Submission on Gene-Editing

April, 2018

Introduction

In this document Friends of the Earth NZ are commenting on issues raised in papers sent us by the Royal Society of New Zealand, Te Aparangi, on the subject of gene-editing. We direct our comments to the Royal Society's discussion panel on this subject. We are a not-for-profit company that has been involved in environmental research and campaigning since our establishment here in 1975. In 2001 we participated in the Royal Commission on Genetic Modification and brought before that commission scientific and legal witnesses from New Zealand and several other countries. We have since submitted on the Hazardous Substances and New Organisms Act and other matters involving genetic manipulation. We are including with this response some further documents, the largest, now seventeen years old, being our main witness brief presented to the 2001 Royal Commission - "Epistemological, Methodological and Cultural Problems Associated with Genetic Modification".

We are making this available so the Royal Society discussion panel can see that arguments made in 2001 still need iteration, despite ever more evidence emerging in support of them. Our approach in 2001 was that organisms cannot be explained simply in mono-causal ways, as if they are mechanical artefacts, an assumption that has underlain far too much thinking in the history of bio-technology.

Discussion

One of our arguments in 2001, as now, concerns the way we use language in the discussion of biotechnology and the way such usages entrench our perceptions of the subject. We question the perception of 'genes' as a sovereign molecular structures telling other genes what to do - a concept that produces the popular saying: "it's all in the genes". By 2001 it was evident that it was not "all in the genes". It was plain that the intra-cellular world was an intricate, co-operative democracy, not a monarchy or dictatorship run by DNA. In the intervening seventeen years, despite ever-increasing evidence that gene sovereignty was

not real, these embedded ideas continue to create scientific and public misconceptions.

The emergence of epigenetics reveals that far more than genes act in the transmission of information.

> *Epigentic inheritance in the narrow sense is cellular....*
> *where the cell is the unit of transmission and variations*
> *that are not the result of DNA differences*
> *are transmitted from mother cell to daughter cell.*
> *Cellular epigenetic inheritance occurs during cell*
> *division in prokaryotes, during mitotic cell division*
> *in the soma of eukaryotes , and sometimes during*
> *the meiotic divisions in the germ line that give rise*
> *to sperm or eggs. In this latter case offspring inherit*
> *epigenetic variations through the germ line .* (1)

Francis Crick's sweeping Central Dogma about the role of nucleic acids in relation to the rest of the cell is now heavily qualified. This dogma insisted that information flowed from DNA to RNA, amino acids and proteins - a significant simplification of what actually happens, including the reverse transcription of meaningful information from RNA to DNA and the essential role of enzymes in the reactions necessary for translation. DNA is one of many agents in a cell, not a single and infallible master molecule.(2)

> *As soon as we think of DNA as part of the living cells*
> *of living organisms, we realize that even a relatively simple*
> *trait, such as eye colour, cannot possibly be "caused" by*
> *a single gene. Just the synthesis of the pigments*
> *that colour the iris of our eyes involves the participation*
> *of several proteins, the composition of each of which*
> *is specified by a different DNA sequence (or "gene").*
> *Further proteins are required to knit the base sequences*
> *of these genes together, these proteins require further*
> *genes for their synthesis, and so on.... We are dealing*
> *with a situation in which even the "simplest" inherited*
> *trait about which we speak as though it were transmitted*
> *by a single gene, such as sickle - cell disease or phenylketonuria,*
> *involves the participation of many proteins, and therefore*
> *of many "genes" (DNA sequences). The synthesis of these*
> *genes, in turn, requires further proteins, and so on and on.*(3)

There are many difficulties in deciding what a gene is. An editorial essay in *Nature,* May 25th, 2006, asked the question, "What is a Gene" and noted disagreement was so

widespread that "most geneticists are instead incorporating less ambiguous words into their vocabulary such as transcripts and exons. When it is used the word 'gene' is frequently

preceded by 'protein-coding' or another descriptor." (4) Hubbard, in "The Mismeasure of a Gene" (as above) enlarges:

> *Another level of complexity in the way DNA functions has to do with the fact that a "gene" - the piece of DNA that gets translated into a particular protein - often does not exist as a continuous base sequence on the chromosome....a base sequence that specifies the composition of a given protein may be interrupted by sequences that were, until recently. thought to be meaningless gibberish, As a shorthand , molecular biologists sometimes call the coding (or "expressed") sequences - those that get translated into protein - exons, and the presumably meaningless sequences, introns. But so far, no one understands how cells know how to cobble appropriate exons together and to splice out the gibberish so as to produce the final sequence (or "message") that specifies the composition of a particular protein.* To *make things even more complicated, exons often overlap, and different parts of a given base sequence may function in different genes. In addition, pieces of expressed coding sequence can be buried inside what are thought to be meaningless introns.*(5)

Are the exponents of CRISPR confident that the ambivalencies of these molecular structures can be anticipated and controlled? In their most commonly used configuration, CRISPR Cas9, it is presented to the public as a high precision tool that can exactly remove, alter or add to a target gene in a species like ourselves. The tool, abstracted from the immune structure of a bacterium has however already undergone engineering.

