating in the human experimentation process. The survey focuses on providing/receiving information and requiring/giving consent in practice and on representations and beliefs related to these practices. The final aim was not to quantify. Our intention was to characterize each collective actor’s specific contribution to the modeling of an emergent feature of our civilization.

In order to define these specificities, the survey covered the whole set of actors participating in the field. Our approach is systematic in that sense, and from that point of view it differs from other empirical inquiries (see Sugarman et al., 1999) which considered only one or a group of actors. We used standard qualitative techniques and tools we detail below. This survey is part of a larger research program, conducted by an academic institution dedicated to history and philosophy of science (IHPST, University of Paris) – and designed in cooperation with a non-academic structure specializing in sociological research about institutions (Institut Novexis, Paris). This program was funded by a pool of governmental institutions, private foundations (including patients foundations), and drug companies. It began in 1996 and is due to be completed in 2000.

METHOD

Our program included two phases. During the first phase, we interviewed 23 “main witnesses” who reported on the situation prior to the 1988 French law: researchers, public servants in the health institutions, and political leaders. They told us about practices when human experimentation was still under the scheme of common law, and about the pressures and necessities which led Parliament to pass the 1988 legislation. Interviews (recorded) were not directive. They were transcribed entirely. During the second phase, semi-structured interviews were conducted with physicians, patients, CCPPRB members and sponsors.

We will not present here any results about CCPPRBs, though their role is very important, because this particular survey is still in progress. Interviews were recorded (there was an interview guideline specific to each category) and then transcribed, following a pre-analysis schedule. To understand the diversity of the research situations, we developed a matrix, organized according to two mainlines. The first one is linked to different types of research: involving ill or healthy people; with or without possible therapeutic benefit; with or without therapeutic alternative; degree of severity (from no disease to possibly fatal illnesses). The second reflected the degree of autonomy of the person with respect to her legal and mental capacity (to understand, to make a judgment, to decide).

Our questioning focused on the production of narratives. Interviews were conducted by a small team of sociology and philosophy students trained in the techniques of interview. The people we interviewed were informed that the survey was anonymous, and they were told about the goals of the survey. They all agreed to be recorded.

III. PRELIMINARY FINDINGS

This survey shows that the actors proceed according to heterogeneous rationalities. This can be evidenced through analyzing practices and discourses along two lines: discrimination between care and research on the one hand, and representations and practices about information on the other.

A. SPONSORS

The distinction between care and research is clear for all types of sponsors (pharmaceutical firms, public research institutions, patients’ research foundations). There is no ambiguity about the nature of the acts carried out on subjects.

Sponsors	34 interviews (12 sponsors, including 5 pharmaceutical companies)
Investigators	35 interviews (19 in public hospitals, 16 in private practice or with a double-status)
Subject-persons	40 interviews (including 6 healthy volunteers)

Fig. 1. Number and Profile of the Parties Interviewed.

In a French context, even for phase I trials, sponsors in general have no direct contacts with subject-persons: investigation and information are the privilege of physicians who are both researchers and

clinicians. Sponsors – especially the firms – are the main authors of the information documents given to the patients. Whatever the writing process, these documents are first seen as legal documents. Since the formulation of these documents has to do with the sponsor's legal safety, he claims control over it. In the case of private firms, investigators are rarely involved in the redactional process.

These documents are actually designed for the bureaucracy and the CCPPRB. The subject-persons remain in the background: they are elements in a legal system of relationships. It is known, among sponsors, that these documents are often barely intelligible and not very carefully written. The investigating physician is seen by sponsors as the one delivering the “true” information to the patients during their interaction.

Whenever efforts are dedicated to making the documents more readable, they consist in informal procedures (e.g., in a laboratory, the investigator asks a layman to read the documents). The point of these efforts is to make inclusion of persons easier. The design of information documents is slightly different when trials involve patients organized in powerful pressure groups. In such cases a more formal procedure takes place in which representatives of patients associations are viewed as potential censors, just like CCPPRBs and the bureaucrats. The patient himself as a person going through the trial remains essentially absent from the scheme.

