THE DIVERSE AND PROMISING WORLD OF ANIMAL DERIVED MEDICATIONS

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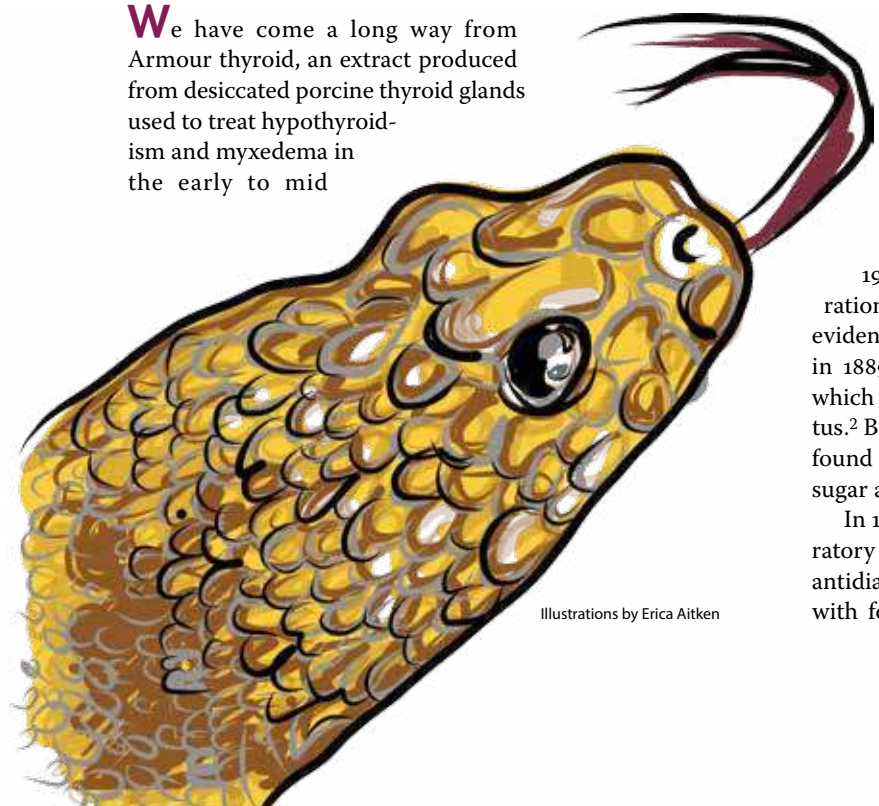
> Poisons and medicines are oftentimes the same substances given with different intents.
>
> —Peter Mere Latham, MD (1789–1875)[1]

We have come a long way from Armour thyroid, an extract produced from desiccated porcine thyroid glands used to treat hypothyroidism and myxedema in the early to mid 1900s. The literature is rich with examples of medications derived from plants and herbs, yet few articles have reviewed the list of pharmaceuticals developed from animal sources. The number is ever-growing, with discoveries ranging from Gila monster saliva and snake venom to goat milk. In addition to compounds used to replace lost or depressed functions, such as insulin and thyroid hormones, poisons produced by animals for competitive advantage can be repurposed for medical use, as Dr. Latham observed more than a century ago.

