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Race and Hypertension Science and Nescience

Richard S. Cooper, Jay S. Kaufman

Although race is widely used in hypertension research as a marker of increased risk, its meaning as an etiologic quantity is obscure.¹⁻⁵ Because of its importance as a social category in American life, separating what we “know” about race through socialization from what can be known on the basis of scientific inquiry is difficult.⁶ This dilemma represents a specific example of how social influences impact the conduct of science. While the process by which evidence is gathered and evaluated is usually constrained by an existing theoretical model (the “hypothetico-deductive process”), hypotheses arise more informally from the interplay of “inspiration” and “intuition.”⁷ Although hypothesis generation is at the core of scientific activity, it is peculiarly vulnerable to the influences of ideology. Contemporary perspectives on science as a practical human activity thus acknowledge that inspiration and intuition are the products of imagination and, as such, are derived from the investigator’s experience—both inside and outside the laboratory.⁸

While it is necessary to take account of the assumptions about race that are generated by our participation in a racially stratified society, it is also necessary to define exactly what we can know about race through the conduct of science. In this discussion, we are interested in moving beyond concerns about social influences on hypothesis generation and will attempt to address the logic of studies that use race comparisons to examine causal relationships. Specifically, we ask the question, “Can available statistical adjustment methods lead to valid inferences when race is regarded as an etiologic quantity, rather than a broad indicator of risk factor status?” Despite the popularity of racial hypotheses, we argue that comparative studies based on observations of broad phenotypes—such as high blood pressure, obesity, or glucose intolerance—have little potential to contribute new knowledge. The attempt to interpret race as a causal entity founders on technical and logical flaws, above and beyond the ambiguity of race as a biological construct. To support that assertion, we review the use of race in hypertension research

and make specific methodological criticisms. We close with a recommendation for at least one alternative direction for etiologic research on hypertension when investigators wish to exploit the “ethnic paradigm.”

Race as Hypothesis

The flaws inherent in race as a biomedical concept have been discussed exhaustively elsewhere.^{4,9,10} As an extension of this discussion, the need exists to examine how those concepts apply to specific areas of health research. Racial comparisons surface with great regularity in the hypertension literature. In Volumes 27 through 30 of *Hypertension*, for example, 30 articles (13% of all investigations involving humans) sought to use this design to support a conclusion about racial/ethnic variation in physiological processes or disease. The underlying hypothesis that emerges from this literature is the existence of innate physiological differences between population groups. This general theory has a long tradition, and a broad discussion has taken place on its historical antecedents and the limitations of its theoretical framework.¹¹ The rationale for gathering data using this model appears to have no clear evidentiary foundation (in terms of the dynamics of human evolution, for example) but grows out of the social reality in which scientists work. We have previously described this process as “circularity.”⁶ Investigators begin with the social reality of racial difference and are motivated by this reality to hypothesize the existence of significant biologic difference. They gather facts based on this theory, accumulating examples of difference for a melange of unrelated physiological quantities, and they conclude that the groups are in fact different. This conclusion of difference is seen as the end in itself, although it merely restates the social reality as putative scientific reality.

Suppose, for example, that one entertained the hypothesis that left-handedness is deleterious in comparison to right-handedness. In gathering evidence to support this theory, one might find that a wide variety of tasks (eg, operating a manual transmission or a can opener) are completed more successfully by right-handed subjects and thereby make a scientific statement in support of the original hypothesis. In effect, this merely restates the social reality (the world is designed for right-handed people) as a scientific finding. It is not a “wrong” conclusion per se, but it has no bearing on the question of etiology (ie, how the world came to be organized in that fashion). Likewise, the practice of haphazardly gathering various examples of racial difference has no potential to reveal the meaning (ie, etiology) of these differences. In the contemporary view of scientific progress, random fact gathering has no potential to increase understanding; it is only in light of some theoretical context that facts are meaningfully interpreted.¹² Given that the theory underlying this version of

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the “ethnic paradigm” involves nothing more consistent than the proposition of racial difference, the facts gathered could never yield more than a circular proof: difference is observed in general, difference is hypothesized, difference is observed in particular, and the conclusion is difference.