B. INVESTIGATORS

The distinction between care and research is a problem for most investigators we met when they deal with patients (when they deal with healthy volunteers, obviously there is no ambiguity). At the two extremes we find:

- The investigator for whom “it is the same thing,” or the same “with something more”;
- The investigator who states that research is “a specific practice, completely different from caring, and patients should not be confused about the two.”

There is a halfway point between these extremes: “it is not the same thing but it does not make any difference for the patient.” Therefore, in practice, if not in theory, there is confusion. In all cases, the theme of trust is omnipresent in interviews with investigators, whether they deny any distinction between care and research, or they neutralize the distinction. Trust is a crucial element of the frame within which physicians build and protect their conception of the professional medical identity. It is viewed as a frame that protects the patient from “unpleasant truths,” “that he doesn't want to know,” or “which he is not able to understand.” (What is said of the patient could be said also of the investigator-physician: that he needs protection against an “unpleasant truth”: he has difficulty reconciling the role of the physician who knows and that of the investigator who does not know.)

1. Information Practices in Case of Denial of the “Care vs. Research” Distinction

These positions of denial or neutralization of the specificity of the research situation are common to most private physicians we interviewed. Involved mostly in phase III or IV trials, they claim that the experiments they carry out on patients are not dangerous. Though they do not express it quite so abruptly, this feeling is shared by some physicians in hospitals, in spite of doubts: “We are somewhat torn between the two,” or: “What bothers me are trials against placebo.”

In either case the investigator's relation with the subject-patient fits in a scheme of care. If the investigators know they are taking part in research, they do not feel it necessary for the situation to be clear to the subject-patient. Acute or insistent questions from patients are interpreted by physicians as a sign of distrust. The investigators protect themselves by anticipation, very carefully preselecting and choosing the patients they want to include in the protocol: “I try to select patients I have known for a long time. It's more comfortable” (INV-12); “There is a good patient profile (...). We could not possibly propose to all patients” (INV-21); “There is a subjective selection process operating” (INV-01).

Thus, one can say there is a type of the “good” subject: the patient who trusts, and who does not insist on the physician being specific about the distinction between care and research: “I never thought that a

parent [in pediatrics] would ask me to look at the investigator's brochure [i.e., the protocol itself]... It is precisely the kind of parent [sic] I would not have included!" (INV-11). Here information practices, as described by investigators, exhibit recurrent characteristics: belittling of what is written ("bureaucratic papers"), calls for trust rather than understanding: "If possible, I hand the information sheet over to the patient, for him to read quietly at home. I may also move away from good practices and tell him: `You know, I am going to leave it with you, but don't read it. I'll tell you everything that's in it. It's so written that you would have a hard time making sense out of it' " (INV-12). Such investigators are careful to inform patients about practical aspects and constraints (including side effects): the belief is that a patient who is ill-informed in that respect is less compliant and more likely to drop out of the study before its end. In that perspective, information is seen as a tactical means in a recruitment strategy.

2. Information Practices in Case of Clear "Care vs. Research" Distinction

We now take into consideration those investigators who draw a clear line between care and research. For some of them, whom we mostly met in hospitals, the distinction between care and research may be blurred by the fact that there actually is an objective link between care and research in pathologies such as AIDS or cancer. In those cases there may not be any other treatment alternative but a research protocol. (Such a link is absent in many other situations where reference treatments exist, or in genetic research, for example.)

At any rate, for all investigators, patients must understand that they are in a situation different from standard medical care, and they must also grasp the scientific rationale of the experiment in which they are taking part. "Before asking someone to join the research, you have to explain what your model is of those disorders – so they may understand why you are interested in factors of biological vulnerability" (INV-19). Otherwise, patients will not be included. That is already evident during preselection: the investigator looks for subjects apt to understand, before he looks for acceptance: "To the extent that you want the person who consents to be really informed... inevitably you select a population of patients who are more apt to understand" (INV-06). The differentiation is neatly suggested to the subject-patient: "From the very beginning of the process we differentiate the encounter with a clinician investigator for the purpose of participating in some research, from the appointments made for the purpose of therapeutic follow-up" (INV-19). It often takes the form of a geographical parting of the locations and/or of a parting of agents, when investigators are not involved in the general care given to the patient.

