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Defending Against Biochemical Warfare: Ethical Issues Involving the Coercive Use of Investigational Drugs and Biologics in the Military

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Introduction

The threat of biological or chemical warfare raises urgent questions about how best to protect both civilian populations and military personnel from biochemical attacks. We shall focus here on some issues that arise specifically in the military context, with regard to prophylactic or therapeutic administration of *investigational* drugs and biologics to servicepersons--that is, drugs and biologics lacking FDA approval for the use in question (though they may or may not be approved for other uses). These issues came into sharp focus during U.S. missions in the Gulf and in Bosnia, and the ethical questions arise again in the context of the current "War on Terrorism" and
(as of this writing) likely renewed military action against Iraq. Of particular relevance are ethical concerns over the waiving of ordinary consent requirements for the administration of investigational drugs or biologics to protect soldiers in emergency situations.

Under current law, the President may waive the consent requirement for "the administration of an investigational new drug or a drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation," when it is determined that "obtaining consent (A) is not feasible; (B) is contrary to the best interests of the member; or (C) is not in the interests of national security."[2] The nonconsensual use of investigational prophylactic or therapeutic compounds raises important questions about the nature of the justification for such measures, the conflict between individual autonomy and military objectives and interests, and the relation between such innovative protective measures and research involving human subjects.

We shall argue that despite legitimate concerns over respecting autonomy, which do need to be addressed, certain features specific to the military context can in principle justify the mandatory administration of certain protective medical compounds that presently count as "investigational"
because they lack approval for the use in question. This has largely been obscured by the grouping, for legal reasons bound up with regulatory history, of widely disparate practices under the single heading of "investigational" uses of drugs or biologics, which has in turn misled some into viewing even plainly therapeutic but innovative uses of drugs as a form of "research," which would raise all the ethical issues associated with research on human subjects. At a recent conference on "Bioethics and Bioterrorism," for example, an epidemiologist for the state of New Jersey described how "the CDC's prophylaxis response" to the recent anthrax contamination incidents made "many individuals in New Jersey [feel] they were being experimented upon, rather than prophylactically treated," because it made "medication and vaccination available as an 'investigational new drug trial'."[3] This misperception that the use of "investigational" compounds automatically amounts to research is perhaps understandable on the part of the general public, and it poses certain obvious practical problems. More problematic from a theoretical point of view, however, is that such a misperception exists also on the part of some ethicists, including those debating the use of investigational

compounds in the military.[4] In this way, conceptual artifacts of regulatory evolution have, we believe, tended to distort thinking about the ethical issues, which should not rely as heavily as it often does on contingent legal categories such as “investigational” uses. If we are clear about the ethically relevant distinctions between research and treatment, as discussed below, then it will be clear that waiving the consent requirement for certain “investigational” treatments in combat situations need not amount to coerced participation in research.

Some of the perceived difficulty here may be avoided simply through certain regulatory modifications. For example, the FDA has recently amended its rules to allow for the approval of some potentially life-saving drugs and biologics without requiring the usual human *efficacy* studies, in cases where it would be clearly unethical to carry out such studies; animal efficacy studies may now suffice in certain circumstances (in conjunction with human *safety* studies).[5] This "animal efficacy rule" allows for the possibility of moving some hitherto "investigational" compounds into the category of *approved* drugs or biologics, which would also obviate the need in such cases for a special Presidential waiver of the consent requirement for the administration of such compounds: their use could be ordered by commanding officers just as use of the Influenza vaccine may be, for example. This change in status has in fact just occurred in the case of pyridostigmine bromide (discussed below in connection with the Gulf War), which was approved for combat use on 5 February 2003; it need not therefore be administered any longer as part of an investigational new drug trial, with all of the labeling and documentation requirements that involves--requirements that may be impractical in combat situations. Alternatively, some have argued instead for a new FDA product category, such as "Licensed for Contingency," to permit military contingency use of what have so far been investigational products.[6] Again, such an approach would avoid giving any misimpression of coerced participation in research, by avoiding the pairing of the “investigational” label with a waiver of consent: if the compound is licensed for contingency use, then such use by the military will not be "investigational.”

With suitable oversight, such steps may well be the best practical course for both securing effective protection for troops and mitigating negative public perception: they would eliminate the burden of operating under clinical trial requirements for "investigational" products in battle conditions, eliminate (what we shall argue are) misperceptions about coerced participation in research, and also eliminate the tipping off of adversaries that would likely result from use of the specific Presidential waiver of consent for "investigational" products in time to make them effective. At bottom, however, the very same fundamental *ethical* issues need to be addressed, whether we are talking about waiving the consent requirement for the use of “investigational” products or about measures to reclassify these products so as to allow for their nonconsensual administration as standard treatment. And in any case, despite recent changes in FDA rules, there may be other compounds of potential military importance that remain "investigational," so that the issue of waiving consent for investigational compounds remains a live issue. We shall therefore stick to this question, and argue in part that such waiving of consent in the administration of certain "investigational" products in military contexts may sometimes be justified at least in principle.

It is, however, important to be clear about the nature of this justification, which is compatible with respect for persons only because it is *not* ultimately paternalistic in the way it is sometimes portrayed as being. Moreover, we will argue that there are further conditions that must be met if such nonconsensual administration of investigational drugs or biologics is to be properly justified. In particular, a reasonable and ethically significant surrogate must be found for the autonomy that is being forfeited, such that proper respect for persons is maintained. (Again, this is equally true on the alternative approach, where autonomy is simply forfeited in a different way, i.e. through reclassifying a use as *non*-investigational so that it can be mandated in the way other *approved* treatments already are.) Typical justifications do not go far enough in this respect, and they also tend to miss an important point about proportionality that likewise needs to be stressed. We will suggest ways to remedy those shortcomings, so that the military’s goal of both effectively protecting all its personnel and promoting its objectives can be achieved in a way that is consistent with the
ideal of respect for individuals.

