

## COMMENTARY

# Darkness in El Dorado: human genetics on trial

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*A recent book by a freelance journalist makes major accusations against genetic studies by J. V. Neel in the Amazon a generation ago. Contrary to these charges, there was no connection of Neel's work with human experiments conducted by the Rochester Manhattan Project twenty years earlier, nor did the studies serve as a control for survivors of the atomic bombs in Japan. Neel was not a eugenicist. His program of measles vaccination reduced mortality, and was not in any sense an experiment. Given the passage of time and lack of supporting evidence, further investigation of these charges is pointless. However, the political climate in which human populations are studied has changed dramatically over the last generation. Unless guidelines reflect an international consensus, the benefits of population studies to human welfare and science will be jeopardized. The World Health Organization guidelines should be extended to cover current research.*

Last September two anthropologists sent an e-mail message to the president of the American Anthropological Association about an impending scandal to be revealed in a book then in press. The principal charge was that the late James Neel deliberately spread measles among the Yanomama Indians of the Amazon. This letter was circulated on the Internet and provoked responses from newspapers and scientists. Reproductions of a few uncorrected proof copies from the publisher were circulated and the main allegations appeared in a lead article (Tierney 2000a), but scientific societies responded cautiously while awaiting the finished book (Tierney 2000b). The dust has now settled, and both the evidence and its implications for human genetics can be assessed.

### **A geneticist in the Amazon**

Neel's career was well established before he turned to Amerindian studies. Attracted to genetics while an under-

graduate, he completed his Ph.D. on mutation in *Drosophila* but became increasingly intrigued by human genetics. He entered medical school and took his post-graduate medical training at the University of Rochester. While there he worked out the genetics of thalassaemia with William Valentine. The exigencies of World War II made him an army officer, and his genetics training led to appointment as head of the programme on genetic effects of radiation in Hiroshima and Nagasaki. As a civilian he took up the chairmanship of the Department of Human Genetics at the University of Michigan, where he carried out important studies in medical and biochemical genetics, including the genetic basis of sickle cell anaemia, effects of inbreeding, diabetes and mutation.

In 1960 population genetics was just beginning to split into epidemiological and evolutionary branches. The theme of human adaptability was part of the International Biological Program initiated in 1962 and active during the next decade. Neel's ambitious vision was to 'obtain as comprehensive a picture as possible of the circumstances under which man evolved', including breeding structure, disease experience and differential fertility as indicators of selection. His Amerindian studies developed the fission–fusion model of population structure, the role of polygyny in natural selection, and the environmental basis of the sensitivity of isolated populations to diseases such as smallpox, measles and tuberculosis. Beginning in 1970 he combined these preliminary studies with his interest in spontaneous mutation, based on the theory of Kimura and Ohta (1969), which was applicable only to stable population structure. Simultaneously he conducted studies on isozyme mutations in children born to survivors of the atomic bombs and appropriate controls. After retirement Neel continued his scholarly activity, with increasing emphasis on ways in which genetics and society interact. For a lifetime of seminal research he received many honours, including membership of the US National Academy of Sciences and presidencies of the American Society of Human Genetics and the International Genetic Epidemiology Society. He died just before Tierney's book went to press.

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## A journalist in the Amazon

Patrick Tierney was an anthropology undergraduate in the 1970s. In 1983 he set out for the Andes to study ritual murder. Six years later, in contradiction to anthropologists, he 'concluded that, among some tribes, ritual murder is a prestigious act. In 1989 [he] decided to study the Yanomami, first in Brazil, where the Amazon gold rush had brought epidemics, guns, alcohol and prostitution, and then in Venezuela' (Tierney 2000a). Having abandoned an academic career, he was now a freelance journalist. He surfaced first in an article by Leslie Sponsel (1998), who cites as 'forthcoming' a book by Tierney entitled *Last tribes of El Dorado: the gold wars in the Amazon rainforest*. The one reference to Neel (on the penultimate page of that article) questions whether medical research was of immediate benefit to its subjects (few among us make that claim). There is no allegation against Neel, and Tierney is not cited among the four references to that query. If Sponsel is to be believed, Tierney had found no reason to besmirch Neel after nine years of journalistic research.