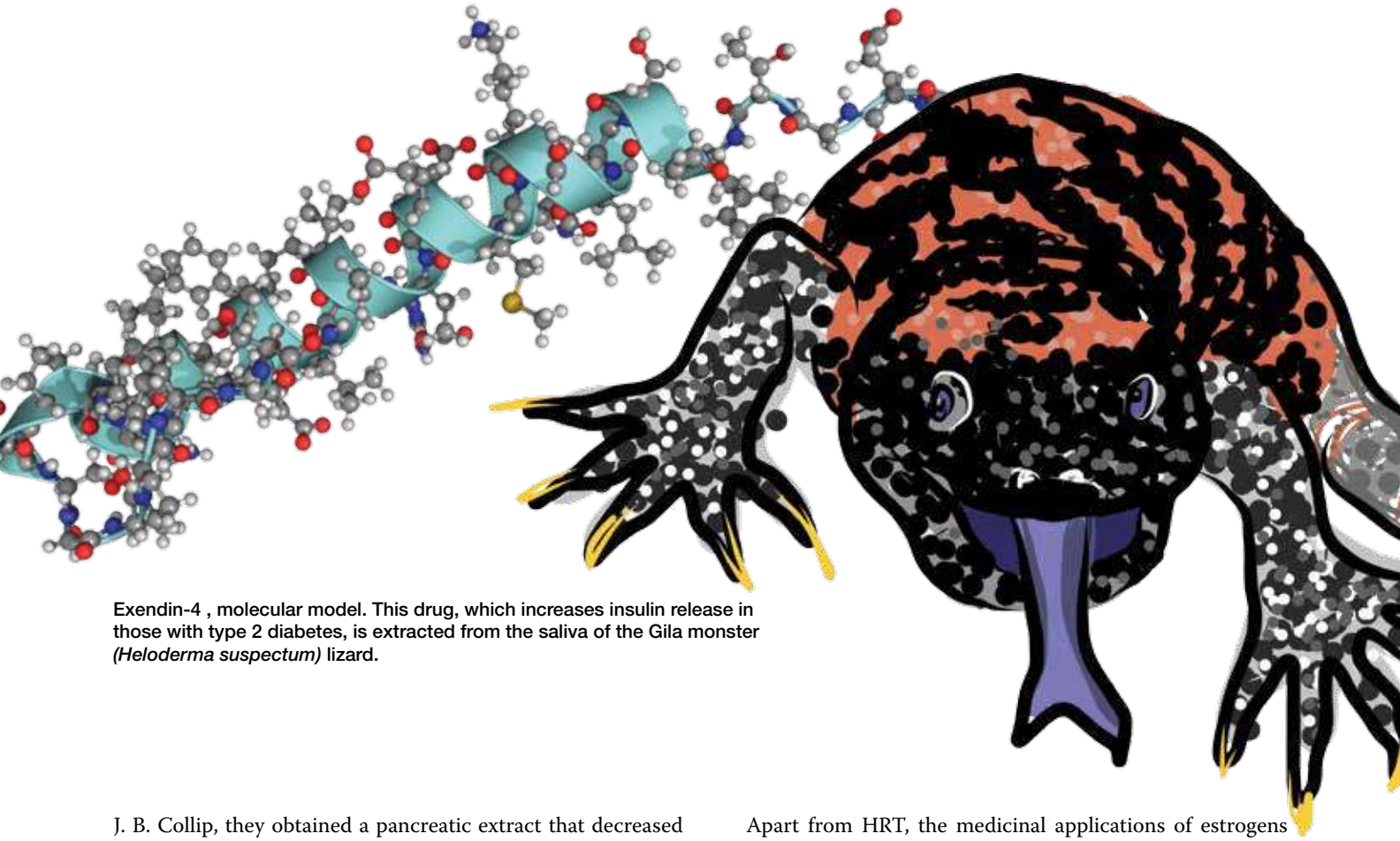


Illustrations by Erica Aitken

Heparin, insulin, and pituitary hormones were some of the earliest animal-derived therapies. By today's standards, the methods by which these drugs were discovered and purified may seem rudimentary, yet these drugs have saved countless lives and are still widely used today. Furthermore, the extraction and manufacturing processes developed with these medications have been applied to the isolation of many other subsequent drugs.

For over seventy years after insulin's discovery in 1921, diabetic patients were treated with insulin preparations from porcine or bovine pancreatic extracts.[2] Direct evidence for the function of pancreatic islet cells first came in 1889 through experiments with pancreatectomized dogs, which exhibited a syndrome similar to human diabetes mellitus.[2] Between 1903 and 1909, the physiologist Nicolas Paulesco found that injections of pancreatic extracts reduced urinary sugar and ketones in diabetic dogs.[2]

In 1921, Frederick Banting in the University of Toronto laboratory of professor of Physiology J. J. R. Macleod isolated the antidiabetic compound insulin from the pancreas.[2] Working with fourth-year medical student Charles Best, and chemist



Exendin-4 , molecular model. This drug, which increases insulin release in those with type 2 diabetes, is extracted from the saliva of the Gila monster *(Heloderma suspectum)* lizard.

J. B. Collip, they obtained a pancreatic extract that decreased the concentration of blood glucose in diabetic dogs. For this work, Banting and Macleod received the Nobel Prize in Medicine in 1923.[2] Insulin has saved the lives of millions of patients with uncontrolled diabetes and ketoacidosis.

Heparin, one of the oldest and most widely used drugs today, was discovered in 1916 by Jay McLean, then a second-year medical student at Johns Hopkins University. McLean originally isolated heparin from canine liver cells, hence its name (*hepar* is Greek for "liver"). It wasn't until the 1930s that an effective, safe, and economical version was synthesized using porcine intestines and bovine lung.

Now in the tenth decade since its discovery, heparin is still widely used for treatment of acute coronary syndromes, deep venous thrombosis, pulmonary embolus, cardiopulmonary bypass surgery, atrial fibrillation, extracorporeal membrane oxygenation circuits, and surgical procedures requiring anticoagulation.[2] And what would be the state of hemodialysis and the countless lives saved by it without heparin?

Further, protamine sulfate, the medication used to reverse heparin, was derived from salmon sperm.[2] Today, it is synthesized by recombinant DNA technology.