Competing Levels of Interest

The major problems specific to the military context arise from the tension between the person who has volunteered as an autonomous individual to undertake the role responsibilities of military service, and the military institution, which must in large part treat service members collectively in order to accomplish its objectives. On one hand, the moral sensibilities and laws of the civilian society from which the volunteers come tend to regard the individual as the primary unit of concern in medical decisions involving participation in research or treatment.[7] This is not to deny that utilitarian considerations play an important role in some medical decisions, as with the mandatory vaccination of public school children; nor is it to deny that individuals may bear some social responsibility for the state of their own health, given the extent to which lifestyle decisions affect health, which in turn affects health care costs that are in part borne collectively.[8] The focus, however, is generally on individual autonomy concerning medical interventions directly affecting one’s own body, as having general priority over any collective interest in the health of the individual.

In the military context, on the other hand, while it is true that "servicemen and women do not subordinate themselves entirely to the 'mission' or to the welfare of their fellows,"[9] they have volunteered to take on both the special risks and the special duties of military service. So although they enjoy similar rights and protections with regard to participation in research in military laboratories, they are subject to mandatory standard vaccinations, physical examination and reasonable treatment "to protect the health and overall effectiveness of the command as well as the health of the soldier."[10] The special element of collective interest that is a structural part of the military makes it importantly different from the civilian context, though it is worth noting that such a compelling level of collective interest is not altogether without parallel in civilian society. For while normally adult civilians are not compelled to submit to medical interventions as servicepersons are, they have been so compelled under special circumstances, as during an epidemic of a dangerous disease. In *Jacobson v. Commonwealth of Massachusetts*, 197 U.S. 11 (1905), the Supreme Court famously upheld the constitutionality of legally mandated vaccination for smallpox where this was deemed necessary for public health, noting that the Court had already "distinctly recognized the authority of a State to enact quarantine laws and 'health laws of every description'."[11] The general reasoning in the opinion delivered by Justice Harlan is relevant to our present discussion:

> There are manifold restraints to which every person is necessarily subject for the common good. On any other basis organized society could not exist with safety to its members. Society based on the rule that each one is a law unto himself would soon be confronted with disorder and anarchy. Real liberty for all could not exist under the operation of a principle which recognizes the right of each individual person to use his own, whether in respect of his person or his property, regardless of the injury that may be done to others.
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> . . .[Thus,] in every well-ordered society charged with the duty of conserving the safety of its members, the rights of the individual in respect of his liberty may at times, under the pressure of great dangers, be subjected to such restraint, to be enforced by reasonable regulations, as the safety of the general public may demand.

This reasoning is meant to be very general, and when applied to civilian society in ordinary circumstances it still leaves the vast majority of health care decisions to individuals. But when applied to the military, the element of collective interest in the health of individual members becomes far more pervasive. Servicepersons take on their duties as part of a hierarchical organization of mutually dependent individuals prepared to risk life and limb together for the sake of collective military objectives. Since the organization exists to achieve certain collective outcomes, and individuals volunteer to join the organization knowing that they will be taking on responsibility for facilitating those objectives with fellow service members who depend on them for success and safety, each service member is responsible for maintaining his or her combat-readiness—both for the sake of the military objectives and for the safety of fellow service members.[12]

Because of the collective nature of military action, the management of risk to personnel and the promotion of military ends must be coordinated by commanding officers, and would often be hindered by a policy allowing for individual exceptions based on personal preference. Therefore, where there is an imminent threat of biochemical warfare, for example, there is an obvious corporate-level interest in ensuring that all members are protected as well as possible—given available information and medical technology—from the relevant biological or chemical agents. Indeed, "if servicepersons who refused to grant consent were permitted to enter combat without these protections, not only would they face increased and unnecessary risks themselves, they would also imperil other servicepersons insofar as the risk becomes actual, disabling harm, and also thereby diminish the likelihood of the military's succeeding [in its mission]."[13] (We will return to consider this argument in more depth later.)

What makes the case of "investigational" compounds more complicated and difficult than ordinary cases of protection, however, is that it goes beyond the use of drugs or vaccinations that have been approved for the specific contexts and purposes in question. In the Gulf War, for example, U.S. troops were ordered to take Nerve Agent Protection Packs of pyridostigmine bromide (PB) in anticipation of possible exposure to soman from Iraqi chemical weapons. While this drug already had an established use for the clinical treatment of myasthenia gravis (at dosages much *higher* than that prescribed for troops for protective purposes), PB had not been approved for military uses on the basis of substantial evidence of efficacy in human trials. Thus, it fell into the regulatory category of "investigational" use (though as noted earlier, this has just recently changed). The same was true of the use of the botulinum toxoid (BT) vaccine, which had established uses in certain occupational settings, but was not human tested for efficacy or approved for the military use in question. Again, such use of investigational compounds raised special concerns for many, echoed by the ongoing concerns of some service members over the implementation of the Anthrax Vaccine Immunization Program (AVIP), intended to vaccinate all service personnel in response to a threat of weaponized *Bacillus anthracis*.[14]

In the case of PB, questions about the safety and efficacy of such investigational use arose in light of uncertainty about how it might interact with nerve agents *other than* soman which might equally have been encountered by troops engaged in operations

against Iraq.[15] This led to general questions about whether the military's right to coercive administration of what it believes to be reasonable protective measures should extend to such cases of investigational medical intervention. The U.S. Department of Defense (DoD) argued that it should, and negotiated with the FDA to develop grounds for a policy allowing the Military to mandate wide administration of PB and BT. The DoD's arguments for the necessity of protecting the troops collectively, and the impossibility of seeking informed consent individually (let alone honoring refusals), were important in the development of an interim rule issued by the FDA to permit the investigational use of the compounds in the military context—and to waive the consent requirement where it was judged not feasible to obtain consent.[16] Again, the possibility of such a waiver of the consent requirement is now provided for by law, but it raises important questions. Does this amount to treating service personnel as human *research* subjects without their consent? Is it a dehumanizing failure to respect their autonomy? It is to these issues that we now turn, with the aim of showing that mandatory administration of investigational compounds need not amount to anything like coerced participation in research, and that *if* certain conditions are met, it can be done in a way that does not fail to show proper respect for human autonomy.

