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HIGHLIGHT

Mapping Progress in Toxicology Research by the Content of the Best Papers Published in Society of Toxicology Journals: A Synopsis of the Best Paper Awardees (1974–2011)

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In 1973, an anonymous donor contributed funds in honor of Dr Frank Blood for an award that would bring recognition to the best paper published in the Society of Toxicology journal. As time was needed to establish criteria for the award and review papers, the first award was bestowed in 1974. At its inception, responsibility for selecting the best paper was assigned to the Awards Committee, but over time, this role was transferred to the Board of Publications. Members are encouraged to nominate papers for consideration, but the Editorial offices have also played an active role in selecting papers for consideration. In general, articles selected as the best paper are recognized because they contain novel, new data, represent significant progress in understanding mechanisms of toxicity and/or advance the protection of human and environmental health.

A total of 51 papers have been awarded best paper honors in *Toxicology and Applied Pharmacology* (specifically designated as the Frank R. Blood awardee), *Fundamental and Applied Toxicology*, and *Toxicological Sciences* since 1974. The complete list of the papers selected as the best manuscripts published in Society of Toxicology journals is presented in Table 1. It is not possible to provide a full account of the scope and significance of each manuscript recognized as the best paper since 1974. Rather, the purpose of this article is to highlight the content of these papers as they reflect on fundamental tenets in toxicology. Additionally, this collection of papers also serves to illustrate important advances in toxicologic research.

Although the papers are diverse in content, several general themes emerged while reviewing the collection of best papers, and these themes served to organize the content, scope, and significance of the articles. The general themes by which the papers are discussed in this article include the following:

- compound-specific research, with emphasis on heavy metals, polychlorinated aromatic hydrocarbons (PAHs), and acetaminophen (15 of the 51 articles),
- research emphasizing risk assessment, including quantitative estimates of risk and extrapolation to humans (14 articles),
- studies on the role of xenobiotic disposition in toxicity, including mechanisms of toxicity and species differences in toxicity (13 articles),
- contribution of receptor-mediated events to toxic mechanisms (5 articles),
- role of cell proliferation and tissue regeneration in toxicity and repair (2 articles), and
- development of predictive tools in toxicology (2 articles).

TOXICITY OF HEAVY METALS

Metals such as lead and arsenic are some of the oldest toxicants known to humans, and they remain important environmental contaminants that exert a variety of adverse effects on human health. Research on heavy metals including causal association of exposure with toxicity and mechanisms of adverse effects has been a major focus in toxicology. Articles delineating adverse effects of methylmercury on microtubule networks (Miura *et al.*, 1984) and alterations of intrasynaptosomal concentrations of calcium (Denny *et al.*, 1993) have been recognized for their contribution to understanding mechanisms of toxicity. Lead toxicity including increased neonatal sensitivity to lead-induced inhibition of retinal Na^+/K^+ATPase (Fox *et al.*, 1991) and fetal exposure by transplacental transfer of endogenous lead (Franklin *et al.*, 1997) have contributed to the hazard identification of developmental toxicity of lead. Additionally, alterations in dopamine function observed at environmentally relevant blood lead levels provided relevant mechanistic data to explain lead-induced behavioral effects (Zuch *et al.*, 1998). Finally, mechanistic studies defined the paradoxical effects of arsenic, that although used to treat hematological tumors, low