Sex steroids, pituitary hormones, and chorionic gonadotropin have been studied for decades, with a myriad of applications developed. Premarin, a combination of conjugated estrogens derived from pregnant mare's urine (*pre*gnant *mar*es' ur*in*e), has been marketed since the 1940s.[3] Popular for treating postmenopausal sequelae such as hot flashes, dyspareunia, mood disorders, and osteoporosis, it was used by millions of women until the results of the Women's Health Initiative study urged restraint for the use of hormone replacement therapy (HRT).[3]

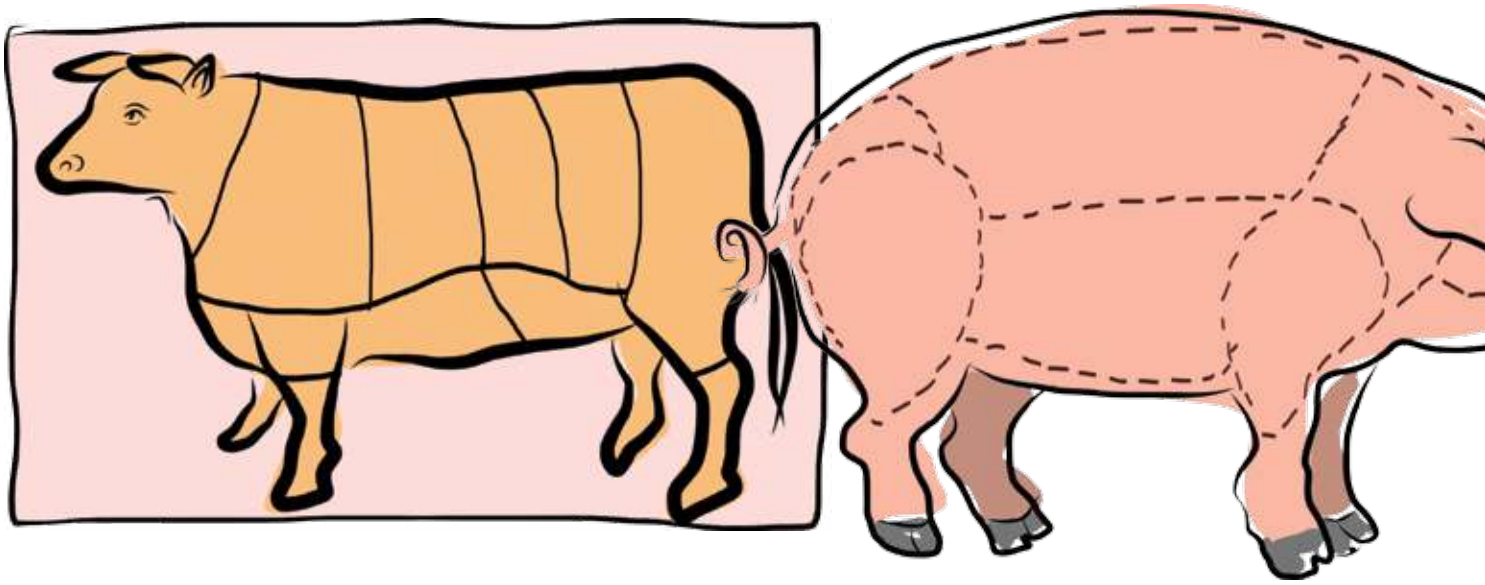
Apart from HRT, the medicinal applications of estrogens are ever-growing. Uses today include contraception, treatment of menorrhagia, polycystic ovary syndrome, endometriosis, induction of sexual differentiation, assisted reproduction technology, and treatment of androgen-dependent conditions such as acne and hirsutism.

Puffer fish, snakes, leeches, and Gila monsters

In the last few decades, pharmaceutical development from animal products has significantly diversified. The study of venoms, toxins, and secretions from animals has been productive in medication discovery and scientific research. The utility of these purified agents is partly due to the specificity for their targets, including channels and enzymes. One of the earliest investigated toxins in this category was tetrodotoxin, a potent neurotoxin produced by symbiotic bacteria in puffer fish and other aquatic animals. It was a keystone in the study of voltage-gated sodium channels in the 1960s, and more recently, in the study of pain pathways and anesthetics.[4]

Specific medications commonly used today that are derived from animal venoms, toxins, or secretions include captopril, eptifibatide (Integrilin), lepirudin, and exenatide (Byetta).

In the 1970s, captopril, a potent angiotensin converting enzyme (ACE) inhibitor, was derived from a peptide in the venom of the Brazilian pit viper (*Bothrops jararaca*).[5] Approved by the FDA in 1981, it was the first ACE inhibitor and catalyzed the development of numerous other agents in this class. Captopril and its cousins are widely used today as first-line anti-hypertensive drugs and for their protective properties in congestive heart failure, post-myocardial infarction, and prevention of diabetic nephropathy.