Treatment, Innovation and Research

When the FDA approves drugs or biologics for marketing, it approves them relative to a given indication, which is limited by the population and conditions in which safety and effectiveness were experimentally assessed. After an approval, licensed physicians may use the product according to their professional judgment in individual cases, not limited to the labeled indication—a practice referred to as "off-label" use. Any deviation from the population, condition or dosage set out in the approved product labeling constitutes off-label use. If the manufacturer wishes to market the product for a new use (for example, for children in addition to adults, or for treating a different type of condition), then the company must undertake clinical research and submit supplementary studies supporting the safety and effectiveness of the product in the new conditions. But physicians may prescribe whatever legal products they deem appropriate for the particular patient.

Off-label use is a normal and ethical part of good medical practice. What is distinctive about the sort of off-label use we are considering in the military is that (i) it is applied to a collective body rather than to an individual patient, and (ii) the decision to administer is driven not solely by the aim of treatment for each individual patient as such, but also by (a) the interests of fellow service members who depend on the fitness of that individual, and (b) the military's interest in maintaining the collective combat-readiness of the troops for the sake of the military objective. This is significant for at least two reasons. First, the adoption of an off-label use as a matter of policy to apply to a collective body is importantly different from the case-by-case exercise of professional judgment by an individual physician with regard to an individual patient—which is why the U.S. military services are not ordinarily allowed to employ off-label use in the practice of medicine on a large scale. Second, in those special circumstances where a product is used in a manner that departs from its labeled indication, the appeal to the above collective concerns, over and above the individual's own welfare as such, might be construed as implying a lack of respect for the dignity of individual servicepersons. This impression is likely to be compounded where the consent requirement is waived, so that the individual may be left feeling "that he has become a 'guinea pig' in a grotesque experiment," coerced into serving as a human subject for utilitarian medical research.[17] The dignity of the individual—the fact that "though a mere 'number' to the High Command, he is not a token and not a thing"—might seem to be lost in such a scenario.[18]

It is a mistake, however, to infer from the fact that a medical intervention is innovative—i.e. involves use of a compound that is classified for *legal* purposes as "investigational"—that it must therefore constitute *research* in an *ethically* relevant sense, and that waiving consent thus amounts to coercive use of troops as human research subjects. And it is a mistake to infer, from the fact that the purpose of the intervention is not *solely* the benefit of the individual patient as such, that the patient's dignity is not being respected. While a host of jokes from every war testifies that these points may often not be apparent to recruits, they are crucial for the project of ethical justification, and for clearly setting such cases as the mandatory administration of PB in the Gulf apart from the sort of abuse condemned in Nuremberg.

To begin with, treatment with an investigational product differs from research proper in the *principle aim* of the activity and in the different structures imposed by that aim.[19] The relevance of intent is well recognized in the *Belmont Report*—the influential statement of ethical principles and guidelines produced by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[20] The report specifies that while the "purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals [or groups of individuals]," research aims instead "to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge."[21] Thus, "the fact that a procedure is 'experimental,' in the sense of new, untested or different, does not automatically place it in the category of research." As Hans Jonas noted in the context of a single physician-patient relationship:

> As long as a doctor can say, even if only in his own thought: "There is no known cure for your condition (or: you have responded to none); but there is promise in a new treatment still under investigation, not quite tested yet as to effectiveness and

> safety; you will be taking a chance, but all things considered, I judge it in your best interest to let me try it on you"—as long as he can speak thus, he speaks as the patient's physician and may err, but does not transform the patient in to a subject of experimentation.[22]

In the context of large-scale off-label use of drugs or biologics, as in the use of PB or BT to protect troops during the Gulf War, the matter is slightly complicated by the fact that an aim of knowledge does enter the picture: for presumably if it is at all feasible to gather data on adverse effects of such treatment, then efforts should be made to do so for the sake of improving safety for possible future uses. This aim of knowledge acquisition, however, need not change the essential nature of the activity, and it will not do so as long as it remains *secondary* in the relevant sense. The principle here is this:

> If the aim of prevention or therapy constitutes a *sufficient reason* for a certain intervention—as in the above example, where the concern to protect troops was sufficiently compelling quite apart from any furtherance of research, and would have been done even if the data gathering had been impossible or ineffective—then the intervention falls under the category of treatment rather than research.

The existence of a *secondary* aim of gaining knowledge, as of adverse effects, no more transforms such an activity into research, in any ethically significant sense, than a secondary aim of learning about the deleterious side-effects of chemotherapy (in order to improve treatments in the future) transforms that activity from therapy into research.

An innovative, off-label intervention may thus count as "investigational" for legal purposes, and even have a contingent secondary aim of data-gathering, while still plainly being done with the primary and sufficient aim of treatment or protection; and in such a case, while we may wish to qualify its description by calling it "innovative treatment," it is just misleading to group recipients of such treatment with human subjects of research. One obvious reason is that the design of a research study, unlike clinical medical practice, includes the use of controls. This reflects genuine ignorance of the outcome, acknowledging the possibility of spurious associations, previously unrecognized common causes, etc., in a *principal* effort to advance knowledge rather than to protect or to treat *all* participants. By contrast, the protective use of PB and BT in the Gulf War was not part of some general research study involving controls, but was aimed specifically at treating *all* troops at risk of attack involving biochemical weapons. And this makes its nature—as *treatment* rather than research—clear.