TABLE 1
Best Paper Awardees in Society of Toxicology Journals

Year	Title	First author/journal[a]
1974	Sensory irritation of the upper airways by airborne chemicals	Alarie (1973)/*Toxicology and Applied Pharmacology*
1975	The influence of pure polychorinated biphenyl compounds on hepatic function in the rat	Johnstone *et al.* (1974)/*Toxicology and Applied Pharmacology*
1976	Comparison of cochlear toxicity of sodium ethacrynate, fuorsemide and the cysteine adduct of sodium ethacrynate in cats	Brown (1975)/*Toxicology and Applied Pharmacology*
1977	Characterization of the metabolites of methyl-n-butyl ketone, methyl iso-butyl ketone and methyl ethyl ketone in guinea pig serum and their clearance	DiVincenzo *et al.* (1976)/*Toxicology and Applied Pharmacology*
1978	Fate of [^{14}C]vinyl chloride following inhalation exposure in rats	Watanabe *et al.* (1976)/*Toxicology and Applied Pharmacology*
1979	Comparative distribution and embryotoxicity of acetylsalicylic acid in pregnant rats and rhesus monkeys	Wilson *et al.* (1977)/*Toxicology and Applied Pharmacology*
1980	Chromate inhibition of metabolism by rat lung tracheal explants. II. In vitro exposures	Last *et al.* (1979)/*Toxicology and Applied Pharmacology*
1981	Immunologic sensitization and pulmonary hypersensitivity by repeated inhalation of aromatic isocyanates	Karol *et al.* (1980)/*Toxicology and Applied Pharmacology*
1982	Determination of the kinetic constants for metabolism of inhaled toxicants in vivo using gas uptake measurements	Andersen *et al.* (1980)/*Toxicology and Applied Pharmacology*
1983	Chemical urolithiasis 2. Thermodynamic aspects of bladder stone induction by terphthalic acid and dimethyl terphthalate in weanling Fisher 344 rats	Heck (1981)/*Fundamental and Applied Toxicology*
1984	Species differences in kidney toxicity and metabolic activation of tris (2,3 dibromopropyl) phosphate	Soderlund *et al.* (1982)/*Fundamental and Applied Toxicology*
1985	Effects of methylmercury and some metal ions on microtubule networks in mouse glioma cells and in vitro tubulin polymerization	Miura *et al.* (1984)/*Toxicology and Applied Pharmacology*
1986	SAR of retinoids in developmental toxicity. I. Studies on the nature of the polar terminus of the vitamin A molecule	Wilhite *et al.* (1984)/*Toxicology and Applied Pharmacology*
1987	Skin penetration and metabolism of topically applied chemicals in six mammalian species, including man: An in vitro study with benzo[a]pyrene and testosterone	Kao *et al.* (1985)/*Toxicology and Applied Pharmacology*
1988	Potential role of activated macrophages in acetaminophen hepatotoxicity. II. Mechanisms of macrophage accumulation and activation	Laskin *et al.* (1986)/*Toxicology and Applied Pharmacology*
1989	Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust	Wolff *et al.* (1987)/*Fundamental and Applied Toxicology*
1990	Selective protein arylation and the age dependency of acetaminophen hepatotoxicity in mice	Beirschmitt *et al.* (1989)/*Toxicology and Applied Pharmacology*
1991	Teratology of 2,3,7,8-tetrachlorodibenzo-p-dioxin in a complex environmental mixture from the love canal	Silkworth *et al.* (1989)/*Fundamental and Applied Toxicology*
1992	Developmental lead exposure inhibits adult rat retinal but no kidney Na+,K(+)-ATPase	Fox *et al.* (1991)/*Toxicology and Applied Pharmacology*
1993	In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin. 2. Effects on sexual behavior and the regulation of luteinizing hormone secretion in adulthood	Mably *et al.* (1992)/*Toxicology and Applied Pharmacology*
1994	Assessment of binding of 2,4,4-trimethyl-2-pentanol to low-molecular weight proteins isolated from kidneys of male rats and humans	Borghoff and LaGarde (1993)/*Toxicology and Applied Pharmacology*
1995	Methylmercury alters intrasynaptosomal concentrations of endogenous polyvalent cations	Denny *et al.* (1993)/*Toxicology and Applied Pharmacology*
	Risk assessment in immunotoxicology. II. Relationships between immune and host resistance tests	Luster *et al.* (1993)/*Fundamental and Applied Toxicology*
	Induced cytolethality and regenerative cell proliferation in the livers and kidneys of male B6C3F1 mice given chloroform by gavage	Larson *et al.* (1994)/*Fundamental and Applied Toxicology*
1996	Glucocorticoids enhance intracellular signaling via adenylate cyclase at three distinct loci in the fetus: A mechanism for heterologous teratogenic sensitization	Slotkin *et al.* (1994)/*Toxicology and Applied Pharmacology*
	Dose-response toxicity assessment for developmental toxicity. III. Statistical methods	Allen *et al.* (1994)/*Fundamental and Applied Toxicology*