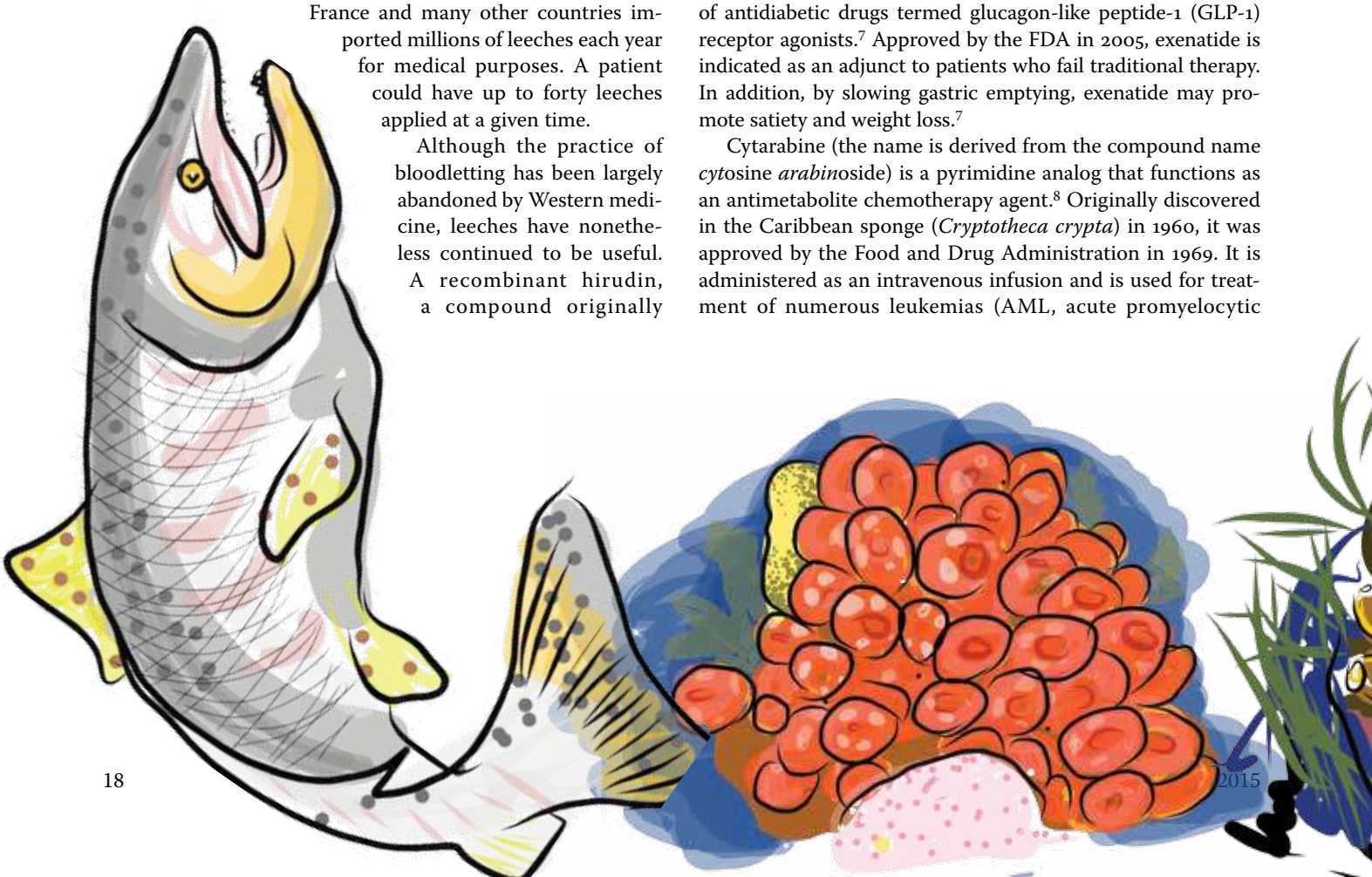
Eptifibatide (Integrilin), a cyclic peptide derived from the venom of the southeastern pygmy rattlesnake (*Sistrurus miliarius barbouri*), is an inhibitor of the platelet glycoprotein IIb/IIIa receptor, the binding site for fibrinogen, von Willebrand factor, and other ligands.[5] Inhibition of binding at this final common receptor reversibly blocks platelet aggregation and prevents thrombosis. Eptifibatide is used in acute coronary syndromes, usually at the time of percutaneous coronary intervention in combination with aspirin and heparin.

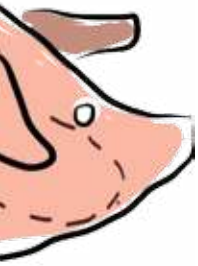
Since the time of Hippocrates, bloodletting has been a popular remedy, and leeches (*Hirudo medicinalis*) played a key role. They became especially popular in the 1800s, when France and many other countries imported millions of leeches each year for medical purposes. A patient could have up to forty leeches applied at a given time.