The book cited by Sponsel was assigned ISBN: 067083372X in 1995, but not published. Sponsel was one of the anthropologists who alerted the Internet about Tierney's new book, without divulging that the object of opprobrium had changed from goldminers to scientists. Sponsel and Terence Turner, the other e-mail correspondent, belong to an extreme group of social anthropologists who regard their role as one of advocacy rather than observation. They believe in the nonviolence of 'primitive' societies, and are bitterly opposed to biological anthropology. They are especially critical of the branch associated with E. O. Wilson (1975), who defined sociobiology as 'the systematic study of the biological basis of all social behavior'. He supported his arguments by a magisterial review from invertebrates to man, where distinguishing between the roles of genes and culture is currently impossible. Unless the hypothesized genes can be identified, the impact on human genetics will continue to be small, with no reference in standard texts. However, sociobiology has led to significant observations (and game theory) in evolutionary biology. By entering this fray on the side of the morally engaged militants and borrowing allegations made by Turner (1994) and Sponsel (1998), Tierney became a leader in a field he had abandoned a decade earlier. He writes (p. xxiv): 'I gradually changed from being an observer to being an advocate. It was a completely inverted world, where traditional, objective journalism was no longer an option for me.' It is hardly surprising that his perception of good and evil changed in a way that rivals the conversion of St Paul on the road to Damascus. To borrow Tierney's literary style, the realization that scientists buy more books than goldminers cannot be discounted, nor the misapprehension

that there would be no evidence to defend Neel after his death. Sponsel and Turner are thanked (p. xviii) for 'their comments and encouragement', before the shock they expressed when they saw the galleys.

## The accusations, and a defence

Tierney makes five major accusations against Neel that can be tested.

1. *There is a logical connection between human experiments without informed consent in the Rochester Manhattan Project 1943–1945 and observations in the Amazon 1966–1974.*

Tierney devotes the last chapter of his book to this hypothesis. It includes a pedigree stretching from Rochester to the Atomic Bomb Casualty Commission, isotope studies by Marcel Roche, and 'measles injection'. No motive is suggested, except that 'these men had some of the best minds in the world, but they had gone temporarily unhinged under the stress of the Cold War'. Tierney's allegations have been demolished. Although Neel took his medical training at the University of Rochester, there is no evidence of any connection to the Metabolic Unit in which the physiological experiments were carried out. They had no genetical content. William Valentine, the only survivor mentioned by Tierney, is connected to Neel as a colleague in the 1940s and to the Metabolic Unit by working in a nearby laboratory under the Chief of Haematology. He denied use of radioactive substances of any kind during this period, any approach by the Chief of the Metabolic Unit regarding isotope injections, or any knowledge of these secret experiments until they became public in the 1990s (letter to N. E. Morton, 20.11.2000).

Marcel Roche was a Venezuelan physician who carried out tests with small doses of radioactive iodine. Contrary to Tierney's statement (p. 306), Roche was temporarily engaged in research in the Ocamo Mission, was not part of Neel's team, and did not participate in any genetic study. He has been eloquently defended by Venezuelan colleagues (Bosh *et al.* 2001).

The Atomic Bomb Casualty Commission (ABCC) was not an outgrowth of the Atomic Energy Commission (AEC) or under its control, but was run by the National Academy of Sciences (NAS). It did not participate in human experiments related to radiation. Tierney's multiple errors in describing the ABCC have been detailed by Bruce Alberts, as president of the NAS (National Academy of Sciences 2000).

Without a credible link to the Rochester Manhattan Project, Tierney's other claims are reduced to speculation and misunderstanding.