TABLE 1—*Continued*

Year	Title	First author/journal[a]
1997	Increased [3H]phorbal ester binding in rat cerebellar granule cells and inhibition of 45Ca2+ sequestration in rat cerebellum by polychlorinated dipheny ether cogeners and analogs: SAR	Kodavanti *et al.* (1996)/*Toxicology and Applied Pharmacology*
	Mechanism for species-specific induction of Leydig cell tumors in rats by lansoprazole	Fort *et al.* (1995)/*Fundamental and Applied Toxicology*
1998	Identification of a 54-kDa mitochondrial acetaminophen-binding protein as aldehyde dehydrogenase	Landin *et al.* (1996)/*Toxicology and Applied Pharmacology*
	Activation of CGS 12094 (prinomide metabolite) to 1,4-benzoquinone by myeloperoxidase: Implications for human idiosyncratic agranulocytosis	Parrish *et al.* (1997)/*Fundamental and Applied Toxicology*
1999	Low level lead exposure selectivly enhances dopamine overflow in the nucleus accumbens: An in vivo electrochemistry time course assessment	Zuch *et al.* (1998)/*Toxicology and Applied Pharmacology*
	Diet restriction enhances compensatory liver tissue repair and survival following administration of lethal dose thioacetamide	Ramaiah *et al.* (1998)/*Toxicology and Applied Pharmacology*
	Use of sequentially administered stable lead isotopes to investigate changes in blood lead during pregnancy in a nonhuman primate (*Macaca fascicularis*)	Franklin *et al.* (1997)/*Fundamental and Applied Toxicology*
2000	Overexpression of the ant-apoptotic oncogene, blc2, in the thymus does not prevent thymic atrophy induced by estradiol or 2,3,7,8-tetrachlorobenzo-p-dioxin	Staples *et al.* (1998)/*Toxicology and Applied Pharmacology*
	Modulation of serum growth factor signal transduction in Hepa1-6 cells by acetaminophen: An inhibition of c-myc expression, NF-kappa B activation and Raf-1 kinase activity	Boulares *et al.* (1999)/*Toxicological Sciences*
2001	The extracellular signal-regulated kinase pathway contributes to mitogenic and antiapoptotic effects of peroxisome proliferators in vitro	Mounho and Thrall (1999)/*Toxicology and Applied Pharmacology*
	Increased mitochondrial superoxide production in rat liver mitochondria, rat hepatocytes and HepG2 cells following EE treatment	Chen *et al.* (1999)/*Toxicological Sciences*
2002	Role of human GABA(A) receptor beta3 subunit in insecticide toxicity	Ratra *et al.* (2001)/*Toxicology and Applied Pharmacology*
	Protection against Fas receptor mediated apoptosis in hepatocytes and nonparenchymal cells by a caspase-8 inhibitor in vivo: Evidence for a postmitochrondrial processing of caspase-8	Bajt *et al.* (2000)/*Toxicological Sciences*
2003	Identification of butyrlcholinesterase adducts after inhibition with isomalathion using mass spectrometry: Difference in mechanism between (1R) and (1S)-stereoisomers	Doorn *et al.* (2001)/*Toxicology and Applied Pharmacology*
	A physiologically based pharmacokinetic modeling-based approach to account for interactions in the health risk assessment of mixtures	Haddad *et al.* (2001)/*Toxicological Sciences*
2004	Inhaled environmental combustion particles cause myocardial injury in the Wistar Kyoto rat	Kodavanti *et al.* (2003)/*Toxicological Sciences*
2005	Arsenic stimulates angiogenesis and tumorigenesis in vivo	Soucy *et al.* (2003)/*Toxicological Sciences*
2006	A toxicogenomic approach to drug-induced phospholipidosis: Analysis of its induction mechanism and establishment of a novel in vitro screening system	Sawada *et al.* (2005)/*Toxicological Sciences*
2007	Thiamethoxam induced mouse liver tumors and their relevance to humans: Part 1: Mode of action studies in the mouse Part 2: Species differences in response Part 3: Case Study: Weight of evidence evaluation of the human health relevance of thiamethoxam-related mouse liver tumors	Green *et al.* (2005a,b); Pastoor *et al.* (2005)/*Toxicological Sciences*
2008	Seqeuntial exposure to cytokines reflecting embryogenesis: The key for in vitro differentiation of adult bone marrow stem cells into functional hepatocyte-like cells	Snykers *et al.* (2006)/*Toxicological Sciences*
2009	The PPAR alpha-humanized mouse: A model to investigate species differences in liver toxicity mediated by PPAR alpha	Yang *et al.* (2008)/*Toxicological Sciences*
2010	Identification and characterization of toxicity of contaminants in pet food leading to an outbreak of renal toxicity in cats and dogs	Dobson *et al.* (2008)/*Toxicological Sciences*
2011	Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia	Lu *et al.* (2010)/*Toxicological Sciences*