Although the practice of bloodletting has been largely abandoned by Western medicine, leeches have nonetheless continued to be useful. A recombinant hirudin, a compound originally isolated from leech saliva that leeches use to prevent coagulation during the harvesting of blood from their hosts, lepirudin is an anticoagulant and direct thrombin inhibitor.[2] Lepirudin is used in situations in which heparins (including low-molecular weight heparins) are contraindicated because of the risk of heparin-induced thrombocytopenia. Leeches are also being used directly to preserve the viability of tissue grafts in the presence of significant vascular congestion.[6]

Gila monsters (*Heloderma suspectum ssp.*) now play a role in treating one of the most common diseases in the United States: diabetes mellitus. Derived from the saliva of this large venomous lizard, exenatide (Byetta) belongs to a relatively new class of antidiabetic drugs termed glucagon-like peptide-1 (GLP-1) receptor agonists.[7] Approved by the FDA in 2005, exenatide is indicated as an adjunct to patients who fail traditional therapy. In addition, by slowing gastric emptying, exenatide may promote satiety and weight loss.[7]

Cytarabine (the name is derived from the compound name *cyt*osine *arabin*oside) is a pyrimidine analog that functions as an antimetabolite chemotherapy agent.[8] Originally discovered in the Caribbean sponge (*Cryptotheca crypta*) in 1960, it was approved by the Food and Drug Administration in 1969. It is administered as an intravenous infusion and is used for treatment of numerous leukemias (AML, acute promyelocytic





leukemia, ALL, CML, and CLL), as well as primary CNS lymphoma, and Hodgkin and non-Hodgkin lymphomas.

Development of pancreatic enzyme replacements from bovine and porcine pancreases, such as pancreatin (lipase, protease, amylase) has allowed treatment of exocrine deficiency and steatorrhea in thousands of patients with cystic fibrosis, surgical pancreatectomy, and chronic pancreatitis.[2] The utility of these enzymes came to fruition through studies in the 1980s.[2] Interestingly, in the late 1980s, pancreatin was also used for the development of enzymatic contact-lens cleaning solutions containing pancreatic extracts, and was found to be better than prior cleaning solutions.[9]

Ursodeoxycholic acid occurs in high concentrations in the bile of many mammals, including bears (*Ursus sp.*, hence the name), and is thought to protect hibernating bears from developing gallstones.[10] Ursodiol, a purified version manufactured for medical use, has been marketed since the 1980s for treatment of cholelithiasis, as well as conditions causing cholestasis, including primary biliary cirrhosis.[2]

Even roosters have been a subject for drug discovery. Rooster combs were used for the purification of hyaluronic acid and development of drugs such as Synvisc and Hyalgan.[11] Intra-articular injection of hyaluronic acid is used in treating osteoarthritic knee pain in patients who have failed non-pharmacologic treatment and simple analgesics. Intradermal injection is used for correction of moderate-to-severe facial wrinkles or folds. Hyaluronic acid is also used in ophthalmology as a surgical aid in cataract extraction, intraocular implantation, corneal transplant, glaucoma filtration, and retinal attachment surgery.

For over sixty years, the common chicken egg has served its role in the pharmaceutical industry.[12] Each year, hundreds of millions of influenza vaccines are produced by inoculation of the virus into fertilized chicken eggs. After incubation for two to three days, the virus multiplies in the egg white, producing millions of vaccine viruses. The egg white is harvested and the virus is purified, followed by treatment with chemicals to inactivate it. Subsequently, the outer viral proteins are extracted. Up to fifteen percent of the world's egg supply is used for vaccine manufacture, but as the demand for vaccine production increases, research is being done on other production methods, including cell culture.[12]

Bovine and porcine surfactants (Beractant, Calfactant, and Poractant alpha) are used for treatment of premature infant lungs. They work by preventing alveolar collapse during expiration and are used to replace deficient or ineffective endogenous lung surfactant in neonates at risk of developing respiratory distress syndrome.[13]