C. SUBJECT-PERSONS

1. Diseased Persons

The diseased persons we interviewed could usually describe quite exactly the details of their being "protocolized." Their first motivation to participate was the hope of being cured. Noticeable also is the awareness of taking part in scientific progress, in an action useful for others (altruism). However, when people were asked to grade the reasons of their participation from 1 to 5, the highest scores were obtained by "to get a better treatment," "because it is the only way to get the treatment": "Of course you know very well that when you enter a protocol the results will be helpful for other patients. That is obvious for me. But here in this case it was to try and bring improvement in my own personal situation" (PER-14).

The difference between care and research means that "care" and "research" are both related to the treatment of the disease: "The primary reason was that the standard treatment did not work; one had to try and find something else" (PER-18). As was shown by Schaeffer, Krantz, Wichman, Masur, Reed & Vinicky (1996), patients perceive the experimental situation differently, according to the severity of their disease.

Patients whose vital or functional prognosis is at stake think of the protocol as an additional therapeutic chance or as the only therapeutic chance left. What we found is that, even when freedom to maneuver is limited to a binary alternative (to take or not take this opportunity), patients claim

responsibility for their choices. They appear to make calculations, with a view to select the better alternative available: “No one forced me to do it, I myself judged that I had to do it... You know, when you are in that situation [cancer], you have no choice” (PER-19); “I have no regret. In any case, I’ve got to try and get cured...” (PER-07).

Such assertions appear paradoxical only if we appreciate them from the perspective of some rationality (legal, ethical, medical) other than their own. Seen from outside, patients are the objects of care and/or research. From inside, when they talk about their disease experience, they develop a rationality in which they are the subjects of their recovery. It is in that logic that we must understand the claim for autonomy of decision, even in patients faced with narrow choices: their quality as subjects is at stake.

2. Healthy Volunteers

Healthy volunteers we interviewed could be divided into two categories: paid or unpaid. For the first ones (mostly biology students), participation was seen as a “summer job.” Regarding information, they were mostly interested in practical aspects (how long it would take and how much money they would get in return). Possible drawbacks of the trials were conceived in terms of pain more than as a risk for health.

The unpaid volunteers whom we met participated in HIV vaccine trials. Such volunteers embody the ideal volunteer – very motivated, compliant, responsible, disinterested, informed – a model designed by the recruiting party. They are the product of a selection process, there being far more candidates than recruited subjects. The selection process is harsh, with at least two interviews (one with a physician, one with a psychologist). As a result, cohesion between volunteers and researchers is in this particular case very strong.

IV. CONCLUSION

At the end of the partial presentation of our survey which was just completed, we can produce the following conclusions.

1. Early in the 20th century, society “closed its eyes” to the practices of human medical experimentation. Late in the 20th century, medical experimentation on human beings is a phenomenon that has gained social recognition and control. The legal, ethical, and scientific regulation of human research practices (“good standards”) have driven human research out of its clandestine status and brought it out into the open. It then emerged as a massive phenomenon. In 1996, the French ministry of health gave a figure of 865,000 persons “protocolized” in one year within the health care system, an estimate based on protocols examined by the CCPPRBs. Those persons “under protocol” are less and less perceived as “guinea pigs.” In Bongrand’s times, be they viewed as heroic or criminal, human experiments had a scent of transgression, as evidenced by the literary examples mentioned (see note 1). Human experiments have now become commonplace: the actors we interviewed see them as a necessity, the participation in which is normal, nay socially valuable (and valued).

2. Acknowledging the fact that human research is socially both controlled and valued does not amount to saying that its rationale is uniformly understood. That the actors’ intentions, objectives and strategies are remarkably heterogeneous is one of our main findings.