[a]Full citation is provided in the reference section.

doses of As (III) also stimulate angiogenesis and enhance tumor growth (Soucy *et al*., 2003).

TOXICITY OF POLYCHLORINATED AROMATIC HYDROCARBONS

The plethora of toxicities manifested by the broad class of polychlorinated Ahs and the recognized human exposures from environmental accidents has stimulated considerable research on these compounds. Although 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is the most widely studied compound, research on numerous polychlorinated biphenyls (PCBs) and polychlorinated diphenyl ethers (PCDE) has been recognized. The breadth of the research on the numerous target organs affected by these compounds is illustrated by early studies defining structure-activity relationships (SAR) for PCB-induced alterations in hepatic metabolic function (Johnstone *et al.* 1974) to sophisticated analyses of the SAR for PCDE-induced alterations in neuronal Ca^{+} homeostasis and protein kinase C translocation (Kodavanti *et al*., 1996) and the use of bcl-2 transgenic mice to establish that apoptosis is not a key event underlying TCDD-induced thymic atrophy (Staples *et al*., 1998). Research delineating adverse effects of TCDD on sexual behavior in adult male rats after *in utero* or lactational exposure (Mably *et al*., 1992) has been recognized. Finally, an important manuscript that provided translational evidence for the teratogenic potential of TCDD showed that an organic extract of leachate from the Love Canal chemical dump site was teratogenic as the leachate and TCDD caused cleft palate and hydronephrosis in Ah receptor–sensitive mice (Silkworth *et al*., 1989).

TOXICITY OF ACETAMINOPHEN (APAP)

The hepatic and renal toxicity of this widely used analgesic is a clinically important problem that has been the subject of countless research articles. Four papers detailing metabolic and cellular responses to APAP have been recognized for their significant advances in understanding the mechanism(s) involved in APAP-induced hepatic toxicity. The focus of these papers has included seminal work determining how macrophages accumulate and are activated in APAP-induced toxicity (Laskin *et al*., 1986). Additional research defined selective protein arylation rather than total covalent binding as a critical determinant of hepatotoxicity (Beirschmitt *et al*., 1989) and extended that work to identify covalent modification of an aldehyde dehydrogenase as a potential target that can impair mitochondrial function (Landin *et al*., 1996). Finally, studies showing how APAP altered growth factor signaling in a manner that could potentially interfere with cell cycle regulation and organ regeneration to exacerbate hepatotoxicity were honored (Boulares *et al*., 1999).

RISK ASSESSMENT: METHODS AND MODELING

It is generally recognized that the risk assessment process includes the identification of potential hazard, determining the dose-response relationship for the hazard, defining exposure and characterizing risk. To some extent, all the articles selected as a best paper have elements of risk assessment in them, particularly as we seek to extrapolate findings to humans. However, obtaining an absolute measure of human exposure or sensitivity to a response is often difficult, thereby requiring models and methods that provide reliable accurate assessments of potential human risk. A variety of papers have been recognized for their contributions in this area. In fact, the first paper awarded best paper distinction evaluated sensory irritation in the upper respiratory tract for 27 chemicals and developed a model that enabled comparison of the activity of the compounds and the molecular features associated with sensory irritation (Alarie, 1973). Additional research in the general area of models and methods for risk assessment included determination of the solubility product for terephthalic acid (TPA)–induced bladder stones in rats, with extrapolation of the results to estimate TPA-induced calculi formation in human urine (Heck, 1981), development of models to define quantitative relationships between immune function tests and host resistance tests to improve immunotoxicology risk assessment (Luster *et al*., 1993), evaluation of statistical models to be applied to dose-response modeling for developmental toxicity tests with advancement of benchmark dose estimates (Allen *et al*., 1994), and development of an integrated physiologically based pharmacokinetic model that enabled evaluation of the impact of metabolic interactions to facilitate risk assessments for complex mixtures (Haddad *et al*., 2001).