It is instructive to contrast this sort of case with a clear example of something that does clearly count as military *research* on defense mechanisms relation to biochemical threats. Operation Whitecoat was a series of experiments on human subjects carried out in the U.S. between 1954 and 1973. The subjects were Seventh Day Adventists who were conscientious objectors and served in non-combat positions of various sorts, including service as test subjects. They were told about each experiment, and after a period of some days to consider the details and to ask questions, they were then asked to provide informed consent if they still wished to participate. (Recruits could be conscientious objectors without joining Operation Whitecoat, and even then could decline particular protocols, so that there was no obvious coercion to participate.[23]) The subjects were also told they would be cared for if taken ill, and while some did become ill, no subjects died during the operation or later of causes attributed to it. The work involved testing, by direct exposure, the efficacy of vaccines and therapies for a variety of infectious diseases thought to be likely risks from biological weapons attacks, and the trials were run under controlled conditions. In other words, the trials were explicitly carried out as research, not in any sense as preventive or therapeutic treatment for the participants, setting this sort of case—with its sole aim of advancing knowledge—clearly apart from cases involving the protection of troops in combat situations.

The absolute requirement for free and informed consent in any such research project aimed at producing generalizable knowledge and not treatment may be taken as given. But when the issue is not such research, but instead the coordinated effort to protect troops in combat from biochemical attacks, then the use of innovative treatments where there is no satisfactory alternative need not in itself compromise the ethical principles at issue—even where consent is not obtained because this might be unfeasible. Indeed, it is the *very same* concern for persons that largely justifies, at least in principle, the call for potentially innovative uses of drugs and biologics in combat exigencies. As noted before, this is not the whole story, because the concern is not solely with the individual's health for its own sake, but also with his or her fitness the sake of *others* who depend on it; and even the collective well-being is viewed by the military as important not only intrinsically but also for the sake of the military objectives in question. But the existence of these further instrumental interests in the individual's well-being does not undermine the fact that the administration of the compound *is* being done to protect the individual, rather than to use him or her as an unwitting "research subject": it is simply that in a military context this aim is pursued for *multiple* reasons, rather than *only* for the sake of the individual as such. If those further reasons are legitimate ones, as must in general be possible unless we reject the institution of the military itself as inherently illegitimate, then they need not contribute to any disrespect for the individual who is being protected (though they *may*, if the various considerations are not properly balanced according to reasonable standards of proportionality, as discussed further below). It is thus plainly an exaggeration to suggest, for example, that mandatory innovative treatment measures necessarily "treat servicepersons as nonpersons, obliterating their individuality and rendering them

fungible."[24] Such measures instead treat them precisely as *servicepersons*—persons who have voluntarily (in the U.S. at present) given up a measure of autonomy with respect to certain decisions in order to facilitate the cooperative achievement of certain objectives.

It is important, then, to distinguish between *plausible off-label uses of approved compounds*, characterized by the primary and sufficient aim of preventive or therapeutic treatment, on one hand, and various forms of *research*, characterized by such primary and sufficient aims as the testing of hypotheses and the advancement of general knowledge, as through the use of controlled studies. Both of these may fall under the general *legal* or *regulatory* category of "investigational" uses, but the deep differences in intent, justification and structure warrant their careful separation for purposes of *ethical* assessment. Whether a product counts as investigational or not can turn on something as specific as whether it has been shipped across state lines for a purpose other than the labeled indication—something that is legally significant, perhaps, but not of any obvious ethical significance to the recipient. Similarly, a drug's investigational status may just be largely a result of the fact that few manufacturers identify the military as a potential market justifying the expense and risk of product development—so that "prevention of effects from biochemical weapons in military service" is not, in any event, likely to appear as an indication on the labels of many approved products.[25] But again, it is a mistake to allow such factors and related regulatory categories to determine our thinking about the relevant ethical concerns, questions and distinctions.

A good example of this tendency to conflate regulatory and ethical categories and concerns may be found in Annas and Grodin's argument that the military's use of PB, for example, could not relevantly count as *treatment*. They note that the DoD "recognized [such] products as investigational when it requested an exemption to use them without its troops' consent," and they find it contradictory "that the DoD needs a special exemption from its own *research* regulations to provide *treatment* for its troops"; for "if treatment were really at stake, no exemption and no consent would be required: the U.S. military can treat its troops at will because they have an obligation to remain fit."[26] But this is simply to beg the question against their opponents, assuming without argument that "treatment" *in the ethically relevant sense* must be understood simply in relation to actual regulatory stipulations, so that nothing that might require a special exemption for particular reasons can possibly count as treatment. But one can surely grant that a product has the *legal* status of being "investigational," so that its use requires a special exemption as a matter of regulatory fact, without denying that for purposes of *ethical* assessment it is a case of treatment—any ethical concerns arising only insofar as the specific reasons for its investigational status are ethically significant.