> *Jennifer Doudna and Emmanuelle Charpentier re-engineered the Cas9 endonuclease into a more manageable two-component system by fusing two RNA molecules into a "single guide RNA" that when combined with Cas9 could find and cut the DNA target specified by the guide RNA*.(6)

Two issues concern me about the micro-ecology of this. Firstly, is it conducive to cellular and molecular stability in the organism into which it has been introduced as an "editor"? Secondly, it is, strictly speaking, a kind of transgenesis. It introduces, in an engineered form,

a structure from a species other than the target species and makes the genome and DNA of that species subject to the action of an entity not previously know in nature. If this is not mixing taxa in some form, we don't know what is. And there may be very good reasons why *Homo sapiens* and numberless other target species for CRISPR do not have such endogenous cutting systems in their immune repertoire, and have evolved without them. We wonder whether the cutting system could prove to be irreconcilable with the morphogenic histories and future stability of ourselves and our innumerable non-bacterial relatives.

A FurtherDiscussion: Concerning Language, Human and Molecular

Language is crucial. The language used in the Royal Society papers on CRISPR and gene-drives conveys a particulate concept of the gene as a unit of heredity. Given the complexities already alluded to, this seems inadequate. To the examples of reductionist or mechanistic usages I gave in the 2001 Witness Brief I would add one or two taken from the current position papers.

The paper, "Gene Editing Update" makes the statement that long DNA molecules "carry instructions on how to build an organism." We accept that DNA contains stable information, but not that it" instructs". Instructions are the result of human cognition. To imply that DNA " instructs" is to suggest that an abstract human concept is equivalent to cellular information - embodied information - and that it will result in exact cellular obedience. Cells certainly demonstrate volition and reflexivity, but also infinite powers of choice and subtlety. Humans may "build" unliving things - a process whereby information moves from human prescription to an inanimate object. Cells are infinitely complex galaxies of knowledge that flows multi-dimensionally among populations of minutiae so numerous that no single fixed set of such entities - for instance Clustered Regularly Interspaced Palindromic Repeats - could be regarded as an instruction in the sense we conceive the word. They demonstrate rather, a process orchestrated by themselves as a totality, with input from the entire organism (if multi-cellular), and the environment as well.

For a long time the word "mutation" has been used to account for phenotypic change, assumed to be arising from changes in DNA. The Royal Society papers are not alone in using it in this way. It might be time to examine the implications of this usage. It suggest an almost

accidental or random change, even a mishap. It also suggests unexpectedness and often, speed of the event. The word creates what we might call a "semantic field" in our minds

that legitimizes our entry into the genome of living beings to bring about sudden alterations. We do so in the hope that the alteration will be benign - for someone. We say that mutations occur "naturally" and therefore, in "editing' genes, we are mimicking what nature does.

However, the semantics mask a problem. We do not really know what a mutation in an organism that is living in the real world, as distinguished from the world *in vitro,* might be. We assume that it is equivalent to our clean, swift, mono-causal"editing" of elements in a gene. In fact, a naturally occurring mutation may be a process of vast complexity, not random, but intricately modulated by the cell, organism, environment. Our thinking then proceeds from our strictly discrete concept of a mutation to the argument that organisms, by a combination of mutation and (Darwinian) selection, change almost by accident, as it were. Accidents do happen, and sometimes they work; but agency in living beings is very much more than the accidental.

A false parallel arises from this use of the word, mutation. This is the comparison of the selective breeding of plants and animals for human purposes, and the changes made by various forms of genetic manipulation. For millennia farmers have bred for observed and desired phenotypic traits in their crops and stock This process enables the species in question to retain their normal reproductive processes and draw on any genetic basis for the traits wanted without intrusion in the genotype by human action. CRISPR and other forms of genetic manipulation do not allow for this natural modulation in an organism undergoing selective, or human-guided breeding at the phenotypic level. Instead, the desired change or 'mutation' is forced into the organism from outside, without allowing the endogenous processes to modulate the change.

The way teosinte grass was changed into the modern maize plant was slow and allowed for the intrinsic ability of the plant to modulate those changes. Gene-editing would be fast. Indeed, that is cited as one of its virtues. It runs counter, in its time frame, to the time-frames both of ordinary evolutionary change and the selection for variation under domestication of agriculture for the past many millennia.

The very slowness of variation under domestication (now seen as too slow) may have been the factor that first assured viability and then non-toxic results in the alteration of teosinte grass into maize. Its stability as a food crop is possibly accounted for by the fact that normal ontogenic processes were not being disturbed by the gradual process of selective breeding.