RISK ASSESSMENT: HUMAN RELEVANCE

Ascribing significance of toxic responses to humans is the ultimate goal of risk assessment, and numerous best paper awardees have contributed major advances in this regard. In several cases, the research established that observations in laboratory animals were not relevant for human risk assessment as exemplified by research on the induction of Leydig cell tumors in rats by lansoprazole (Fort *et al*., 1995) and the trio of articles that included application of a framework for evaluating key events and a plausible mode of action involved in thiamethoxam-induced mouse liver tumors to support the conclusion that this compound was unlikely to be carcinogenic in humans (Green *et al*., 2005a,b; Pastoor *et al*., 2005). In another paper, human kidney samples were used to definitively establish that compounds causing α2u-globulin nephropathy by binding to this male rat–specific protein did not bind to protein in human kidneys (Borghoff and LaGarde, 1993).

Alternatively, several articles have confirmed the relevance of laboratory data for human risk assessment. These include research on the mechanism and potency of ototoxicity induced by clinically used loop diuretics (Brown, 1975) and the characterization of myocardial injury resulting from exposure to particulate matter that supported epidemiological associations of cardiovascular morbidity and mortality from ambient particulates

(Kodavanti *et al*., 2003). In another case, the observation of idiosyncratic agranulocytosis associated with exposure to the anti-inflammatory drug, prinomide, was evaluated. In this case, there was no evidence of adverse effects in any preclinical studies, thereby requiring studies with human enzymes and tissues to elucidate possible mechanisms of toxicity (Parrish *et al*., 1997). Finally, the application of toxicologic research to defining human relevance is highlighted by research characterizing the PPARα-humanized mouse, a model that defined important similarities and differences between how the receptor regulates lipid metabolism and hepatocyte proliferation in mice and humans, providing a novel platform for evaluating the effects of peroxisome proliferating compounds in humans (Yang *et al*., 2008).

XENOBIOTIC DISPOSITION: IMPORTANCE OF METABOLISM IN TOXICITY

There is no doubt that xenobiotic disposition is an important determinant of toxicity, and numerous best paper awardees have focused on the metabolic and dispositional components of toxic responses. This research is extremely diverse and has included research on (1) the metabolism of aliphatic ketones to assess the role of metabolism in neurotoxicity of compounds such as methyl-n-butyl ketone, hexane, and 2,5-hexanedione (DiVincenzo *et al*., 1976); (2) the fate of inhaled vinyl chloride relative to its carcinogenic effects (Watanabe *et al*., 1976); (3) the comparative distribution of acetylsalicylic acid between rats and rhesus monkeys to assess species differences in sensitivity to embryotoxicity (Wilson *et al*., 1977); (4) the SAR for retinoid-induced developmental toxicity (Wilhite *et al*., 1984); (5) the identification of stereoisomer-specific modification of butyrylcholinesterase by isomalathion as a mechanism for aging of the enzyme (Doorn *et al*., 2001); and (6) the identification of crystals formed as a melamine-cyanuric acid complex that precipitated in the renal tubules of animals fed diets containing gluten contaminated with these simple triazine compounds (Dobson *et al*., 2008). These last two articles applied state-of-the-art analytical tools by which protein adducts and crystal content were unequivocally determined.

Two additional research articles were recognized for their broad-based evaluation of metabolism across multiple species, including contribution of metabolic activation of the flame retardant tris (2,3-dibromopropyl) phosphate in rats, mice, hamsters, guinea pigs, and humans to assess species differences in renal toxicity (Soderlund *et al.* 1982) and the assessment of dermal penetration and metabolism in mice, rats, rabbits, guinea pigs, marmosets, and humans to advance methods for *in vitro* studies in skin absorption (Kao *et al*., 1985).