There is thus no obvious reason, if we are careful to keep regulatory and ethical categories distinct, to conclude as Annas and Grodin do that "it is the experimental or investigational nature of the intervention, not the intent of the physician or researcher, that determines whether or not an intervention is research or therapy," and hence determines what ethical standards are appropriate for evaluating it. Indeed, our point has been that the "investigational" nature of an intervention by itself determines very little, and that the *aim* of the intervention along with other features of the context—such as the imminent threat of combat, the real need for protection and the absence of comparably effective alternatives—are crucial for determining how we should think ethically about the intervention in question. As one study concludes, the term "investigational" is "a term without precise meaning. It does not demarcate the boundary between research and treatment with a bright orange line. Rather, it constitutes a gray zone in which most of the activity is research, much of the activity involves both research and treatment, and some activity is solely treatment."[27] Or we might say that it is a term that has a precise legal meaning but a vague operational meaning, as products in this category can be in significantly different stages of development, reflecting how well they are understood and the different purposes for which they are administered, all of which makes for varying degrees of ethical significance. The point, then, is that the investigational uses we are discussing—in connection with protecting troops against threats of biochemical weapons—are clearly not research studies, but amount to what might be called "*innovative preventive or therapeutic treatment*" under special circumstances that are *already* recognized to justify other forms of nonconsensual preventive or health-promoting treatment.[28]

This is not to deny, however, that there remain special concerns here, particularly with regard to *preventive* treatment, due to the greater uncertainty surrounding such innovative uses and the increased limitation of personal autonomy that is entailed by waiving the consent requirement. We shall consider these issues in the next two sections, and also return to examine more fully the justification for nonconsensual administration of investigational compounds in certain circumstances.

Innovative Preventive Medicine

Preventive medicine in general raises its own set of ethical concerns, due to the fact that preventive interventions are carried out on presently healthy patients or populations. To foreseeably cause suffering in the course of treatment for a condition from which a patient *is* already suffering is regrettable, but it is distinctly problematic foreseeably to put healthy persons at risk of suffering, as from side-effects or complications of preventive medicine. It has also been suggested by critics of "medicalization" that the

treatment of healthy persons may foster unnecessary anxiety, and perhaps even the feeling of obligation to submit to such medical intervention in light of thoughts mentioned earlier about responsibility to others for one's own health.[29]

The last concern is less problematic for military personnel than for civilians, because service members are already obligated to submit to medical intervention. But questions about the risk of the intervention itself in a healthy patient or population certainly remain. Obviously this needs to be balanced against the risk to be avoided by means of the intervention, taking into account both its severity and the likelihood of its occurrence. For most civilians in the continental U.S., for example, a typhoid immunization, which may result in soreness and systemic illness, is not warranted, though that will change with plans to travel to areas of greater typhoid risk. Our topic here, however, is the protection of troops who face significant risk of attack involving biochemical weapons—in connection, for example, with operations against an enemy that has used such weapons in the past—where the severity of harm would likely be very high. This makes the case for preventive measures correspondingly strong, at least insofar as the risks of the treatment are outweighed by the risks in the absence of it.[30]

One special difficulty, however, about the use of such preventive interventions in this context—even where individual consent is respected—is that service members will tend to lack both the expertise and the access to information that would be necessary for full participation in threat assessment. This naturally imposes a heavier responsibility on officers and members of relevant institutional review boards (IRBs), who are cleared for the information and do participate in that assessment. And this is obviously all the more true where consent is waived and the decision is made *for* service members *by* others.

A serious ethical worry here is that there may be a bias among commanding officers toward using any available preventive medicine to maximize the short term fitness of troops for the sake of present military objectives, without sufficient regard for the long term welfare of
individual servicepersons. Suppose, for example, that in order to keep troops fit for the sake of a certain mission, a drug were administered to protect them from certain temporarily disabling but not otherwise serious effects of some disease or agent they might encounter. Such a use may well be unethical if the mission were of comparably little importance and there were substantial uncertainty about the long term adverse affects of the drug. *Proportionality* matters here as elsewhere, and if individuals are not given the right to make informed decisions about such matters, this places a very heavy ethical burden indeed on those to whom the decision-making falls—particularly the IRBs responsible for informing and reviewing such decisions.

The ethical legitimacy of such nonconsensual and innovative medical interventions will thus turn not only on the existence of a suitable risk/benefit analysis, but on the proper functioning of a suitably constituted IRB that takes the full range of considerations—including the intrinsic value of service members' long term welfare—into account and balances them appropriately in determining whether or not such measures are appropriate on given occasions.[31]
We imagine a range of possible scenarios, including (a) cases where the IRB might recommend a particular compound appropriate for mandated administration without further restriction, (b) cases where the compound might be deemed fit for mandated administration but only to service members to be deployed to a particular high risk mission, (c) cases where the compound is of such uncertain efficacy in the particular situation that might be offered only with (perhaps verbal) consent, and finally, (d) cases where so little is known about the compound that its only proper use would be in controlled research situations. And part of the proper functioning of such an IRB is its being sufficiently respected by the military to be allowed to do its job effectively. If, for instance, the IRB were to advise that the compound were in one of the latter two categories and the military were to override this recommendation and mandate administration anyway, one might expect disciplinary problems among some service members and a wider erosion of trust in senior military decision-makers. Without effective and balanced ethical oversight in place it is doubtful that such limitations on individual autonomy can be ethically justified, as there is simply too much room for decisions to be made with too little weight given to individual welfare as such, and too much given to short term fitness for the sake of other objectives.

The Argument for Waiving Consent

Let us return to the argument for waiving the consent requirement, in certain circumstances, for the use of an investigational drug or biologic in order to protect troops at risk of encountering biochemical weapons. Military medicine is obviously paternalistic in the sense that doctors possess the right to make medical decisions for service members where established preventive or therapeutic treatments are involved. But it is important to see that the justification for paternalism in *this* sense is not merely the thought that this is in *the individual's* best interest, which latter is a more specific notion of paternalism. Indeed, the latter sort of paternalism—making decisions for an individual simply because it is in his or her best interest *as* an individual—has no more place in a military context than it does elsewhere, and would be equally insulting to the individual.