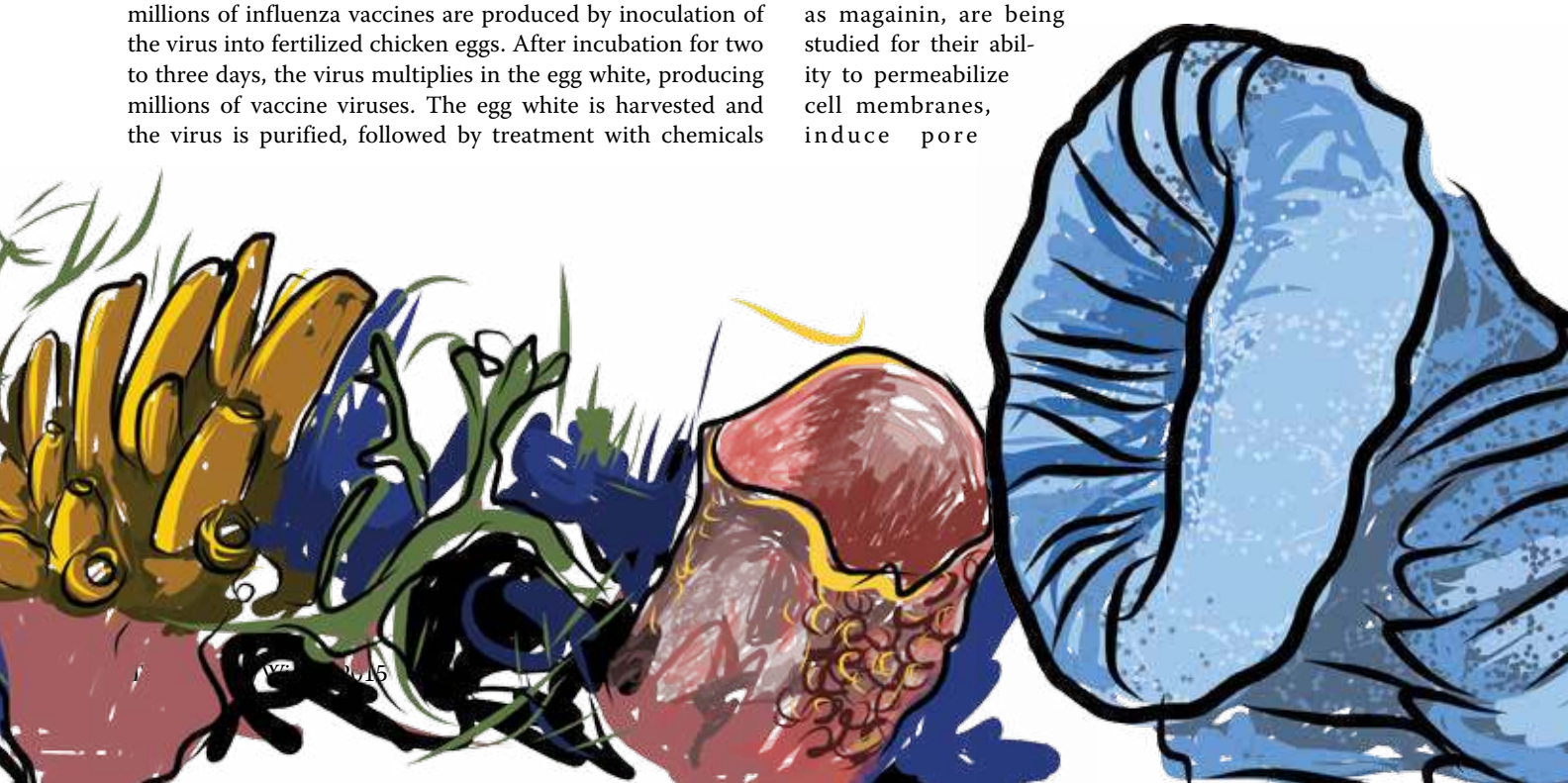
Lastly, calcitonin hormones (Calcimar and Miacalcin) were derived from thyroid-like glands in fish, particularly Coho salmon. They are used to treat postmenopausal osteoporosis, hypercalcemia, and Paget's disease.[14] Calcitonin is also being studied for its potential importance in analgesic pathways and migraines. In fact, "in addition to inhibiting bone resorption, it is a powerful analgesic agent with a potency in certain circumstances which is 30-50 times that of morphine."[14]

A look into the future: Alligators, frogs and scorpions

The animal-derived medications discussed thus far are impressive achievements. Even more exciting, however, are the many new potential therapies on the horizon.

Antibiotics

Open wounds in reptiles and amphibians rarely become infected, so investigators wanted to know why. Researchers have shown that alligator blood contains peptides that can destroy multiple types of bacteria, including MRSA, as well as HIV and amoebae.[15,16] Antimicrobial peptides have also been found in the skin of frogs and toads, as well as in Komodo dragons. Many of these peptides, such as magainin, are being studied for their ability to permeabilize cell membranes, induce pore



formation, and potentially augment beta-lactam antibiotics.[17] The hope is that these compounds can be purified as systemic and topical antibiotics, including creams for diabetic foot ulcers, with activity to combat MRSA infection and/or colonization.

Cancers

TM-601, a chlorotoxin derived from the venom of the deathstalker scorpion (*Leiurus quinquestriatus*), is currently in Phase II studies for treating high-grade gliomas.[18] Exerting its effects through chloride channels, it appears that the drug has high selectivity for the cancerous cells and does not adversely affect normal neurons or glial cells.