The phrase "gene-editing" is also a homocentric projection. It suggests a controlled, quasi-literary process on a text with semantic entities like letters and words. The genome and its

nucleic acids have long been thought of as a language, but it is a language with many more terms than the various human languages that we make with our conscious minds and cultural experiences. The grammar is little known, the semantic elements in mind-boggling numbers. We have difficulty in knowing what a gene is. There is less difficulty in knowing the identity of a word, a letter, an ideogram. Even so, there remains intense disagreement over the meanings projected by our social and cultural languages. Every poet, every philosopher, every critic, novelist, dramatist and actor knows that context determines meaning, along with the nuances of the particular culture and period in which the language is being used. These meanings are infinitely plastic, argument about them unceasing. We can agree that molecular languages may have analogies with our cultural and social languages, but we have to admit the probability also that they have much more complexity, much more plasticity.

We also acknowledge that the creation of meaning in a society or a cell depends on the social or molecular language having interpreters. The interpretations are in perpetual process and vary widely in both social and molecular environments. In a cell, if we pursue the analogy, the interpretation of any edit or transgenic construct that comes in from the outside may be various according to the circumstances of cell, organism and environment The intended 'edit' will be no more sovereign or infallible than interpretations latent in DNA or other cellular information. There are many entities in cells with many purposes and meanings. Some of these may be acting in a role interpretive of the 'edit'.

The existence of an interpreters of cellular information has been discussed in this country by Dr Peter Wills, and described by him as a "molecular biological interpreter".(7) This phenomenon he sees as being inherent in life, which has the unique capacity of self-construction.

> *the possibility of self-construction derives from a formal semiotic relationship of reflexivity between structures, and functions, which is at most only implicitly dependent on the physical principles that underlie the structure-function relationship."* (8)

The relationship between structure (embodied information) and function (embodied interpretation) is a semantic one. In a recent personal communication Dr Wills enlarged on this as follows:

> *You asked me what I meant by the term "molecular biological interpreter. The essential idea is that no*

"written" information that is an encoded record (like a DNA sequence) has any intrinsic meaning. It has to be "interpreted" and that requires something that

"operates" on the information or "processes" it into another form.... What distinguishes biological Information processing from all others is that the the interpreter is self-constructung, but only on the basis of extant genetic information. In other words DNA information and its means of interpretation are inextricably, inexorably and existentially linked together. You could not have one without the other, so the process of their evolution must have been highly co-operative. Computers have interpreters that have been designed to act as kind of "one way algorithms" (like the Central Dogma) to produce results from input information. Molecular biological interpreters are completely different in that they are physically constructed by using information according to rules that they themselves set to construct themselves.(9)

CRISPR is put forward as a high precision technique to edit DNA information. It is important to remember that the claim of precision has been made about earlier forms of genetic modification such as transgenesis. These technologies all still have the assumption in them that the structure of entities called genes is fixed as if they are ball-bearings in a motor. The tenor or writing in the Royal Society's "Gene Editing" position paper supports this: "The genome contains all the genetic information needed to build that organism and allow it to grow and develop." In fact it contains an inert datum that is without meaning until subject to interpretation.

Organisms are not machines. That was the Cartesian fallacy; and it's still to be found throughout the biological sciences. Insofar as we can understand the principles embodied in life, they are not just those of Newtonian physics. Newton is great in prediction about inanimate objects, but animate beings require further levels of causal, or even acausal behaviour, such those explored by quantum theory. The arrival of that discourse in biology has not made organisms seem any simpler. In putting forward a theory of quantum phenomena being involved in human consciousness, the scientist, Stuart Kaufmann says:

Before we know anything else, this is really important.

Humans have about two thousand five hundred transmission factor genes. The number of possible combinations of activities of these genes is 2 to the

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two thousand five hundredth or about 10 to the seven hundred and fiftieth. There are only an estimated ten to the eightieth particles in the known universe, which means that the number of possible states of our regulating genes is enormously, vastly larger than the number of particles in the universe. (10)

Why Research Gene-Editing in New Zealand?

The most public reasons stated for gene-editing in New Zealand are to do with the control of "pest" species, principally animal. This is a question of great complexity and acrimonious debate. Less fraught is the question of gene - editing in health care. None can disagree with the proposition that it is good to cure intractable diseases. But in the background to this hover social, moral and political issues, and in the foreground are the inadequacies, dangers and unknowns of gene technologies. Further still in the background, but underpinning some of the cash for research are military interests.

The pest-control discussion has taken on attributes of moral panic and naïve sloganising in recent years. Individuals who suggest pest control methods might be ineffectual or harmful, or might need changing are, even in 'green' circles, viewed as ecological traitors to indigenous Aotearoa/New Zealand. The situation is the worse because pest controls have not restored the pre-human ecosystem of the country, and clearly that is an impossibility. Qualified success is achievable in oases that are insulated by the ocean or by expensive and fallible fencing systems. The goal of pest-free New Zealand is, in our opinion, unattainable on the mainland, and is leading to strategic misjudgements which are in some cases threatening to the very organisms they are meant to be protecting. The fact that the situation is serious and that drastic technologies of species elimination in this country are even being considered in the Royal Society Paper, "The use of gene editing to create gene drives for pest control in New Zealand" tells us present approaches are having at best temporary success, and at worst are dangerous and destructive. Nor is there any prospect of being able to stop pest control operations, ever.