What justifies the compromised autonomy in the military context, as we observed earlier, is the fact that the individual is part of a cooperative group of individuals who depend heavily on each other both for the achievement of their corporate-level military

goals and for their very safety. An individual's heath is not merely his or her own concern, but the concern of those whose lives may depend on it, and of those who are responsible both for protecting the unit and for carrying out the relevant objectives.[32] This is not a paternalistic justification in relation to the individual, as with the justification of a parent's healthcare decision-making on behalf of a child, but an other-regarding justification in relation to fellow service members and to the mission the individual has pledged to serve.

The appeal to "the best interests of the member" in U.S. law governing the waiving of the consent requirement is therefore somewhat misleading: it is doubtful that one can justify coercive medical intervention in the case of a person of sound mind, by appeal to his or her own welfare itself.[33] The commanding officers' duty to protect servicepersons does not plausibly imply a paternalistic duty to protect individuals from themselves, as it were, e.g. where someone might prefer to forego a vaccination that the military believes is in his or her best interest. It rather involves the protection of servicepersons as members of a body of mutually dependent individuals, so that if an individual is ordered vaccinated against his or her will, the reason is not simply that this is judged best for that person, but that it is judged of sufficient importance to the safety of fellow service members and to the carrying out of the mission. And the structure of this justification is the same whether we are discussing the nonconsensual administration of a standard vaccine or a special nonconsensual administration of an investigational vaccine through a waiver of the usual consent requirement for such compounds.

By clarifying the non-paternalistic nature of the justification for nonconsensual medical intervention, we can better see that such intervention need not involve any failure to respect the dignity of the individual. A paternalistic justification—where a military doctor orders a serviceperson to submit to an intervention for his or her own good simply *as* an individual—would arguably fail to show respect for the individual's autonomy to make his or her own decisions on matters that simply affect *him or her* individually. But a justification that appeals to the individual's duties to fellow service members and to commanding officers does not similarly denigrate his or her autonomy: for though it implies limitations in the scope of the individual's *exercise* of autonomy, those limits are justified by the weight of the competing considerations in the special context of the military organization, and not by any denial of his or her decision-making capacities.

Having said that, however, it is important not to understate the significance of such limitations in the scope of the exercise of autonomy. Howe and Martin argue that the principle of *respect for persons* that is normally satisfied through protecting autonomous decision-making may instead be satisfied in the present context simply by "maintaining the military's explicit and implicit promise to servicepersons to protect them from unnecessary harm," along with providing servicepersons with information about the investigational compounds they are being ordered to take.[34] This position would in principle be supported by their claim that "the serviceperson freely agrees when joining the military to relinquish individual autonomy" to various degrees under various circumstances. For that free agreement is *itself* an exercise of autonomy, tying later limitations in the exercise of autonomy to a legitimate autonomous act of the individual. The problem, however, is that as things in fact stand, the free agreement to which they appeal here is far too broad to support their position satisfactorily.

Recruits certainly understand that they are forfeiting some autonomy when they enlist, and that they may be ordered into dangerous and even life-threatening situations. But even an agreement to accept orders to put one's very life on the line in certain circumstances does not entail an agreement to forfeit one's autonomy generally. No one thinks that because a recruit is willing to be ordered into battle he or she has therefore indicated a willingness also to be ordered to participate in dangerous research studies, or to donate an organ to a fellow soldier—even if the risks of such activities are *lower* than those of the battlefield. Now we have argued that under certain circumstances there *is* ultimately justification for nonconsensual medical interventions involving compounds not approved for the use in question. But we cannot simply assume that a recruit *understands* this to be implied as part of the sacrifice of autonomy. Such a possibility will never even occur to many recruits at the time of enlistment, when they may have only a vague understanding of what forms of autonomy they are or are not forfeiting. Yet if the autonomous decision to enlist is to make up for specific later limitations in the exercise of autonomy, then clearly that decision must be made with an awareness of *those* limitations—at least where especially significant forms of autonomy are involved, such as a say in what is done to one's own body in the name of medicine. At present, there is nothing we are aware of in the enlistment documents for the armed forces of the United States that calls a recruit's attention to the issue of possible nonconsensual use of investigational medical interventions.

We suggest that appropriate respect for persons as autonomous agents can be shown only if good faith efforts are made to inform recruits of at least the central forms of autonomy they are freely subordinating when they enlist, so that the latter act allows for a meaningful tracing of later possible limitations in the exercise of autonomy to the agent's own informed, autonomous decision. This idea has been discussed under the heading of "*anticipatory consent,*" which could in fact take place at various stages, such as recruitment, basic training, or just before a deployment where nonconsensual use of investigational compounds is likely to become an issue.[35] Obviously such anticipatory consent at the time of recruitment would be very limited in detail, b ut this is the stage where the explanation of the new relationship within which the medical intervention might be ordered is appropriate. Limitations on the expression of autonomy can be less of an affront to the dignity of the individual as an autonomous agent if he or she has earlier made an informed autonomous decision to take the risk of being placed in such a position of diminished exercise of autonomy.

This would not—indeed could not—require a detailed knowledge, at the time of recruitment, of what biochemical agents are likely to be encountered where, what investigational drugs or biologics are likely to be used, with what risks, and so on. But there is no reason that recruits in the U.S., for example, could not be made explicitly aware of the provisions of section 1107f of Title 10 of the United States Code (described earlier), just as they are made aware of the relevant regulations concerning illegal drug use, and similarly required to indicate their understanding and acceptance of it; this would constitute an explicit agreement to receive investigational interventions as ordered, should that circumstance arise. It is doubtful that such a practice in connection with enlistment would place an undue burden on the military or significantly hurt recruitment, given (i) that recruits are already willing to put themselves in potentially lethal danger, (ii) that the prospect of such nonconsensual interventions with investigational compounds is restricted to particular military operations where they would be in danger in any case, and (iii) that those compounds are, in the best available medical judgment, their best protection.