2. *The Yanomama studies provided a control for survivors of the Hiroshima and Nagasaki bombings.*

There is not the slightest evidence that radiation studies were conducted on the Yanomama or their cells by Neel's group, or that this was ever considered. At the start of the ABCC the nonirradiated city of Kure was taken as a control for Hiroshima. It soon became evident that Kure differed from Hiroshima in many ways and that immigrants into Hiroshima were better controls. Neel promptly discontinued the Kure studies. He was too good a scientist to replace them with Yanomama. It is true that spontaneous mutation rates were and are of basic and practical interest. Neel was fascinated by electrophoretic variants of proteins, the population structure they revealed, and the later revelation that they give indirect estimates of mutation rates. This was an innovative and useful approach to a difficult problem, posing no conceivable hazard to human subjects. For a quarter of a century the AEC was a conduit through which the US government supported research on mutation and human population genetics. Bioethical issues were monitored by universities and other institutions as well as the AEC review process.

Before 1970, direct estimates of mutation were limited to rare dominant genes and isozymes. The ABCC studies were originally limited to complex phenotypes, such as neonatal mortality, congenital malformations and birth weight, that could be compared with controls in the same city. When isozymes were identified by starch gel electrophoresis they were incorporated in the Japanese studies. Then Kimura and Ohta (1969) introduced an indirect estimate based on protein variants in stable populations. Beginning in 1970 this was useful for Amerindians, but its reliability was in dispute and the conditions for its validity were not met in Japan or Michigan.

Tierney did not understand that AEC support to Neel was largely for his Japanese studies of isozyme mutation, secondarily for population genetics of Amerindians, and not at all for comparison of the two. Much later Neel summarized estimates for nonirradiated samples, concluding that the differences were not significant. This increased confidence in the assumptions on which the indirect method depends, but it does not use the Yanomama as controls. No comparison with an irradiated group was proposed or ever made.

3. *Neel was a self-professed eugenicist, and this determined his research in the Amazon.*

On the contrary, Neel was a critic of eugenics from his graduate days. When the Eugenics Record Office was closed and its files offered to Neel, he refused them on the grounds that storage space in his institute was too valuable to waste on worthless records. His last publication (Neel 2000) as he was dying of cancer deplored the ill-conceived Law of the People's Republic of China on Maternal and Infant Health Care, and contributed to the pressure against this law from scientists in China and abroad. (This pressure failed to get the eugenic provisions

modified or rescinded, but at least they are not enforced.) In that paper he advocated that efforts to control population growth be noncoercive and without regard to real or fancied genetic differences among individuals and populations. His neologism for this principle was 'isogenic', which will survive after 'eugenic' and 'dysgenic' have been relegated to history, as obsolete as alchemy. Gene frequency and effect can be discussed without such labels, which Neel used as descriptors and not as policies. Under the circumstances this was not Neel's best scientific paper, but it articulates his respect for the Hippocratic injunction 'do no harm'. Like Sewall Wright, his basic assumptions did not change with his interests. I knew Neel well for 50 years. He did not entertain eugenic fantasies.

Unfortunately, as a nonscientist Tierney could not distinguish between eugenics and evolutionary theory. Neel was attracted to the proposition that whatever genetic qualities might predispose to being a headman, they would be favoured if, as is the case among the Yanomama (Biocca 1996), headmen acquired more wives than other, less successful men (Neel 1994, pp. 178–180, 302–303). The syllogism is impeccable, but there is no evidence on the magnitude of any effect. Neel admitted failure to devise a test of headmanship, without which heritability cannot be estimated (and would be unreliable if it could be estimated). To *isolate genes for male leadership* lies far beyond our capabilities now, and no scientist would have hoped to do that a generation ago. The hypothesis may violate some notions of political correctness, but speculation is perfectly ethical. No one familiar with Homer's *Iliad*, in which the war against Troy was started by abduction of one woman and almost abandoned in a dispute between headmen over possession of another, will argue that it is demonstrably wrong.

