**////Title: Insect Juvenile Hormone: A Rich History of Surprising Discoveries**

**////Standfirst:**

The story of research into juvenile hormone, a fundamental chemical that regulates insect life history, follows the same thread as many other tales of scientific discovery. A series of serendipitous findings and observations led researchers to identify this unique hormone and isolate it from a moth. Additional studies focused on its potential as an insecticide, given that it has diverse effects on various aspects of insect physiology. In a recent review paper, Professor Lynn M Riddiford of the University of Washington details major developments in the history of juvenile hormone research.

**////Main text:**

Endocrinology, the study of the endocrine system and the hormones it secretes, has demonstrated the importance of these chemicals to a variety of physiological functions. In the insect world, hormonal control of metamorphosis – when an insect transforms from juvenile to adult – was not appreciated until the early 1900s.

Since then, our understanding of insect juvenile hormone and its application has grown tremendously. In a recent review paper published in *Frontiers in Cell and Developmental Biology,* Professor Lynn M Riddiford takes the reader through a fascinating series of major breakthroughs in this field.

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Research into hormonal regulation of insect metamorphosis took off in 1934, when British entomologist Vincent B Wigglesworth, working with the insect *Rhodnius prolixus* [rod-nee-us pro-lix-us] found that a hormone prevented the metamorphosis of juvenile insects.

Through a series of ingenious parabiosis [par-uh-bi-oh-sis] experiments, in which two living organisms are joined surgically, Wigglesworth removed the heads of insects at one life stage and attached their headless bodies to the headless bodies of insects at another life stage.

By manipulating the life stages of the pairs, he showed that there must be a hormone secreted in the head that determines whether an insect would undergo metamorphosis. Wigglesworth then determined that this ‘inhibitory hormone’ – which he termed the ‘juvenile hormone’ – was derived from a region of the insect’s head known as the ‘corpus allatum’ [core-puss ah-lay-tum], located behind the brain.

Later, Wigglesworth published research that showed that the corpus allatum reactivates in adult insects. However, in adult insects, the hormone had a different function. Rather than affecting metamorphosis, it regulates reproduction in adults. This unique finding – that one hormone regulated both metamorphosis and reproduction in insects – was ground-breaking, spurring other researchers to conduct similar experiments in different insects. These studies showed that, in most insects – such as grasshoppers, flies and cockroaches – the corpus allatum is necessary for reproductive maturation.

Since its discovery by Wigglesworth in the mid-1930s, the juvenile hormone, its applied use, and its associated cellular receptors have been the focus of rigorous research.

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In the early 1950s, zoologist Carroll M Williams began to explore Wigglesworth’s unique experiments. When Williams attached the abdomen of an adult Cecropia [See-**crow**-pee-ah] moth to a pupa, he was surprised to see that the pupa developed into a second pupa, rather than into a normal adult! Williams posited that there was a natural reservoir of juvenile hormone within the abdomen of the moth that inhibited pupal metamorphosis into an adult. Eventually, Williams extracted the juvenile hormone from the abdomen of the moths, calling it the ‘golden oil’ for its bright yellow colour.

In her paper, Professor Riddiford emphasises how Williams’ discovery of this yellow extract had immediate potential for applied use. Williams himself commented on the efficacy of using the extract to disrupt metamorphosis, indicating that it may serve as a potent insecticide, since insects would be hard-pressed to develop resistance against their own hormones. When Karel Sláma [Kar-**ell** **Slah**-mah] came to Williams’ lab to study, the pair made another chance discovery.

While rearing linden bugs in glass jars, Sláma put paper towels in the jars to mimic the Czechoslovakian linden trees on which the insects naturally live. However, he noticed that the bugs did not undergo metamorphosis. Eventually, he discovered the cause – the paper towels. However, the insects were particular – the linden bugs underwent metamorphosis when reared on European paper towels, typically made from pine, but did not when exposed to American paper towels, which are made from balsam fir. The researchers were able to isolate a particular chemical within the fir, calling it the ‘paper factor’ that was chemically similar to insect juvenile hormone.

Future research showed that this chemical would only prevent metamorphosis for certain insects in the same family as the linden bug. This finding gave Williams and Sláma hope that they would find other similar selective juvenile hormone analogues that could allow for the development of pesticides with high specificity, preventing pests from undergoing metamorphosis without affecting beneficial insects, such as bees.

Throughout the story of juvenile hormone research, Professor Riddiford stresses the accidental yet ground-breaking nature of some of these findings. This research, for example – stemming from a completely random choice of paper towels – was crucial in the development of certain insecticides that are now commonly used against mosquitoes and fleas.

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Once juvenile hormone was identified, a search for its cellular receptors began. Such research has proven to be long and complicated. However, although our understanding of the interactions between the hormone and the cell membrane is incomplete, strides have been made in the identification of its intracellular receptor.

In 1986, scientist Tom Wilson exposed male fruit flies to a chemical mutagen, then exposed their offspring to a diet containing a high concentration of methoprene [meth-oh-preen] – a chemical that is very similar to insect juvenile hormone. This experiment selected mutant larvae that were tolerant of the effects of methoprene and 100 times more resistant to the effects of juvenile hormone. This led to the discovery that an intracellular receptor later termed ‘methoprene-tolerant’ – or ‘Met’ for short – is likely associated with insect juvenile hormone.

In 2007, this hypothesis was confirmed by a team who suppressed the production of Met in early-stage beetle larvae and obtained precocious metamorphosis. The absence of Met in the cells of these larvae prevented the usual responses to juvenile hormone, suggesting that Met is a crucial receptor for juvenile hormone necessary for its action.

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In her seminal review paper, Professor Riddiford details numerous milestones in the history of insect juvenile hormone research. From Wigglesworth’s initial, ground-breaking parabiosis experiments, to future research that hinged upon opportune and unexpected findings, our understanding of the myriad roles and functions of juvenile hormone has grown tremendously.

Given that there are many aspects of this hormone that are still poorly understood, such as the molecular mechanisms involved in its action, we can only anticipate further surprising discoveries in years to come.

This SciPod is a summary of the paper ‘*Rhodnius,* Golden Oil, and *Met:* A History of Juvenile Hormone Research’ from *Frontiers in Cell and Developmental Biology*. [doi.org/10.3389/fcell.2020.00679](https://doi.org/10.3389/fcell.2020.00679)

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