What might hurt recruiting is the perception that the military would be likely to make such decisions in a way that failed to give proper weight to servicepersons' long term welfare, as discussed earlier. But if the military is worried about this perception, that is simply further reason to guarantee that there is sufficient and effective oversight by an appropriately constituted IRB, and to make this known to the public and to recruits. If servicepersons are already willing to trust their commanding officers with their lives, there is no reason they will not equally be willing explicitly to consent to this subordination of autonomy in relation to medical interventions, as long as the above conditions are met. The real concern about this proposal is a different one: namely, that the anticipatory consent could easily become just another form to sign, of little apparent importance at the time and hence of little real significance. We could avoid this however, by treating it as an essential part of the explanation of the individual's relationship with the military, and the reasons behind the sacrifices he or she is being asked to make.

Conclusion

We have argued that in circumstances where troops are faced with a threat of attack involving biochemical weapons, and the best protection for them appears to be a uniform intervention using an investigational compound, then the military's duty to protect its troops may justify nonconsensual use of such a compound. Such justification requires a careful distinction between treatment (including innovative preventive treatment) and research, and between paternalistic and non-paternalistic rationales for nonconsensual treatment. When the relevant points are kept clearly in mind, such nonconsensual interventions may be seen to be compatible with respect for persons as autonomous individuals (even where the scope of their exercise of autonomy is necessarily restricted), and to bear no problematic resemblance to the use of servicepersons as involuntary human subjects of research.

In order fully to satisfy the requirement of respect for persons, however, the possible limitations in autonomy must be traceable back to an informed, autonomous decision on the part of each individual to forfeit such forms of autonomy in such circumstances. This is a condition that does not presently appear to be built into recruitment practice in the U.S., and yet seems important to the proper justification of waiving the consent requirement for the use of investigational compounds. Moreover, the latter can be justified in practice only insofar as certain ethical hazards are carefully guarded against by a suitably constituted and effective IRB, whose functioning is not hindered by military command. Finally, despite the existence of a sound justification for waiving the consent requirement for the use of investigational drugs or biologics under certain circumstances, it may well be that a better approach is to modify regulatory practices, as by adding a special category (or range of categories) of licensing for such particular uses as the protection of troops from biochemical weapons, so that the special waiving of consent for investigational compounds needn't arise. Our primary concern here, however, has been to illuminate the ethical issues surrounding the nonconsensual administration of such compounds for the sake of protecting military personnel, however exactly those compounds are categorized for regulatory purposes.[36]

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[1] The opinions expressed herein are the author's and may not reflect those of current or former employers.

[2] United States Code, Title 10 (Armed Forces), Subtitle A (General Military Law), Section 1107f (henceforth 10 U.S.C. 1107, etc.).

[3] From the report by B. Garland, on the "Bioethics and Bioterrorism" conference at the National Press Club in Washington, D.C., 28 February 2002, in *The Journal of Philosophy, Science and Law*, Vol. 2,

March 2002.

[4] See G.J. Annas and M.A. Grodin, "Commentary. *The Hastings Center Report* (March-April 1991): 24-27, which will be critically discussed below.

[5] Federal Register, May 31, 2002; 67(105): 37988-98.

[6] This case has been pressed by Arthur O. Anderson
, M.D., Chief, Department of Pathology and Office of Human Use and Ethics, and Chairman of USAMRIID Human Use Committee, Fort Detrick, first in a memorandum to U.S. Army Medical Research and Materiel Command (6 December 1994) and a letter to Mary K. Pendergast, J.D., Deputy Commissioner and Senior Advisor to the Commissioner, FDA (26 October 1995), and more recently in a memo (11 October 2002) described in a Bureau of National Affairs report entitled “Human Subject Protection Army Researchers’ Plan Seeks Exemption From FDA Experimental Product Safety Rules,” *Medical Research Law and Policy Report*, Vol. 2, No. 2, p. 56 (15 January 2003). It appears, however, that the FDA is instead moving more in the direction of a "Streamlined IND" process that would speed up the approval process for products relevant to protection against biochemical or nuclear warfare. This has already been used in the re-licensing of the smallpox vaccine, for example.

[7] In the wake of increasing concern over terrorism, however, there may be some pressure toward at least incremental shifts away from such emphasis on the individual. See J.D. Moreno, "Bioethics after the Terror," *American Journal of Bioethics*, 2:1 (2002): 60-64.

[8] See R. Bayer, "Voluntary Health Risks and Public Policy," *The Hastings Center Report* (October 1981): 26.

[9] Annas and Grodin, "Commentary,” 25.

[10] Army Command Policy, AR600-20, 5-4: “Command Aspects of Medical Care,” b2.

[11] Jacobson v. Commonwealth of Massachusetts, 197 U.S. 11, 25 S. Ct. 358 (Mass. 1905).

[12] On the concept of role responsibilities, which may extend well beyond any list of enumerated duties, see G. Dworkin, "Taking Risks, Assessing Responsibility," *The Hastings Center Report* (October 1981): 26-31.

[13] E.G. Howe and E.D. Martin, "Treating the Troops," *The Hastings Center Report* (March-April 1991): 21-24, at 23.