4. *'It cannot be determined with any accuracy how many died after receiving the vaccination' for measles (Tierney 2000a).*

Sponsel and Turner interpreted this to mean that 'hundreds, perhaps thousands' of Yanomama died as a result of vaccination. In response to a flood of contrary evidence from measles experts (see, for example, Katz 2000), they insisted that they were reporting an allegation without accepting its veracity. Tierney then made minor changes in the galleys for his book, without altering pagination. Having done his best to smear Neel and his team, he retreated to (International Genetic Epidemiology Society 2001): 'I don't think their intention was malicious at all . . . I do not claim that it was done deliberately and I do not reach a clear conclusion about whether or not their vaccination was responsible for the spread of the disease. What I do show is that it was reckless behavior. There was widespread distribution of trade goods and filming during the epidemic that certainly contributed to its spread beyond its original point, and some people who

were vaccinated died, which is a terrible thing.’ A reader of Tierney’s book or subsequent statements must admire how completely he has assimilated the ‘invaluable legal advice’ he acknowledges in his book (p. xviii), leading to revision that is contradictory enough to be defended against a libel suit.

Tierney attacks the choice of measles vaccine. Samuel Katz, a paediatrician who spent 44 years studying various vaccines, especially measles, wrote in rebuttal (Katz 2000): ‘Edmonston B vaccine which Neel administered at a time when an epidemic of measles was already underway [Neel *et al.* 1970], was a scientifically established and proven method of attempting to interrupt an outbreak. Nearly 19 million infants and children between 1963 and 1975 in the United States and internationally received this licensed (by FDA) vaccine with or without immune globulin. Vaccine virus has never been transmitted to susceptible contacts and cannot cause measles even in intimate contacts.’ Katz and Mark Papania, another measles expert, have stated that they were extensively misquoted in Tierney’s book, which misinterpreted the observation that in the history of measles vaccination there have been only three attributable deaths, all of individuals immunosuppressed by cytotoxic chemotherapy or immune deficiency syndrome. Tierney specifically misinterpreted ‘immunosuppression’ to include illnesses like dysentery, anaemia and malaria. Therefore the standard precaution that ‘vaccination with live attenuated measles virus is absolutely contraindicated in immunosuppressed patients’ (Weatherall *et al.* 1983, p. 5.480) was misapplied by Tierney to all Yanomama. ‘If Sam Katz had originally told me this vaccine could never start an epidemic, I don’t think I would have pursued this study’, Tierney has said (Mann 2001).

Tierney has identified only one individual who was allegedly vaccinated and died ‘about a week’ later of alleged measles. After more than 30 years the ascertainable facts are scanty. According to Tierney, vaccination was recalled by the boy’s father. Measles was diagnosed, with bronchopneumonia, by the priest at the Mavaca Mission where ‘the French doctors were’. The patient’s family had come from Ocamo Mission, where a measles epidemic was raging, complicated by a high incidence of upper respiratory tract infections that had caused several deaths near Mavaca in the two months before the measles epidemic. Was the patient infected with measles before alleged vaccination, which does not protect against infection by exposure more than 72 hours earlier? The vaccinations at Ocamo before Neel arrived were given without measles-immune immunoglobulin (MIG), and the reaction was ‘unquestionably more violent’ than with simultaneous treatment (Neel *et al.* 1970). Could a strong reaction, mistaken as measles, have been coincident with fatal bronchopneumonia?