Our belief is that we have to make the best of a bad situation, rather than aiming at an unattainable goal of complete freedom from introduced pest species; that we have to study closely and use the population dynamics both of introduced and exotic species to maximize the survival chances for those that are indigenous and threatened. We are not complacent.

Friends of the Earth has a track record of researching and campaigning on wilderness protection that began on the day of their establishment in 1975. Many of us were involved by then in the trying to prevent the destruction of South Island beech and beech/podocarp forests and had founded the Beech Forest Action Committee in 1973.
Thanks to 45 years of engagement is such issues we have no option but to define the worst pest species in New Zealand as *Homo sapiens.*

It is perhaps because this is so obvious, that it scarcely figures in the discussion. We are the worst part of the problem, but must also be part of the solution. Habitat destruction carried out by human beings over the last 800 years in these islands is the single greatest factor threatening indigenous species. All others are secondary to it. Until our laws and institutions and social habits are made equal to the task of preventing further destruction, and to the task of rehabilitating a lot that has already been destroyed, we cannot fully address the problem of achieving a survivable balance between introduced exotic species and threatened indigenous species.

We are surprised at how little note has been taken of the damage humans do directly. It deserved mention in the Royal Society papers, if only to state the huge legacy of damaged environments that we have left, quite independently of the actions of stoats, possums, cats, rats, etc. This damage is ongoing. The principle that indigenous forests on public lands should have the protection of the Crown, a principle established by the Clarke government in 2002, is being eroded by the weakening of protective legislation such as The Resource Management Act, and small but important incursions on conservation lands threatened by mining projects such as the Te Koha open-cast mine project, that would involve habitat destruction in Mt Rochfort Conservation park; or the Buller District Council's mulling over the idea of logging three blocks of indigenous forest on council-owned land in the Grey District.

At the moment we are in a stopgap situation, using emergency solutions to long term problems. The main methods of animal control are chemical and now, possibly, genetic. Neither is satisfactory and the second is still mainly hypothetical. If we must put other species to death the chemical methods are less apocalyptic than the genetic ones, such as the gene-drives discussed in the Royal Society papers. It is clear that poisons like 1080 and brodifacoum cause extensive by-kill, and replacement for them needs to be sought immediately. If the answer is to be chemical then we would advocate for the synthesis of

species - specific poisons that have no further effect in the environment than killing the target species. If science has the ingenuity to contrive species-specific gene-drives, it would be better that some of that ingenuity were put to work on a less risk-prone chemical

approach. 1080, the most universal and drastic of the poisons being used, should be pulled from use as soon as possible. Friends of the earth are against the mass aerial drops of 1080 and brodifacoum even now, and would want their use restricted to the ground in contained situations.

Cyanide compounds are far from ideal. They are dangerous to users and, though mercifully swift in killing the primary target animal, can cause within a short time-frame, some by-kill. The cyanide-killed possum will cause death to a stoat scavenging it for up to a week after the death of the primary target. But it does not pass into arthropod species and affect micro-flora and fauna. Whereas there is some suspicion that 1080 passing into arthropods and soils may pose a serious threat to soil ecology. In this catalogue of horrors, cyanide probably comes out best. It cannot be aerial dropped, but that may encourage its more thorough use in contained ground situations. All this reinforces our request that a lot of effort be put into species specific poisons being developed, and further, into ever better clever devices such as self-re-setting traps. Species - specific poisons could be aerial - dropped without fear of by-kill or pollution of soils and water.

Issues in the Pest-Control Debate

Control of the populations of exotic animals in the wild in New Zealand has been ongoing now for many decades, running back to the 1920s and '30s. It has been done with a set of assumptions about the nature and evolution of forests here in the pre-human aeons of this country's history. Since the inter-war years the ideas of Sir Leonard Cockayne (1855-1934) have dominated our views of forest ecology. Cockayne believed our forests evolved without animal browse.

> *In the forests of primitive New Zealand, except for certain species of Moa, there were no grazing or browsing animals, while so far as the giant birds were concerned these would chiefly live in the open.*(11)

Since 1926 that view has been qualified. In general literature Worthy and Holdaway's *The Lost World of the Moa* (2002) makes it clear that moa were forest dwelling, but offer little

further analysis. Some of that analysis in fact preceded them and is based on material in the gizzards of moa specimens held by Canterbury Museum. In 1941 this was discussed in a "Preliminary Report on Pyramid Valley Swamp" published in the *Records of Canterbury Museum*.(12) The gizzards of the birds, found originally at Waikari, were full of forest

materials, seed and twigs. Other literature on the subject followed. One key paper, published in 1989 by Dr Graeme Caughley, rigorously and specifically outlines the drastic change to forest structure with the loss of the moa as a browser, and hypothesizes that the browse function was restored, albeit differently, with the arrival of vertebrate "pest" species.