The French law of 1988 states that acquisition of new biological or medical knowledge is the objective of clinical trials or experiments. Most actors appear to recognize that they may contribute to “science.” Yet they also appear to function within a generalized *quid pro quo* about such fundamentals as the distinction between “scientific research” and “medical care” (or the notions of “proper information,” of “person,” of “legal” and “scientific” requirements, etc.), which brings them to implicitly negotiate and compromise to get their rationales adjusted to one another. That may be described as a process of “acculturation,” that is, of integration to common culture, of practices hitherto ignored or misapprehended.

3. Patient-subjects do not appear to handle the transaction as poorly as might be thought. In the European context of regulations “protective” of potential subjects of research, it is tacitly assumed that subjects, and especially patient-subjects, are to be passive, the object of negotiations, and devoid of a

full capacity to understand the implications of empirical medicine having turned into experimental science. The patient-subjects we interviewed were not passive. They claimed responsibility for their choices, and showed a real creativity in their manner of living through the research situation. They may be more culturally ready to contract with investigators on an equal basis than is generally conjectured.

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NOTES

1. See for example Daudet, 1894; Adam, 1896; Zola, 1893; Veressaief (Veresaev), 1901.
2. The Council of Europe is larger than the European Union (today, of 15 Western European states). The Council of Europe is an intergovernmental organization created in 1949 to promote cooperation between pluralistic democracies. Its Committee of Ministers, composed of the Ministers of Foreign Affairs of the (currently) 40 member States, serves as a permanent forum for negotiation and discussion of (political or other) problems. After being discussed and reworked for many years, the Convention on Human Rights and Biomedicine was adopted in Oviedo on March 4, 1997.
3. "The person or corporate body who initiates biomedical research in human subjects is hereby referred to as the sponsor. The persons who themselves direct and monitor the carrying out of research are referred to hereafter as the investigators." (Loi no. 88-1138, Art. L. 209-1).

REFERENCES

- Adam, P. (1896). *La Force du mal*, Paris; Librairie A. Colin
- Bongrand, P.-C. (1905). *De l'expérimentation sur l'homme. Sa valeur scientifique et sa légitimité*, thèse pour le doctorat en médecine, soutenue le 27 Jan 1905 devant la Faculté de médecine et de pharmacie de Bordeaux, Imprimerie Y. Cadoret, Bordeaux.
- Council of Europe (1997). *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine*. Strasbourg: European Treaty Series no. 164.
- Daudet, L. (1894). *Les Morticoles*. Paris: Bernard Grasset.
- Fagot-Largeault A. (1985). *L'homme bio-éthique. Pour une déontologie de la recherche sur le vivant*. Paris: Maloine.
- French National Consultative Ethics Committee for Health and Life Sciences (CCNE, 1998). *Consentement éclairé et information des personnes qui se prêtent à des actes de soin ou de recherche [Informed consent of and information to persons accepting care or research procedures]*. Report and recommendation no. 58, 12 Jun 1998, <http://www.ccne-ethique.org>.
- Loi no. 88-1138 du 20 déc 1988 relative à la protection des personnes qui se prêtent à des recherches biomédicales (also called 'Loi Huriet'). *Journal Officiel de la République Française*, 22 Dec 88. Modified: Loi no. 94-630 du 25 Jul 1994, JO, 26 Jul 94. Completing the Code de la santé publique, Livre II bis, Art. L. 209-1 à L. 209-23. Published with English translation: *Bulletin Officiel* no. 90-4bis. Direction des Journaux Officiels, 26 rue Desaix, 75727 Paris Cx 15.
- Schaeffer, M.H., Krantz, D.S., Wichman, A., Masur, H., Reed, E., & Vinicky, J.K. (1996). The impact of disease severity on the informed consent process in clinical research. *American Journal of Medicine*, 100, 261–268.
- Sugarman, J., McCrory, D.C., Powell, D., Krasny, A., Adams, B., Ball, E., & Cassell, C. (1999). Empirical research on informed consent (an annotated bibliography). *Hastings Center Report*, special supplement (Jan-Feb) S1–S45.
- Veressaief (Veresaev), V. (1916 [1901]). *Memoirs of a Physician*. New York: Knopf.
- Zola, E. (1893). *Docteur Pascal*. Paris: Garnier-Flammarion.