These more or less plausible scenarios that might be entertained by a naive reader of Tierney’s book are

probably wrong. A search of Neel’s field notes at the University of Michigan by William Oliver (Oliver 2000), Emeritus Professor and Chairman of Pediatrics at the University of Michigan, has no record of Vitalino Baltasar or his son Roberto receiving measles vaccine. It was contrary to the protocol to vaccinate all family members. The father sought medical care on 5 February 1968 and was seen by two physicians, Neel and Willard Centerwall. He was very febrile with intense conjunctival injection and rashes atypical for measles. He was given penicillin. Two days later he was seen by a French physician working at Ocamo, still with conjunctival injection but no signs of pneumonia. He was given terramycin. On 13 February Roberto was brought to Ocamo and seen by Neel, who wrote that the infant had signs of pneumonia but no rash. He was given penicillin, terramycin and a cardiac stimulant, and quarantined in the infirmary. He died on 15 February. Dr Oliver suggests that father and son had wild measles but were atypical cases without the classical rash. Since exposure, vaccination and diagnosis are uncertain and the Mavaca Mission is not mentioned, the accuracy of Tierney’s additions to the story is in doubt. His unreliable recall of this sad history a generation later without consulting Neel’s medical notes for Roberto is the only support for the last-ditch bleat that ‘some people who were vaccinated died’.

Neel *et al.* (1970) expressed regret that their observations as physicians were fragmentary. Hearsay testimony assessed by Tierney 30 years later is much worse. No deaths in this epidemic or the others that have occurred in Neel’s absence can reliably be assigned to individual journalists, scientists, goldminers, or other visitors. Any effect of researchers on the considerable mobility of Yanomama, missionaries and others along the Orinoco is obscured by the passage of time and lack of critical observation.

##### 5. *The vaccination programme was an experiment.*

Neel’s studies did not include experimentation, and therefore his 1967 grant application is marked ‘No’ with the annotation ‘(not in the usual sense)’ against the question ‘Does the proposed study involve human subjects?’. This was the first year that this box appeared on the face page of the grant applications. It is still debated what ‘informed consent’ implies for participants in nonexperimental studies on a nonacculturated population that is largely illiterate and does not comprehend population research.

All available evidence supports a benevolent vaccination programme added on to Neel’s research solely with the ‘humanitarian implications of extending proper medical services to the Indian’ (International Genetic Epidemiology Society 2001). The measles epidemic that he had foreseen from his serological survey in 1966–67 broke out three months before he returned to the Amazon with vaccine and antibiotics. The time he devoted to

medical care to the detriment of his research is well documented. Not only is there unequivocal evidence that Neel was a conscientious and energetic physician, but he had no motive to behave differently in the Amazon. His studies depended on the Yanomama being numerous, healthy, at peace with one another, and friendly with his team. Any conduct that destroyed these conditions would have been both criminal and insane. The only evidence of such conduct is an entry in the index to Tierney's book (p. 407), which cites 39 pages devoted to the 'measles vaccine experiment' that he now denies.

The accusation has been repeated by social anthropologists with diminishing conviction. The prepublication sensationalism (Brown 2000) was: 'Two anthropologists who have read proofs of the book say it shows that the leader of the measles expedition, James Neel, was a callous, manipulative figure, who coldly observed without intervening as hundreds of Indians fell victim to a disease that he either started deliberately, or at best, let rage unchecked. One of the anthropologists who has seen the book, Terry Turner of Cornell University, says that Dr. Neel deliberately used an unsafe measles vaccine on the Yanomami, without consulting medical experts or the Venezuelan government, held his team back from giving medical help to the sick and dying, and sought to use the tragedy to back up his "fascistic" theories of the survival of the fittest humans.' The idea of using deaths in a measles epidemic to count wives would not occur even to Dr Mengele, with whom Turner compared Neel, and reflects as much on the accusers' wit as on their taste.

Less than three months later and at a higher level a member of the NAS wrote (Sahlins 2001) that Tierney's indictment was 'well-documented speculation', but 'it became clear enough that Neel could not have originated or spread genuine measles by the vaccine he administered. Tierney then revised the conclusion of the relevant chapter in the published version, making the vaccine issue more problematic and, to that extent, the chapter self-contradictory. Other issues such as whether Neel was doing some kind of experiment that got out of hand, remained unresolved.' Even for a social anthropologist presumably familiar with the writing of Franz Kafka, it must seem strange to call an unsupported allegation of an unspecified experiment with no apparent motive an 'unresolved' issue, especially in a country where nominally guilt must be proven. Guilt by inclusion in an index falls short.