> *The history of the New Zealand biota over the last 7000 years may be divided into three phases. BC 5000 to AD 1000 was a period of comparative ecological stasis. That equilibrium was disrupted between AD 1000 and AD 1800 by the destruction of most of the New Zealand plant-herbivore systems, the co-evolutionary relationship between the plants and the vertebrate herbivores being decoupled about AD 1400. After AD 1800 new plant-herbivore systems were progressively developed and new ecological relationships forged.* (12)

Caughley's stark outline seems almost shocking. He takes no position on values or sentiments that favour any species or human culture as being more or less ecologically damaging. His concern is purely with the dynamics of connections between plants and herbivores. His evidence is sharply objective. The picture is obviously more complex and detailed than his summary allows, but it establishes that the forests were browsed at those levels that could be reached by moa species and accounts for the divarication in some indigenous plant species that is commonly interpreted as evidence they evolved to deal with browsing herbivores. An independent researcher, William F. Benfield has collated the research around this question and concludes:

> *There was a big population of moa, they were browsers, the land was substantially forested, the moa lived in the forests and consumed foliage. This would have had an impact on the forest. Removing moa would also have an effect on the forest.* (13)

The theory of an entirely unbrowsed pre-human forest has led to possible distortions in pest-control policy, causing a major focus on the brush-tailed possum, an introduced herbivore that can climb trees and indisputably eats foliage. It is a prime target of aerial 1080 drops. Here again the picture is not simple. There are important disagreements about

the actual population of possums, which is now being cited by the Department of Conservation as about 70 million. This is widely contradicted. The Royal Society in "The Use of Gene-Editing to create Gene Drives for Pest Control in New Zealand", p 10, uses data from which we infer a possible figure of twenty-five million possums. In 2009 Landcare

Research carried out a thorough study of possum numbers, the first since 1980: "How many possums are now in New Zealand following control and how many would there be without it?" The conclusions were that the carrying capacity of the country at that time was 47.6 million possums, but that the actual number was lower, 30 million, due to the operation of human controls. The figure of 70 million in use in 2009, as it is now, would not be possible because it is above the estimated carrying capacity of the country as a whole. Some estimates, credibly argued put possum numbers now as low as 5 million.

> *Possums have been harvested for their skins and fur around eighty years and the fur industry peak harvest occurred in 1979 at 3.2 million animals when helicopters allowed trappers into previously difficult country. Since then the annual harvest has dropped to around 1.2 million and has been stable at that for some years. Industry insiders believe the population is less than 10 million possum....All figures are at best estimates. My shrewd guess is probably little more than 5 million.* (14)

No-one disputes that possums eat foliage, but the amount eaten depends on population, its range varying in possibility between 5 million and 70 million. It is ironic that Cockayne believd that possum did little damage. W.F.Benfield cites a report by Sir Leonard, June 1930, written for the then state Forest Service:

> *But the forests as far as damage from possums goes, are as they ever were. If damage of any kind there be. It is so slight as to be negligible. Nor do these animals affect the all important floor covering or reduce the seed crop to any extent.* (15)

Important in this question of numbers is the replacing of them. Possums are a marsupial with a low breeding rate - just one offspring per female per year. Whereas other introduced vertebrates - the rat, the cat, the rabbit, the stoat all have many times that reproductive rate. These factors need thorough analysis if long-term control strategies are to be successfully designed, We claim no specialist knowledge in the dynamics of animal populations, but what is obvious is that there is an urgent need for review of the scientific literature, going back many decades, that is concerned with these questions, plus a review

of the experience of those who deal with the practicalities of looking after indigenous forests and balancing the populations of animals within them, indigenous and exotic.

At the moment much energy is spent on the possum, which might be better spent on the fast-breeding predators, and the blitzkrieg policy of mass aerial drops is a too clumsy an approach to avoid serious collateral damage in forest and wilderness eco systems. There is a danger that the drops will become institutionally entrenched - a one-dimensional approach to a multi-dimensional problem. Then the problem emerges that careers are built out of mass -poisonings and careerists become difficult to convince of the need for subtle approaches. Then financial interests get locked in and dependent on what should be no more that a temporary expedient.

1080 was made as an insecticide, but is fatal to all virtually all other animal species. There is no question that it creates by-kill at every level of the biota. In June 1994 a paper studying the by-kill effect at a test site in Taranaki was suppressed by the organization that had commissioned it, the Department of Conservation. Its author, Dr Mike Meads found evidence of by-kill reaching into insect species, some of which are responsible for breaking down leaf litter on the forest floor. This find posed the question of the long-term effects of 1080 on the availability of nutrients in the soil needed by plant life on the site and in forests generally. This study "Effects of Sodium Monofluoroacetate (1080) on non-target invertebrates at Whitecliffes Conservation Area, Taranaki". Investigation No 1414, June, 1994, had to be obtained by the researcher, W.F.Benfield using an Official Information Act Request. (16) We hope the Royal Society discussion panel will assess the paper and others of related subject matter.