[14] Anthrax was until recently an occupational disease of agricultural and textile workers. The anthrax vaccine marketed in the U.S. was first approved in 1970 and the indication on the labeling was “…individuals who may come in contact with animal products such as hides, hair or bones which come from anthrax endemic areas…individuals engaged in diagnostic or investigational activities which may bring them into contact…[and] high risk person such as veterinarians….” Further, vaccines must usually be approved for release on a lot by lot basis, even when the manufacturer is in full compliance, and the manufacturer of the U.S. licensed anthrax vaccine experienced a series of setbacks in achieving compliance with good manufacturing practices (see L.M. Joellenbeck, et al., Institute of Medicine report: *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, D.C.: National Academy Press, 2002). So concerns were raised both about the use of the vaccine in combat conditions and about the lots of vaccine available. Finally, although we deal here only with defense against biochemical threats, some similar issues arise with the military use of certain vaccines for naturally occurring conditions in a particular locale. For example, immunization of troops stationed in Bosnia against tick-borne encephalitis (TBE) again raised concerns because the product,
approved in Europe, had never been approved in the U.S., where TBE does not occur. See:
http://www.armymedicine.army.mil/usammda/info335.pdf and
http://www.gulflink.osd.mil/library/randrep/mr1018.9.chap2.html

[15] See B.A. Golomb, *Pyridostigmine Bromide*, vol. 2 of *A Review of the Scientific Literature as it Pertains to Gulf War Illness* (RAND/NDRI, 1999), ch. 4, at: http://www.gulflink.osd.mil/library/randrep/pb_paper/index.html.

[16] There have been many descriptions and analyses of the DoD's reasoning, but see especially Howe and Martin, "Treating the Troops"; and R.A. Rettig, *Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense* (MR-1018/9-OSD. RAND/NDRI, 1999), ch. 3, at www.gulflink.osd.mil/library/randrep/cover.html

[17] A.O. Anderson, *Memorandum For the Record* (21 September 1990). Subject: "USAMRIID Human Use Committee Position on Waiver of Informed Consent in Wartime."

[18] H. Jonas, "Philosophical Reflections on Experimenting with Human Subjects," chapter 5 in his *Philosophical Essays* (Chicago:
University of Chicago Press, 1980): 108.

[19] See R. Levine, "Commentary," *The Hastings Center Report* (March-April 1991): 27-29.

[20] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report*: *Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (April 18, 1979). http://ohsr.od.nih.gov/mpa/belmont.php3

[21] Ibid., Part A: "Boundaries Between Practice and Research."

[22] Jonas, "Philosophical Reflections on Experimenting with Human Subjects," 127.

[23] Potential volunteers prior to transfer to Fort Detrick were provided with a form for written acknowledgement of the opportunity to participate in experiments, which also made clear the recruit's right to decline any specific protocol. See:
http://www.geocities.com/capecanaveral/hangar/1962/mrvs-ackn.pdf

[24] Annas and Grodin, "Commentary," 25.

[25] Levine makes a related point about the botulinum toxoid vaccine even in a civilian context. While it has long been made available by the CDC for use in certain occupational settings, it has remained "investigational" simply because due to the rarity of botulism, "there is virtually no financial incentive to pursue a marketing permit." ("Commentary," p. 29)

[26] Ibid.

[27] Rettig, *Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense*, ch. 6.

[28] In a letter from Michael A. Friedman, M.D. Lead Deputy Commissioner, FDA, to Edward D. Martin, M.D., Acting Assistant Secretary of Defense for Health Affairs, dated July 22, 1997, the FDA details deficiencies of the DoD in administration and oversight of PB and BT as investigational products. The agreements to allow administration of the products as investigational included detailed requirements for data collection, which the DoD in many cases failed to fulfill. We see no indication that the data required and not produced had any impact either on the health of recipients or on the health of potential future recipients—this latter because the products were not without previous evidence of safety and efficacy in other settings. Certainly the FDA cannot be faulted for requiring what was plainly demanded by current law and regulations; rather, we take this as evidence that the treatment IND is not the ideal regulatory vehicle for innovative use of preventive interventions in the military during a deployment, either from the perspective of the FDA or from that of the DoD.

[29] See M. Verweij, "Medicalization as a Moral Problem for Preventive Medicine," *Bioethics* 13:2 (1999): 89-113.

[30] Particular attention must be paid to vaccines, since unlike a drug or a protective device, the effects of immunization cannot be removed from or washed out of the body when the threat that justified the

intervention ceases to exist (as noted by Annas and Grodin). To date, no long term adverse events have been shown to result from the relevant vaccines. In the case of the anthrax vaccine, the product has been heavily monitored, though very long term data do not exist. The most relevant data may come from studying hyperimmunized personnel at Fort Detrick, Maryland, in which few if any adverse events connected with the immune status of the subjects were observed. See C.E. Fulco, et al. eds., Institute of Medicine report: *Gulf War and Health* (Washington, D.C.: National Academy Press, 2000), and L.M. Joellenbeck, et al. eds. Institute of Medicine report: *The Anthrax Vaccine: Is it Safe? Does it Work?* (Washington, D.C.: National Academy Press; 2002).

[31] Part of what is meant by 'suitable constitution' is the presence on the IRB of at least some members who are not otherwise affiliated with the government (while still possessing security clearance so that they have access to necessary information), to help assure that all relevant interests will be given proper weight. This is explicitly provided for in the Code of Federal Regulations, Title 21 (Food and Drugs), Vol.1, Part 50 (Protection of Human Subjects), Section 23, d2 (i.e. 21CFR50.23d2).

[32] Cf. Howe and Martin, "Treating the Troops."

[33] 10 U.S.C. 1107f: "The President may grant such a waiver [of the consent requirement with regard to the administration of "investigational" compounds] only if the President determines, in writing, that obtaining consent (A) is not feasible, (B) *is contrary to the best interests of the member*, or (C) is not in the interests of national security" (our emphasis).

[34] Howe and Martin, "Treating the Troops," 22.

[35] See Rettig, *Military Use of Drugs Not Yet Approved by the FDA for CW/BW Defense*, ch. 4. There is at present no regulatory mechanism for this form of consent in connection with the possibility of a future need for some sort of "investigational" intervention.

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Return to Home Page

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