### **The ultimate expert committee**

Although expert groups have rejected Tierney's subjective claims, they are accepted by many people who have read the book and newspaper articles about it without questioning their veracity. The two cultures of C. P. Snow are as antagonistic as ever. To a scientist Tierney represents ignorant speculation, misrepresentation, and

unsupported reports of alleged conversations. Social anthropologists tend to be distrustful of human biology and find its venepuncture and ID numbers distasteful and incomprehensible. They prefer norms, not frequencies. Perhaps it is enough for them to think that the preferred marriage in America is with the boss's daughter, without asking whether that is common. In the field do they not need more than a notebook and preconceptions?

In the last century Ruth Benedict (1935, 1946) took social anthropology by storm. Following Nietzsche, she claimed that a society is restrained ('Apollonian') or uninhibited ('Dionysian') to an extent that may be measured by the strictness of child rearing. This hypothesis was reluctantly abandoned not because it is preposterous, but because it is untestable, without any of the venom directed at sociobiology. Nietzsche and Benedict were inside social anthropology, Wilson is outside. To a social anthropologist Tierney has the right training (but sadly incomplete) and his speculations are 'well-supported' (Sahlins 2001), although (Geertz 2001) 'the result is uneven, in many places vague or unsubstantial, and in some it is, as the critics have charged, simply unfair – ideological second-guessing. But as the instances accumulate and their implications come home, it all, in some strange way, begins to add up.' Each false or unsupported allegation decreases Tierney's credibility to a scientist, but to a social anthropologist Tierney becomes a trustworthy ally in the crusade against sociobiology, with Neel not as apostle but as proxy.

The Neel affair has now been reviewed by many individuals and groups with different expertise, interests and credibility. Inevitably this mass of testimony is hard to digest. An unknown commentator (Anonymous 2000) has proposed a radical solution in a journal that favours unknown commentators. Dismissing statements by expert groups (individuals are not worth mentioning), he or she concludes it 'is imperative that a complete investigation is carried out by an independent agency or commission'—not to formulate international guidelines for future research, but to investigate poorly documented events and motives in the Amazon a generation ago under the guidelines of the day.

There is no international agency with the same *gravitas* as the World Health Organization (WHO). For lack of funding the Human Genetics Unit at WHO is suspended at a time when the growth of genetics is arousing bitter prejudice. The International Federation of Human Genetics Societies has three full members, leaving Asia, Latin America and Africa unrepresented. The anonymous commentator is right to question the objectivity of the American Association for the Advancement of Science (AAAS), which has no international dimension and refused to be judgemental about a physical attack on E. O. Wilson when he spoke at their invitation. The National Academy of Sciences, Academia Brasileira de Ciencias, American

Society of Human Genetics and International Genetic Epidemiology Society are disqualified by having issued the results of their investigations.

Since no existing agency is acceptable, how would a commission be selected? Medicine, anthropology and genetics must have voices. In fairness to Tierney, should failed graduate students and muckrake journalists be represented? Ethicists need not read history, law, or philosophy, and may know no more science than an aromatherapist. Nevertheless *ex post facto* ethics is big business, although *ex post facto* laws are illegal. Certainly ethicists should be included, but pronouncements by such an *ad hoc* commission are unlikely to gain wide acceptance.

The most perceptive sentence in the commentary (Anonymous 2000) is that 'the rights of host governments, indigenous peoples and various other interests must all be considered, in a political climate starkly different from when the Neel/Chagnon team first trekked into the forest'. In short, ethical issues have not changed, but political correctness eclipses them. The French and American declarations of universal human rights overthrew centuries of rights awarded to particular classes, ethnic groups and religions, but the last century saw reiteration of such privileges by Fascist and Marxist governments and most recently by ethicists. In this environment any attempt to fine-tune a statement of principles is likely to be controversial and ephemeral. This does not mean that the attempt should not be made, but that 'an independent inquiry' does not provide an enduring answer.