Collateral damage can involve humans and occur in urban areas. In 2009 eighteen people in Murupara were hospitalized after breathing in the toxic gas, hydrogen fluoride that comes from the burning of 1080 bait pellets. In this case a storage building had caught fire. In 2017 23.7 tonnes of 1080 baits were stored in Whitianga for use over Coromandel. No local safety services were notified and the storage, by the Department of Conversation was in breach of safety provisions of several laws, including The Hazardous Substances and New Organisms Act. To date, no explanation has been received by the complainant who sought the facts through the Official Information Act. (17)

We note that 1080 is banned from general use in the mainland of the country where it was developed, the USA. Ironically, New Zealand-based techniques and New Zealand personnel involved in the aerial drop industry are being commissioned for pest control on islands of other jurisdictions, including those of the USA. This is of some relevance if gene-drive

technology is developed in New Zealand. It could be similarly on request by other states. That is why we recommend that the Royal Society study the issues and pressures around the use of poisons on possums and other control species. Similar pressures could be brought to bear in the use here and overseas of gene drives.

Friends of the Earth have had involvement as monitors of aerial drops around the greater Auckland district because of our sustained concern about by-kill of non-target species, pollution of waterways, damage to fish, and damage to humans during the drops and the long subsequent periods when the toxin remains in the environment or the carcasses of poisoned animals. We were approved as monitors for the Auckland Regional Council in the 1080 drop on the Hunua ranges in the early '90s. Subsequently, at Tawharanui Peninsula, we monitored a brodifacoum drop designed to eliminate pest species from the fenced reserve on the peninsula. There we stipulated the design of the drops, to lessen likelihood of brodifacoum overspill into non-target areas. These recommendations were fully developed and used in the aerial drop of brodifacoum on Shakespeare Regional Park, Whangaparaoa, which we also monitored. We believe the techniques, worked out by our Auckland director, Bob Tait, and our Northland director, Paul Tucker, are still in general use in the Auckland region and might well be applied throughout the country. They are not a long term solution, but are at least ameliorative. We continue to be concerned with by-kill and are aware it affects endangered species such as the kea in the South Island and the dotterel on the coasts of Northland. There are also public health issues in regard to humans that have too little attention paid to them. It is vital, for instance, that 1080 does not get into tributary streams or reservoirs of the water supply dams - something very difficult to avoid during an aerial drop in the catchment of the Hunua dams. When dissolved, even in a very large water body like a reservoir, 1080, as an endocrine inhibitor, can affect humans at extremely low dosages. (18)

A new Genetics?

Given that mass drops of poisons are major contributors to the political and ecological minefield of exotic pest controls, should we not welcome the CRISPR technology? It lays claim to no by-kill, does not need expensive aerial drops and, used in a gene drive, is species specific. In the field of human health it could be useful in curing chronic and intractable diseases. These are real advantages. However, for all the reasons discussed in earlier parts of this commentary, and a few more to be discussed, we do not welcome CRISPR, gene-editing or gene-drives with open arms. The rhetoric with which the media have surrounded these still largely hypothetical processes verges on the euphoric. There is much reassurance that it is accurate, high-precision and harmless. The Royal Society itself would seem to be

slightly wary of such claims. In discussing evolutionary resistance in a species to passing on a "driven" gene construct they note that:

> *based on the population genomics results from Anopheles gambiae [mosquito], gene-drives are*
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>
> *unlikely to work unless multiple target sites within those genes are targeted. Increasing the number of target sites in the genome leads to a corresponding increase in the probablity of off-target effects with the associated and ethical concerns*. (19)

The driving of a gene through entire populations of a species on an island, or in a region, may be a sharp technology with rather "blunt" results, entirely unforeseeable.

The appeal of gene-driving in getting the German wasp out of new Zealand is understandable. However, these creatures, loathsome and a danger here, are valuable in the eco-systems of other countries. A driven gene for their sterilization could be transferred to those wasps in a country where they are so valued. The same argument applies to the brush-tailed possum. Both these examples of species that have real value in their own environments are the Royal Society's and we concur with them. In the latter case, the danger of a sterilized female carrying the gene drive into the Australian population of brush-tailed possums from New Zealand is real. There is considerable private traffic by sea between our countries, and the danger of an idiot simply wanting to wreak havoc by smuggling a gene-driven female into Australia is right on the cards.