Race as Risk Factor

In studies that hypothesize an innate physiological difference between racial groups, the difference in environment between groups (eg, socioeconomic status [SES]) is the obvious competing hypothesis.¹³ The relation between SES and hypertension is well established,¹⁴ as is the racial variation in SES.¹⁵ To address this alternative explanation, most researchers attempt to “control” for SES when making racial comparisons. Reported estimates of independent effects of race are therefore biased if there is residual confounding. In fact, the technical requirements for excluding SES as an alternative explanation are never met in practice: residual confounding due to categorization, measurement error, aggregation, incommensurability, and other factors acts to bias results toward spurious or inflated race effects.¹⁶ Furthermore, the problem of incommensurability (variation between groups in the associations between covariates and outcomes) makes meaningful control a practical impossibility. The concluding statement generally made in studies using control for SES covariates is that the “estimated racial difference persisted after adjustment for SES,” and in fact this may be a correct description of the result. The usual interpretation, however, is that the effect estimated for race is what would have been observed had the groups shared equal social status; this inference, on the other hand, is clearly incorrect. Even if the degree of bias were small, the probability of rejecting the null hypothesis of racial equality increases to unity as the sample size increases.⁶ That is, in a sufficiently large study, racial differences will always persist after adjustment, even if there is in fact no true difference in innate susceptibility between groups. No study can perfectly assess covariate status, especially for quantities as ill-defined as SES, and any residual confounding that results is erroneously attributed to race when this analytic design is used.

Race as Cause

A paradox emerges in research on racial differentials. An enormous breadth and variety of descriptive data are available, and the methods required for simple comparative analyses are relatively straightforward. By contrast, the literature devoted to etiologic or explanatory analyses is impoverished and restricted, invariably defaulting to platitudes about the “interplay of genes and environment.”¹⁷ Furthermore, the logical construct through which the “ethnic paradigm” could be used to arrive at valid causal explanations is surprisingly complex and requires the solution of difficult theoretical and analytic problems. As a consequence, journals are filled with studies reporting shades of difference in health status or function, most of which are likely to be derivative effects from a few fundamental processes. The vascular sequelae of hypertension, for example, are dissected in an endless stream of publications, and more often than not, the investigators speculate broadly about the potential “genetic

differences” that underlie these secondary changes. Yet the structure of the inquiry that could lead one to differentiate a bona fide cause-and-effect relationship from a mere epiphenomenon is never defined. On balance, we have accumulated an undifferentiated mass of descriptive studies that seek to persuade us, by repetition rather than analysis, of “intrinsic differences” between blacks and whites.

Under what circumstances can something be said to be a cause? While this problem is a frequent concern to epidemiologists, it receives relatively little formal attention in medical journals. The Bradford Hill criteria, enshrined in the 1965 Surgeon’s General Report, are familiar enough.¹⁸ Likewise the properties of the randomized experiment, which make it unique as the basis for inference, are intuitively understood within the field. These guidelines, however, are based on implicit assumptions about the putative causal factor under study; the attempt to apply the same logic to race exceeds the limitations of the methods used to make causal inferences.^{19,20}

Defining a framework for making causal inferences from either observations or experiments has primarily occupied statisticians, and discussions of this issue run through the statistical literature from its inception.²¹ The formalization of this historical thread articulated by Rubin^{22,23} and colleagues^{24,25} has had a significant impact on the development of contemporary epidemiological theory. Crucial to this reasoning is the concept of “exchangeability” between alternative states. Formalized within the construct of the counterfactual, a framework is created which asks, “What would the outcome have been were this exposed individual never in fact exposed to the putative cause?” In a randomized experiment, of course, this means that we may be justified in inferring that the collective outcome observed in the treated group would have occurred among the control subjects, had they been treated. With this generalization we are equipped to make logically justifiable conclusions about the effect of an intervention for similar subjects in the future.

For observational studies, however, the criterion of exchangeability is much harder to ensure.^{26,27} Control for confounding through stratification or statistical adjustment is the only recourse available. We can be reasonably comfortable with some forms of adjustment, eg, age standardization, which simply involves the weighted average of strata with no inference about a causal effect for age itself. Statistical adjustment becomes seriously suspect, however, when used to identify the independent effects of attributes that define the essential character of an individual, such as gender and race. For example, a researcher might be interested in determining the degree to which women are more susceptible to depression. The traditional approach would involve controlling statistically for environmental factors. On the basis of the underlying counterfactual interpretation of this approach, the researcher would in fact be posing the query, “What would the risk of depression have been for this individual had she not been a woman?” Now the question naturally arises as whether we can speak of a woman as the same individual if she were not female. In fact, we would have difficulty defining what it means for a woman to “not be a woman.” Practically, of course, the alternative is to be a man, but what does that tell us about “womanness” as a cause of depression?

Modeling The Contribution of Genes and Environment

Causal Effects Are Often Assumed to Fit an Additive Model:

$$\text{Genes} + \text{Environment} = \text{Organism}$$

In the Attempt to Isolate "Genetic Effects", this Model is Rewritten:

$$\text{Observed Phenotypic Variation} - \text{Environmental Contribution} = \text{Genetic Effect}$$

However, Because Interactions Occur, Additional Terms are Required:

$$\begin{aligned} \text{Observed Phenotypic Variation} = & \text{Genes} + \text{Environment} + \\ & \text{Genes} * \text{Environment} + \text{Genes} * \text{Genes} + \\ & \text{Environment} * \text{Environment} \end{aligned}$$

Models for the nature-nurture construct.