Hearsay evidence about incidents a generation ago on which objective evidence is lacking or equivocal will probably never be investigated in a society that presumes innocence unless guilt is proven beyond reasonable doubt. That should not concern us. To seek a mote in a dead brother's eye is a mug's game, neither gentlemanly nor productive. The unconsidered beam in the ethicist's eye is the result of the diversity of situations to which general principles apply. Patients, participants in genetic studies, their uncontacted relatives, informants, DNA donors, and subjects in clinical trials have different risks, motives, expected rewards, and often cultural values. The more specific the guidelines, the more restricted their future applicability. Extension should not be attempted to the past, when the same principles but different guidelines were followed. Unless a consensus is reached on these rules of engagement, human biology will be seduced by the maxim of armchair anthropology: 'Stick close to your desks and never go to sea, and you all may be Rulers of the Queen's Navee.'

The temptation to do fieldwork is eroded if political correctness dictates that it should be funded only under guidelines that guarantee failure. Fieldwork in the last century is a subject for historians. We must look to the future if research on human populations is to survive as an international effort.

## Toward ethical guidelines

Neel was elected chairman of two WHO scientific groups that dealt with research in population genetics of 'primitive' groups (World Health Organization 1964) and research on human population genetics (World Health Organization 1968). The last section on 'relations of the research team with the population studied' was virtually unchanged. After more than 30 years it remains the only set of guidelines in this field. As the nearest population genetics has come to the Hippocratic Oath, it provides a basis for elaboration to cover current issues (table 1). The situations to be covered by extended guidelines include but are not limited to the five categories of participants in a population study (table 2).

A *human subject* is uniquely defined by participation in an experiment (clinical trial). Any individual who participates in a medical experiment is a human subject. No individual who is not part of an experiment is a human

**Table 1.** The World Health Organization (1968) guidelines for research in human population genetics.

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Any research team has ethical obligations to the population under study. The investigator should always be bound by the legal and ethical considerations governing the conduct of medical and biological research workers. It is essential that harmonious relations be maintained both during and after each research visit. From previous field experience, the following factors have been found to be especially important.

- (a) The privacy and dignity of the individual must be respected at all times and the anonymity of subjects must be maintained in publications. The comfort and individuality of subjects must be safeguarded, e.g. some people are unwilling to queue, or to have others present during examination or questioning. Care should be taken that individuals do not undergo an excessive number of examinations at any one time.
  - (b) Satisfactory reward should be provided for the subject's participation in the research and for any services provided. The nature of the recompense should receive careful consideration. The advice of local authorities may be invaluable, both on this question and in general, so as to avoid giving offence through ignorance of local customs.
  - (c) The local population should benefit from such studies by the provision of medical, dental and related services.
  - (d) The maintenance of congenial social relationships will be enhanced by methods suitable to particular areas, e.g. eating with families on occasion, exchange of information.
  - (e) All groups have learned individuals, e.g. experts on oral traditions and those with systematized knowledge and interpretations of natural phenomena. Consultation and exchange of information with such persons will often be of value to ensure good relations and lead to the appreciation of the achievements of such peoples. Such information is pertinent to their cultural and therefore biological history.
  - (f) There should be the utmost regard for the cultural integrity of every group. All possible measures should be taken to prevent the activities and presence of the research team from adversely influencing the cultural continuity of the population being studied.
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**Table 2.** Categories of participants in research on human genetics.

Category of participant	Informed consent	Experimentation	International guidelines
Human subject	++	Yes	Declaration of Helsinki (1996)
Patient	++	No	World Health Organization (1998)
Informant	+	No	—
Other	+	No	—

subject. A *patient* is entitled to the same high requirement for informed consent. Both categories are covered reasonably well by existing international guidelines supplemented by national statements, rules and laws, which do not apply to the remaining categories.