Trabectedin (Yondelis), derived from the sea squirt *Ecteinascidia turbinata*, is being studied for the treatment of many different malignancies, including soft-tissue tumors such as liposarcomas. Designated an orphan drug in the United States, it has been approved for use in ovarian and pancreatic cancers, and sarcomas.[2] Interestingly, the anti-tumor properties were discovered in the 1960s, but is wasn't until the 1980s that the structure of trabectedin was elucidated through advances in molecular biology. Aplidine, another drug derived from the sea squirts (*Aplidium albicans*), is also being studied for treatment of multiple types of solid cancers, particularly medullary thyroid carcinoma.[18]

Crotamine is another promising agent, derived from the venom of the South American rattlesnake *Crotalus durissus terrificus*. A low molecular weight peptide with cell penetrating and antimicrobial properties, it has selective action toward some cell types at a given phase of the cell cycle.[20] Importantly, because it can rapidly translocate into actively proliferating cells, crotamine is being investigated for detecting malignant cells with high turnover and for use as a chemotherapeutic adjuvant or drug carrier.

Neuropathic pain

Tebanicline (ABT-594), derived from the skin of a South American poison dart frog (*Epipedobates tricolor*), is being studied for its analgesic properties. It is a less toxic derivative of epibatidine, which is 200 times stronger than morphine, and exerts a novel mechanism of action: partial agonism of neural nicotinic acetylcholine receptors. In initial studies, the drug showed promising analgesic activity, including for neuropathic pain, without the potential addictive properties of narcotics. Unfortunately, Phase II clinical trials demonstrated unacceptable GI side effects, but further research is ongoing to find better derivatives.[21]

Anticoagulation

Using a new avenue for medication manufacture, ATryn is an anticoagulant produced from the milk of goats that have been genetically engineered to produce human antithrombin.[2] It is the first medication produced from genetically engineered animals. In 2009, the FDA approved the medication for treatment of patients with hereditary anti-thrombin deficiency who are undergoing surgical or childbirth procedures. Studies are being conducted to find more applications, including in patients without antithrombin deficiency.

Conclusions

Animal-derived medications have been used to treat patients since the early 1900s, starting with insulin and heparin. In the early decades, these medications (such as Armour thyroid) were primarily derived from tissue extracts. As purification methods advanced, multiple different animal sources have been explored, ranging from puffer fish in the 1960s to, most recently, genetically engineered animals. An increasing number of the agents isolated are highly specific for their targets (such as voltage-gated ion channels and enzymes). The examples above, although not an exhaustive list, demonstrate the myriad of available animal sources, and underscore the possibility for future discoveries. The discovery of new therapeutics derived from animals will undoubtedly bring more advances to medicine. The diversity of the promising world of future medications should intrigue the clinicians in all of us.

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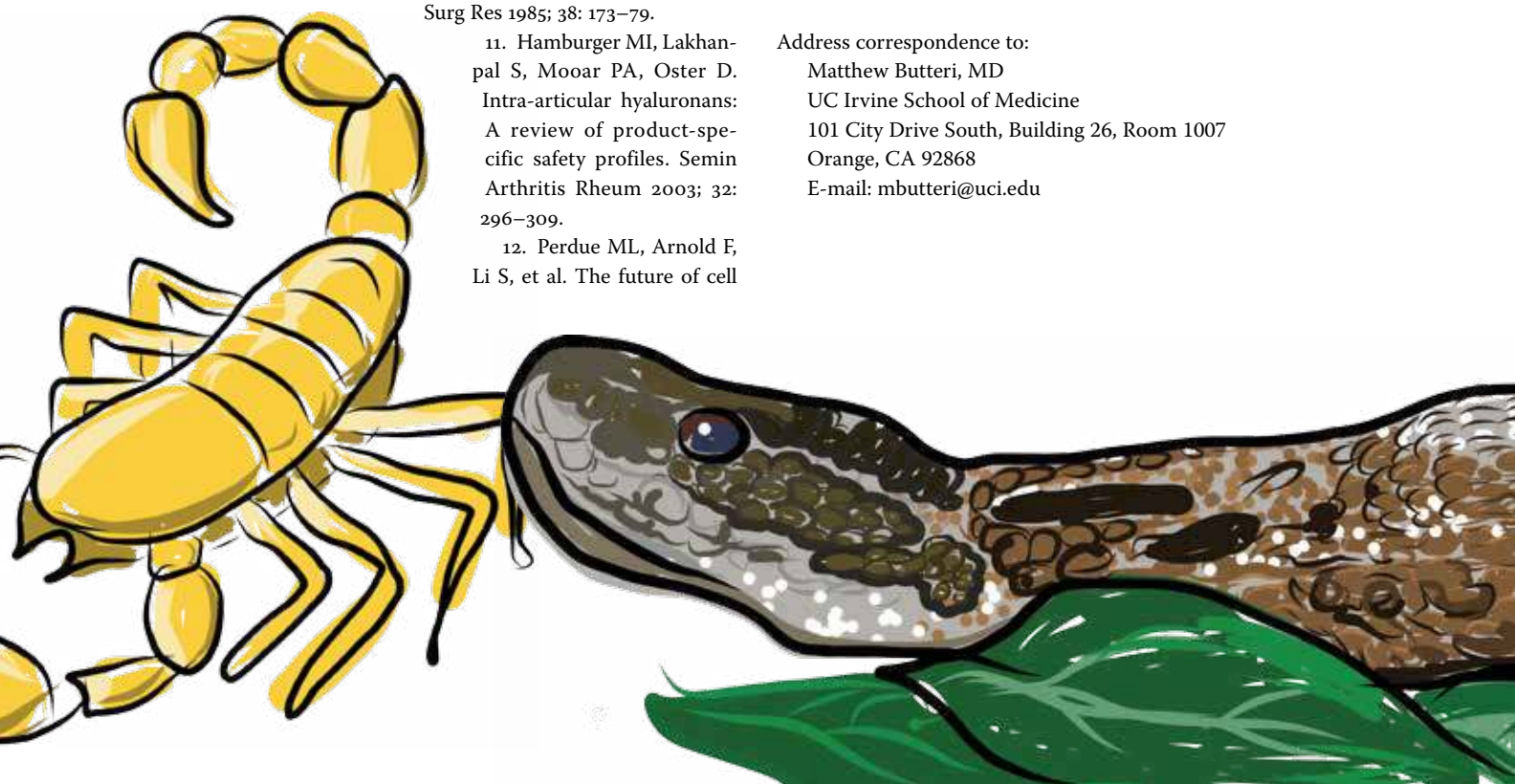