There could not be a more cogent warning of gene drives getting out of control than that given by the US National Academy of Sciences and quoted by The Royal Society

> *Gene-drives do not fit well within the existing regulatory logic of confinement and containment because they are designed to spread a genotype through a population, making confinement and containment much more difficult (or even irrelevant) and the environmental changes introduced by release potentially irreversible....*(20)

Driving a gene through a whole species could be sufficient grounds in itself for it not to be done. The safeguards on p. 16 of the Society's gene drive paper, suggested by Akbari, AS et

al., "Safeguarding gene drive experiments in the laboratory" are common sense, and we certainly agree with them, but they beg the question that, if this process is efficient at driving genes, should it be pursued as research at all? This might be one compartment of Pandora's Box that could remain closed.

16

One force behind this technology is the agenda of those who appear to be ready to finance it in New Zealand, a Pentagon-associated group called DARPA, or Defence Advanced Research Project Agency. In the *NZ Herald*, 5/12/17, a long article by David Fisher outlines the interactions of DARPA with New Zealand government agencies and NGOs such as GBird, involved in pest control research. This sits uncomfortably with clear-headed and dispassionate research. A possible recipient of such funding is Dr James Russell of Auckland University.

> "*in this instance Russell's work was being measured for suitability against a $US 100 million research pot made available by the US Defense Advanced Research Projects Agency. Also being evaluated were remote islands around New Zealand , sized up for live trials of genetically modified rodents. The interest in Russell emerged during an investigation into the activities of a multi-national science advocacy and gene drive research body called GBIrd - Genetic Biocontrol of Invasive Species."* (21)

It appears that DARPA is concerned that gene drive techniques might fall into the wrong (terrorist?) hands. They have correctly assessed them as an inherently weaponised technology. Dr Russell is perfectly up front about this: "We're in the business", he says, of eradicating entire entire populations of animals from an island and so they have cocked their ears towards me once or twice. You don't have to be a genius to see there's a potential military application in that." (22)

Governments are anxious to emphasise that their development of endgame technologies such as nuclear weapons, chemical weapons, and now possibly genetic weapons are pursued for purely preventative reasons. They don't admit that once the technology is made, it is extremely difficult to unmake. The horse has bolted, and having bolted, can readily deliver the weapons to organizations and individuals who are happy to use it for the worst possible reasons.

In the background of the twenty-first century gene drive concept is the nineteenth century concept of scientific eugenics, and the long history in the USA of eugenic programmes and legal structures as tools of social control. The Royal Society's position paper, "Gene Editing in a Healthcare Context" includes on p.8 a section on the "Introduction of a genetic variant to improve prospective offspring: hereditary genetic enhancement." It recognizes the imponderable ethical questions that have to be taken into account and, we are glad to see,

does not recommend eugenic usages of CRISPR. We are less certain that there is an awareness of its possibility outside of New Zealand, practiced by the states or powerful individuals. We recommend a succinct study to the attention of the Discussion Panel: *The Nazi Connection. Eugenics, American Racism and German National Socialism,* Stefan Kuhl, New York, Oxford University Press, 1994.

This is not a past history. Kuhl makes it clear that US eugenics pre-dated and directly influenced those of Nazi Germany. He then shows that co-ordination of US and German racial 'science' continued long after a temporary break in 1941, when the US entered World War II. This relationship was passed down through post-war eugenicists and was still active in 1994 when Kuhl published his study. This writer can vouch for its ongoing during the period of The Royal Commission on Genetic Modification here in 2001. Friends of the Earth made comment on a vigorous eugenics/genetic literature coming out of the USA at that time. The Commission chose not to focus in any way on the possibilities of gene technologies being used in implementing eugenic or racial policies. Gene drives again raise the tired, old, but still socially dangerous, spectre of the perfect human being, the perfect race, protected from an *untermenschen*, who are not allowed to breed, but are allowed to serve the racially perfect.

The scenario on page 8 of the position paper mentions another scenario, perfectly conceivable in modern affluent societies: "a futuristic possibility of parents wanting to modify their embryos to give their offspring a competitive advantage in life." (22) This is not really a "futuristic scenario". It is printed already into the thinking of many wealthy and ambitious families in contemporary consumer societies like ours. It will be activated the instant that genetic technologies like CRISPR offer a chance for its expression. This is not eugenics enforced by the state. It is rather the boutique eugenics of an elite.

In social democracies we might assume that boutique eugenics will be deemed unacceptable; but such services would quickly come to be offered in countries not bound by the scruples that, we hope, would guide the governance of this one. It is easy to imagine "eugenic tourism" taking place, just as now other medical tourisms are happening. Gene-drives in human populations, not for eugenic purposes, but for the control and lessening the numbers of "undesirables", are also a danger - a discreet form of slow sterilization of social

groupings that have been confined by force - Palestinians confined by the Israeli state, Kurds confined by the Turkish state, various ethnic and political factions captive in a future Syria ruled by the likes of Assad?

The more likely scenario though is that gene drives could be utilized as a means of laying waste to a country's agriculture - its crop-plants being an obvious target in a war situation.