An *informant* may or may not be a patient and is almost never a human subject. Typically an informant provides information about his genealogy, perhaps but not necessarily with hearsay evidence about medical conditions in relatives or members of the same community. An informant may therefore be a register of individuals with a particular diagnosis. *Other* participants include relatives of informants and individuals in an experiment or cohort or case/control study. An uncontacted individual is not a participant. If contacted, he may accept or refuse to be a participant.

Principle a of table 1 must be extended to include the confidentiality of this information and to recognize that initial contact with other individuals should ideally be through the informant. Alternatives may be acceptable under certain circumstances, which should be defined in accordance with community values and facilities that determine how conditions of privacy, dignity, comfort and individuality are assured in identification and examination of patients.

Principle b raises difficult problems. Developed societies permit recompense for surrogate motherhood and adoption, but forbid purchase of organs. Donations of blood or semen are recompensed in some countries, but prohibited in others. Many cultures have traditions of gift-giving that cannot be violated without causing offence and jeopardizing research. On the other hand, a universal policy of material recompense adjusted to per capita income would encounter ethical reservations in some countries and the question of equity in others. 'Ignorance of local customs' is as great a problem today as a generation ago. Whatever compromise may be proposed is not likely to be considered ethical 20 years from now.

Principle c raises similar problems. Provision of medical services by investigators competes with research objectives and with governmental, missionary and private initiatives. Anthropologists and other investigators who are not medically qualified cannot themselves provide such services, but should not be less accountable. The extent and duration of services are not calibrated by general principles of beneficence and justice, and will remain controversial.

Application of principle d is now much more complex. Any international research programme requires strong and equitable collaboration with investigators within the host country. Besides joint publication, this ideally includes shared funding, workshops and training. Assertion of 'group rights', although it has a tragic history, is inescapable (Weiger *et al.* 1999). In practice there are many competing spokesmen claiming to represent villages, tribes, nations, ethnic groups, government bureaux, missionaries and researchers in the host country. They do not speak with one voice, but all demand a role in decisions. Good relations with all of them must be sought. Guidelines appropriate to the culture of the researchers do not take precedence over guidelines in the host country.

Provision e includes specialists in genetics, public health and anthropology of the population under study. Familiarity with the languages of that population and its experts is useful, and sometimes essential.

Provision f has the broadest cover. Every contact of a native population with an invasive culture is disruptive, whether the outsiders bring goldmining, ranching, diversified agriculture, lumbering, religion, money economy, or merely different knowledge and beliefs. Every contact with unfamiliar disease brings heavy mortality. The Indians of the United States were reduced in 1900 to only five per cent of their numbers before European contact. It is too late to undo these catastrophes, to which the contribution of scientists is not measurable, but assurance should be given that research activities are not maleficent. Where the cultures of the participants and researchers are in conflict, they should be reconciled in a way that respects the host culture without sacrificing beneficent research.

Obviously these suggestions fall short of guidelines that must be written by an international group. Although this is a controversial area, there is no reason why research on human population genetics should not have safeguards as appropriate as the existing guidelines provided by the United Nations and WHO for clinical trials and medical genetics.

However, it will be many years and perhaps centuries before human research enjoys as much consensus as medicine, which itself is not without controversies as the tempo of medical progress accelerates. Many of the provisions of detailed guidelines are neither ethical nor legal, and will not be accepted for long. Such ephemera have no relevance to research conducted in the past in accord with

principles generally accepted at the time, nor to specimens from that research.

The object of research in human populations is not to advance the careers of researchers, nor solely to advance basic science. Without beneficent investigation a nation stagnates and cannot solve problems raised by an ageing and increasing population, diminishing resources, evolving pathogens, and competition from more enterprising societies. To let research on human populations languish because guidelines are in flux is not merely wrong: it is a mistake.

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