Animal-Derived Medications			
Application	**Medication**	**Original Animal Source**	**Typical Uses**
Cardiovascular	Captopril	Venom of Brazilian pit viper (*Bothrops jararaca*)	Anti-hypertensive, protective properties in congestive heart failure, post-myocardial infarction, and prevention of diabetic nephropathy
Endocrine	Regular insulin	Porcine or bovine pancreatic extracts	Diabetes mellitus
	Premarin and other conjugated estrogens	Pregnant mare's urine	Post-menopausal problems, including hot flashes, dyspareunia, mood disorders, and osteoporosis
	Exenatide (Byetta)	Gila monster saliva (*Heloderma suspectum ssp.*)	Diabetes mellitus
Hematologic	Heparin	Porcine intestines and bovine lung	Acute coronary syndromes, deep venous thrombosis, pulmonary embolus, cardiopulmonary bypass surgery, atrial fibrillation, extracorporeal membrane oxygenation circuits, hemodialysis circuits, and surgical procedures requiring anticoagulation
	Protamine sulfate	Salmon sperm	Acute heparin toxicity/overdose
	Eptifibatide (Integrilin)	Venom of southeastern pygmy rattlesnake (*Sistrurus miliarius barbouri*)	Acute coronary syndromes, usually at the time of Percutaneous Coronary Intervention, and usually in combination with aspirin and heparin
	Lepirudin	Leech saliva (*Hirudo medicinalis*)	Anti-coagulation in patients with heparin-induced thrombocytopenia
	ATryn	Milk of goats genetically engineered to produce human antithrombin	Anticoagulant for patients with hereditary anti-thrombin deficiency who are undergoing surgical or childbirth procedures
Gastroenterologic	Pancreatin/ pancreatic enzyme replacement	Bovine and porcine pancreases	Cystic fibrosis, pancreatectomy, chronic pancreatitis, or other pancreatic deficiency
	Ursodiol	Bear bile (*Ursus sp.*)	Cholelithiasis, conditions causing cholestasis, including primary biliary cirrhosis
Infectious disease	Influenza vaccine	Chicken eggs (incubation)	Vaccine
Oncologic	Cytabarine	Caribbean sponge (*Cryptotheca crypta*)	AML, APML, ALL, CML, CLL, primary CNS lymphomas, Hodgkin and non-Hodgkin lymphomas
Musculoskeletal, integumentary, ophthalmologic	Hyaluronic acid	Rooster combs	Osteoarthritis, facial wrinkles or folds, ophthalmologic surgeries (i.e., cataract extraction)
	Calcitonin hormones (Calcimar, Miacalcin)	Thyroid-like glands in fish, particularly Coho salmon	Post-menopausal osteoporosis, hypercalcemia, Paget's disease
Pulmonary	Beractant	Bovine surfactant extract	Respiratory distress syndrome due to premature neonatal lungs
Selected research drugs	Antimicrobial peptides (i.e., magainin 2)	Alligator blood, skin of frogs and toads, Komodo dragons	Antibiotic synthesis, augmentation of beta-lactam antibiotics
	TM-601	Deathstalker scorpion (*Leiurus quinquestriatus*)	High-grade gliomas
	Trabectedin (ET-743)	Sea squirt (*Ecteinascidia turbinata*)	Treatment of soft-tissue sarcomas, particularly liposarcomas and leiomyosarcomas
	Aplidine	Sea squirt (*Aplidium albicans*)	Treatment of multiple types of solid cancers as well as ALL
	Crotamine	Venom of South American rattlesnake (*Crotalus durissus terrificus*)	Labeling highly replicating (tumor) cells, and use as a chemotherapeutic adjuvant