Apart from bringing about massive starvation of innocent civilians, this would involve the additional danger that "driven" plants could spread in the chaos of war, far beyond regional or national boundaries and cause the gene-drive to become active on a general scale in plants essential to our survival.

It seems gene drives are believed in some cases to have high efficiency, presumably in driving the edited DNA through the target species. To help limit this and make complete elimination of target populations possible to stop, recommendations have been made to use a "reversal" gene drive that could replace the gene originally altered or edited out of the target genome with the gene that had originally been there. Hypothetically this safety measure appears rational. We have doubts whether a reversal of a gene drive that's sterilizing a crop species or an unwanted carnivore in New Zealand forest could easily be achieved out in the reality of the open environment, or neatly in a genome that had already been disturbed by editing. Our reservations about this apply also to the "daisy chain" gene drives as ways of bringing a rogue gene drive back under control. Even at the level of phenotypes being released we know precisely from our experience in this country how hard it is to bring under control a population of exotic animals." Edited" animals will surely pose a similar problem. (23)

Setting aside the question of long-term dangers to our own and other species that could be caused by "driving" and "editing' genes, we ask a second question. Why should New Zealand, a country that has a history of rejecting dangerous and/or weaponised technologies such as food irradiation and nuclear reactors, provide test sites on our offshore islands for research that could be mis-used in war or in a eugenics context?

These are the dangers. We cannot , in the scope of this document, comment in detail on some of the medical benefits that are hypothetically possible, such as a successful treatment for sickle-cell anaemia. On humanitarian grounds we would support the use of gene editing to treat such disorders if they were likely to succeed, and if they involved somatic tissue treatment rather than the placement of edited genes in the human germline. That was basically our position at the 2001 Royal Commission. It's a case of risk versus

suffering, and in cases like these we would accept risk. There are serious questions about how real it is to believe serious chronic illnesses are caused by a single gene or part thereof.

> *Even the symptoms of diseases like Phenylketonuria, cystic fibrosis and sickle cell anaemia, all of which are conditions that were once thought of as being directly caused by the actions of single genes - are now*

> *recognized as phenotypes caused by a variety of factors that interact in complex ways during [their] development.* (24)

It would be a blessing if a neat "edit" of an ambiguous length of DNA could remove the defect that causes sickle cell anaemia. Are the complexities discussed n the literature just cited able to be unraveled , allowing an editing approach to work, or are these complexities that are best treated at the level of the phenotype?

Conclusions

We believe the public debate on genetic engineering has scarcely yet occurred. New interpretations of the respective roles of DNA, the environment, the micro-ecology of the cell, and the organism as a whole are emerging thick and fast but are insufficiently discussed. As the sovereign molecule DNA has had it s day. Because of the very fluid state of genetic theory and the constant pressure to monetize such theory long before its depths and subtleties have been properly understood, we welcome the chance to comment on the Royal Society's position papers and hope such commentary is useful. If we criticize, such criticism is not *ad hominem.* It is done to keep the doors of open debate open.

We are concerned that the media and major agencies of government can still present to the public rather simplified accounts of the science involved in the subjects we have been discussing. The iconic status that DNA has in the debate needs to change. This useful molecule has become a cliché, its true meanings and functions obscured in the public arena. The Royal Society is one of the organisations that has some ability to change this - an ability we would like to see used. Its position papers on CRISPR, gene-drives, and gene editing do provide openings into the discussion and the formulation of policy. But they fail to mention the rapidly developing areas of genetic science, especially of epigenetics, which impinge directly on the technology of gene-editing and its effects. Similarly lacking is discussion of many intracellular structures such as the "interpreters" of information in DNA.

These kinds of factors greatly increase appreciation of complexity and causality in the heredity, metabolism and ontogenesis of living beings. They are not marginal issues , but are central to the debate. In some cases, knowledge of them has been around for decades. Dr Barry Commoner made a cogent critique of the Watson/Crick DNA interpretation in two papers published in *Nature* during the 1960s: "The roles of deoxyribonucleic acid in inheritance", *Nature* 1964, 203, pp486-491 and "Failure of the WatsonCrick Theory as a

chemical explanation of inheritance", *Nature* 1968, 220: pp 334-4. Even the familiar double helix has been credibly questioned in, for instance, "Variety in DNA secondary structure", *Current Science, Vol 85 No 11, 10 December, 2003, CS Delmonte and LRB Mann.* That being the situation, the use of the double helix as a reassuring logo about our knowledge of genetic science, should perhaps be discontinued until we are certain of what its form is, or whether indeed it has a plurality of forms. At the moment the Royal Society's images of the molecule are given in the conventional double helical form.

The time has come to create a new synthesis of the research and interpretation that has appeared since the findings of Watson and Crick in 1953. Sixty-five years have passed, and it is vital that technologies like CRISPR, now being prepared for use, are consistent with the wide range of recent findings in genetic and evolutionary theory .

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