Adrian Vella, Michael D. Jensen, and K. Sreekumaran Nair

Eulogy for the Metabolic Clinical Investigator?

Diabetes 2016;65:2821–2823 | DOI: 10.2337/db16-0923

A recent editorial in the *Journal of Clinical Investigation* by Nathan et al. (1) dwelt on the decision to cease direct National Institutes of Health (NIH) funding of Clinical Research Centers (CRCs). As the authors rightly point out, the lack of extramural support for the CRC infrastructure will doom this valuable resource for human research at academic institutions without the wherewithal to support clinical research. CRCs as they currently exist might no longer require NIH support if we already knew the entirety of human physiology as it relates to disease or if entities such as industry would fund the studies needed to understand the primary mechanisms of complex human disease. We are certain the former is untrue and highly doubtful the latter will occur. The subsequent demise of the CRCs and our diminished ability to perform complex, mechanistic studies in humans will have both immediate and long-term adverse effects on biomedical research. Support obtained by the NIH Research Project Grant (R01) mechanism will be insufficient to maintain the necessary research infrastructure. Consequently, investigators will abandon comprehensive, mechanistic studies in humans because of the costs involved. The eventual fall in the number of investigators capable of designing, conducting, and interpreting such studies threatens to make the U.S. a second-tier biomedical research environment.

This is especially important for the field of diabetes and metabolism where related human studies account for a significant proportion of CRC use. Certainly, rigorous metabolic research requires meticulous control of diet and activity prior to study. Moreover, ensuring participant safety with intensive monitoring often requires extended inpatient stays. The elimination of the NIH-supported CRC system will also substantially constrain the infrastructure necessary for intensive human studies, such as those requiring tissue biopsy, vascular catheterization, and frequent sampling of the arterial or venous circulation.

Although basic bench research and clinical trials continue to be important, CRC-based investigation has certainly accelerated the translation of discoveries to clinical practice. In some cases, observations made during CRC-based clinical investigation have driven discovery and the development of novel therapeutics. For example, insulin resistance was first observed in metabolic studies of obese subjects, leading to substantial bench research to elucidate the pathogenesis of insulin resistance (2,3). Similarly, the observation that enteral glucose delivery stimulated greater insulin secretion than an equivalent parenteral glucose load (4) led to the discovery of incretin hormones (5,6) and, ultimately, to novel therapies for type 2 diabetes (7). Has biomedical science changed so much in the past decade that such work is no longer necessary or relevant? Multiple counterarguments could be made to suggest that this is not the case.

Rodent models of human disease are critical to advancing our understanding of disease but are not substitutes for human experiments. Importantly, rodent life span is much shorter than that of humans, and rodents only live for a few months after their growth has ceased. In contrast, humans experience several decades of life after their full growth potential is achieved. Most diseases like type 2 diabetes occur in older people, and it is optimistic to assume that therapeutic or toxic effects shown in growing animals are relevant to humans "aged" over several decades. Recent carefully conducted studies in rodents and in tissue culture have shown that metformin, a major antidiabetes drug, acts by inhibiting the glucagon effect on hepatic glucose production (8). However, CRC-based human studies now demonstrate that, contrary to the preclinical data, glucagon in fact mitigates metformin's effect on hepatic glucose production (9).

Other examples abound where human reality has "failed" to live up to the expectations generated by preclinical models or epidemiological associations; we will highlight two to illustrate the importance of human studies in helping to focus drug development. Randle et al. (10) demonstrated that free fatty acids (FFAs) compete with glucose for substrate oxidation in isolates of rat heart muscle and rat diaphragm. This led to the postulate

Division of Endocrinology, Metabolism, Diabetes, Nutrition, and Internal Medicine, Mayo Clinic, Rochester, MN

Corresponding author: Adrian Vella, vella.adrian@mayo.edu.

that increased fat oxidation causes the insulin resistance present in obesity through inactivation of mitochondrial pyruvate dehydrogenase, triggering a chain of events that result in decreased glucose uptake (11). Subsequent CRC studies using nuclear magnetic resonance spectroscopy and carefully timed muscle biopsies in humans have shown that FFAs induce insulin resistance by inhibiting glucose transport into, and subsequent phosphorylation by, skeletal muscle (12).

Increased visceral adipose tissue is associated with the metabolic complications of obesity, including type 2 diabetes and ischemic heart disease, leading to the suggestion that portal drainage of visceral adipose tissue–derived adipokines and metabolites directly contributes to the pathogenesis of these comorbidities (13). However, these observations have not been borne out by mechanistic studies that have directly measured the effect of omentectomy on insulin action (14). In addition, splanchnic catheterization techniques that allow direct measurement of visceral FFA flux established that body composition and fat distribution alone cannot predict regional FFA kinetics. Most significantly, the contribution of subcutaneous fat to systemic lipolysis is far greater than visceral fat, such that that only ~20% of systemic FFA in viscerally obese subjects are derived from splanchnic sources, meaning that targeting visceral fat alone is unlikely to improve systemic metabolism (15).

Despite an approximately sixfold increase in research and development spending by the pharmaceutical industry over the past two decades, the number of new therapeutics has remained stable (16). Most new drugs fail in phase 2 studies because of a lack of efficacy or because of toxicity, suggesting that preclinical disease models have a very limited ability to predict patient benefit (17). To take the example of type 1 diabetes (18), more than 200 compounds can prevent the progression of type 1 diabetes in rodent models, but none have proven useful in the human disease—an undertaking that has required an extensive, nationwide, CRC-supported infrastructure to conduct the relevant studies (19).