This result occurs, in the main, because it is impossible to separate the physical and social dimensions of gender. While an adequate explication of this argument requires substantially more detail, it suffices in this context to note that causal inference related to essential attributes, rather than modifiable states, raises insoluble problems for the epidemiological method.²⁸

Similar, perhaps more difficult, problems plague racial comparisons. The infinitude of social influences, some explicit and many buried from view by unconscious prejudice, easily overwhelm the techniques of statistical control, especially in the context of limited covariate sets. While recognizing the risk of overweening inference, we suspect that the complete inability of studies on racial differences to yield useful etiologic insights is due largely to this logical flaw in the pathway to causal reasoning. In effect, it follows from the argument outlined here that no valid inferences about "essential" differences between blacks and whites can be derived from observational data on phenotypes. To restate in more standard terms: no generalized "genetic effects," which constitute the only plausible meaning of essentialism in the biological context, can be justifiably inferred using the methods of observational epidemiology. While the counterfactual basis for epidemiological reasoning may be largely unfamiliar to investigators in the field of hypertension, it nonetheless provides the foundation for all standard techniques related to confounding, adjustment, and causal inference. Extensive review and comment on this topic are available elsewhere.^{20,28-30}

A final technical consideration applies. As argued above, when racial differences are conceived of from an essentialist perspective, the goal of the search is the identification of genes. The usual form of the "nature-nurture" construct assumes an additive model (Figure). Rewriting this formulation, we can isolate the essentialist quality, ie, genes. However, it is apparent that genes and

environment do not share a simple additive relationship, but instead they interact such that the presence of two factors does not imply the sum of the two effects. A fully specified model would thus have five terms (genes, environment, genes×genes, genes×environment, and environment×environment). In this form, the genetic component cannot be isolated to one side of the equality. In light of this expression, the question of whether observed differences in blood pressure control mechanisms between blacks and whites are determined by genes falls properly within the realm of nescience—the unknown and the unknowable. As noted by Oscar Kempthorne³¹ over 2 decades ago, to propose racial "genetic effects" on the basis of observational studies is to engage in nothing more than "idle speculation" because the method can never logically offer support for that conclusion over an environmental alternative. It remains possible, of course, to use the "ethnic paradigm" to elucidate environmental factors, although the simultaneous variation in a host of exposures complicates that task as well.^{17,32}

Conclusion

What have all the attempts at divining genes from complex phenotypic traits yielded in terms of understanding black-white differences? Nothing. Despite the oceans of ink spilled on this question, no credible evidence exists that pathways to hypertension are different between blacks and other ethnic groups.³²⁻³⁴ Race is a troublesome concept on a number of levels. While it is interesting to speculate whether the trouble in the ethical and social dimension has any necessary systematic link to the trouble in its technical and scientific application, it is sufficient to view these deficiencies as parallel rather than serial. Fortunately, we stand at the opening of a new era in medicine, as a result of the revolution in molecular biology. Just as the accelerator made it possible for physicists to observe subatomic particles, not just model them, we now have the capacity to clone genes. Genetic epidemiology is sweeping aside indirect methods. Moreover, the new technology helps to demonstrate the inherent weaknesses of the effort to infer genetic effects from broad phenotypes. This transformation could have salutary effects for studies of race, although technical advances alone will not be enough to eliminate traditional hereditarian views. The scientific standard should now be clear: those who wish to speak of genetic differences should speak of genes.

As for etiologic inferences from the observational study of racial comparisons, we assert that "you cannot get there from here." Those who view our position as nihilistic, and who believe that statistical adjustment moves us one step closer to the truth, might be likened to the defenders of alchemy who pleaded, "But how shall we have gold if not from lead?" Lead has many useful applications, but efforts to turn it into gold yielded nothing in the end. Likewise, our conclusion should not be misinterpreted as an attack on observational epidemiology, which has a long and successful history of valid applications. But there is a need to understand what a method can deliver and what, on the basis of its logical premises, it simply cannot. Likewise, there is a need to understand the extent to which racial differences can ever become the

subject, rather than the object, of inquiry in a racially hierarchical society.

Collectively, we should abjure the use of race as an indicator of intrinsic risk in etiologic studies, a paradigm which is destructive to the scientific search for truth and which, by casting social reality as biological reality, perpetuates racism and harms society at large. We urge the acceptance of this conclusion, not only because as scientists we are convinced that nothing legitimate can be learned, although surely that would be reason enough, but also because we are human beings, and racism in any form—scientific, political, or personal—is an assault on human dignity.

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