XENOBIOTIC DISPOSITION: TARGET ORGAN DOSIMETRY

Several manuscripts focused on xenobiotic disposition but with a fundamental emphasis on target organ dosimetry have also been recognized as best paper awardees. Although this research is also diverse and involves to numerous subdisciplines in toxicity, pulmonary dosimetry is highly represented. Relative to lung dosimetry, the focus has included the application of tracheal explants as functional dosimeters to quantify deposition of diffusible water-soluble compounds on airway surfaces (Last *et al*., 1979), application of an animal model to define dose-response relationships and threshold concentrations for immunologic sensitization and pulmonary hypersensitivity (Karol *et al*., 1980), and determination of the dose-response relationships for particle accumulation and clearance of diesel exhaust in rats (Wolff *et al*., 1987). Additional research on defining kinetic constants for metabolism of a variety of inhaled toxicants such as dichloroethylene and halothane resulted in developing a pharmacokinetic model to describe gas uptake and the role of metabolism in these agents (Andersen *et al*., 1980). Finally, the most recently recognized best paper relied on stable-label compounds to define the target organ dosimetry of formaldehyde-induced DNA adducts, with clear delineation of adducts formed from endogenous and exogenous sources (Lu *et al*., 2010). This research clearly identified the respiratory nasal epithelium as the only target for formaldehyde-induced adducts from inhalation exposure.

RECEPTOR-MEDIATED TOXICITY

Although some of the papers already discussed may include evidence for receptor-mediated toxicity, several papers had a clear focus on receptor-mediated and cell-signaling events as critical elements of mechanisms of toxicity. For example, experiments to assess the teratogenicity of high doses of glucocorticoids revealed the complex regulation of intracellular signaling in the developing fetus that was mediated by adenylate cyclase (Slotkin *et al*., 1994). Research on liver tumor promotion by ethinyl estradiol (EE) confirmed increased respiratory chain activity in cultured hepatocytes or rat liver mitochondria from rats treated with EE, which required metabolism to catechol estrogens and signal transduction mediated through the estrogen receptor (Chen *et al*., 1999). Additionally, evidence for involvement of the extracellular signal-regulated kinase and phosphatidyl-inositol 3-kinase was shown to play important roles in the mitogenic effects of peroxisome proliferators (Mounho and Thrall, 1999), and another paper highlighted the role of Fas receptor–mediated apoptosis, a process involved in cell death associated with inflammatory diseases, and the requirement of caspase-8 activation in Fas-mediated apoptosis (Bajt *et al*., 2000). Lastly, focused mechanistic studies identified that the gamma-aminobutyric acid type A receptor beta 3 subunit contains the sequence target for insecticide toxicity for agents such as alpha-endosulfan, lindane, and fipronil (Ratra *et al*., 2001).

CELL PROLIFERATION AND TISSUE REGENERATION

Two papers featured the role of cell proliferation in tissue responses to injury including comprehensive dose-response and time course studies that determined the contribution of cell proliferation in mouse liver and kidney after exposure to chloroform (Larson *et al*. 1994) and the enhancement of tissue repair after thioacetamide-induced liver toxicity by dietary restriction (Ramaiah *et al*., 1998). Both studies emphasized the reparative processes of tissues as important components of toxicologic responses.

PREDICTIVE TOXICOLOGY

The final two papers contained relevant new data and novel assays for predicting toxic responses. In one case, global gene expression profiles were used to develop a gene expression signature for predicting whether a compound would induce phospholipidosis (Sawada *et al*., 2005) and was the first of this type of approach for toxicity prediction. Finally, a program for differentiating adult bone marrow stem cells into hepatocyte-like cells was developed by in an experimental model in which liver-specific growth factors were added in a time-dependent sequence consistent with embryonic development (Snykers *et al*., 2006), thereby providing a virtually unlimited source of functional hepatocytes.

CONCLUSIONS

The breadth of articles recognized as best paper awardees illustrates the complexity of toxic responses, the importance understanding xenobiotic fate in relation to toxicity, and the ultimate goal of defining the relevance of toxic responses for human and environmental safety. These 51 papers, while representing important new data over time, are only a microcosm of advances in toxicology research. This special supplement of *Toxicological Sciences* contains extensive reviews on broader issues in toxicology, including some that have evolved over many years of research, some that are emerging fields, and a few that prospectively consider how our science may continue to evolve.

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