Indeed, in a recent analysis of a commercial drug pipeline, Cook et al. (17) reported that drug development projects were more likely to succeed if biomarkers of efficacy were available at the start of phase 2 studies or if there was genetic evidence linking the drug target to the targeted disease. Although it could be argued that untargeted investigative techniques, such as metabolomics, whole-genome sequencing, and genome-wide association studies, provide an opportunity to discover novel biomarkers or genetic targets, it is usually the case that significant amounts of in vivo work will be required to establish the physiological or clinical relevance of such discoveries. This is true before addressing the caveat heretofore drilled into generations of scientists that "association does not equal causation."

We hope that these examples refute the contention that biomedical science can always be translated directly from basic discovery or epidemiological observations to industry-supported clinical trials. The loss of CRCs will prevent the biomedical field from understanding how new and existing discoveries impact integrated human metabolism. There is much yet to learn about how the human body works and how it responds to stimuli—apparently that information, together with the competitive edge it currently gives the U.S., will be lost or obtained in countries that have realized the value of, and have copied, our (now vanishing) CRC system.

Hopefully, once the negative impact of this decision is appreciated, support for the CRC system will return. Unfortunately, it is much more costly to rebuild something from scratch than to keep such resources running. If a combination of institutional, NIH, and philanthropic support can keep a handful of the CRCs functioning over the next several years, it will be much easier to return to this type of research once its necessity becomes apparent. From the point of view of diabetes research, we urge the National Institute of Diabetes and Digestive and Kidney Diseases to consider establishing metabolic centers in selected institutions where a critical mass of NIH-supported investigators can continue to use a CRC-like environment to perform their studies without compromising scientific integrity or participant safety.

Duality of Interest. A.V. is funded by the NIH (DK78646) and is an investigator in multicenter studies sponsored by VTV Therapeutics, Novartis, and GI Dynamics. He has consulted for XOMA, Sanofi, Novartis, and Bristol-Myers Squibb in the past 5 years. His studies are performed in the Mayo Clinic General CRC (UL1 TR000135). M.D.J. is funded by the NIH (DK45343 and DK40484) and Aspire Bariatrics. His studies are performed in the Mayo Clinic General CRC (UL1 TR000135). K.S.N. is funded by the NIH (R01 DK10140, U24 DK100469, and R56 DK41973-26), and his research is performed in the Mayo Clinic General CRC (UL1 TR000135). No other potential conflicts of interest relevant to this article were reported.

References

1. Nathan DG, Nathan DM. Eulogy for the clinical research center. J Clin Invest 2016;126:2388–2391
2. Himsworth HP. The activation of insulin. Lancet 1932;220:935–936
3. Himsworth HP. Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types. Lancet 1936;227:127–130
4. McIntyre N, Holdsworth CD, Turner DS. New interpretation of oral glucose tolerance. Lancet 1964;2:20–21
5. Holst JJ, Orskov C. Incretin hormones–an update. Scand J Clin Lab Invest Suppl 2001;234:75–85
6. Kieffer TJ, Habener JF. The glucagon-like peptides. Endocr Rev 1999;20:876–913
7. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006;368:1696–1705
8. Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature 2013;494:256–260
9. Konopka AR, Esponda RR, Robinson MM, et al. Hyperglucagonemia mitigates the effect of metformin on glucose production in prediabetes. Cell Reports 2016;15:1394–1400

10. Randle PJ, Newsholme EA, Garland PB. Regulation of glucose uptake by muscle. 8. Effects of fatty acids, ketone bodies and pyruvate, and of alloxan-diabetes and starvation, on the uptake and metabolic fate of glucose in rat heart and diaphragm muscles. Biochem J 1964;93:652–665
11. Randle PJ, Priestman DA, Mistry S, Halsall A. Mechanisms modifying glucose oxidation in diabetes mellitus. Diabetologia 1994;37(Suppl. 2): S155–S161
12. Shulman GI. Cellular mechanisms of insulin resistance in humans. Am J Cardiol 1999;84(1A):3J–10J
13. Klein S. The case of visceral fat: argument for the defense. J Clin Invest 2004;113:1530–1532
14. Fabbrini E, Tamboli RA, Magkos F, et al. Surgical removal of omental fat does not improve insulin sensitivity and cardiovascular risk factors in obese adults. Gastroenterology 2010;139:448–455
15. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest 2004;113:1582–1588
16. Plenge RM, Scolnick EM, Altshuler D. Validating therapeutic targets through human genetics. Nat Rev Drug Discov 2013;12:581–594
17. Cook D, Brown D, Alexander R, et al. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov 2014;13:419–431
18. Phillips B, Trucco M, Giannoukakis N. Current state of type 1 diabetes immunotherapy: incremental advances, huge leaps, or more of the same? Clin Dev Immunol 2011;2011:432016
19. Mahon JL, Sosenko JM, Rafkin-Mervis L, et al.; TrialNet Natural History Committee; Type 1 Diabetes TrialNet Study Group. The TrialNet Natural History Study of the Development of Type 1 Diabetes: objectives, design, and initial results. Pediatr Diabetes 2009;10:97–104