HORMONES AND ME

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Australasian Paediatric Endocrine Group

SERONO SYMPOSIA AUSTRALASIA

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Table of Contents

About this Book

Congenital Adrenal Hyperplasia (CAH) provides a basic understanding of the role of the adrenal glands, how congenital adrenal hyperplasia affects adrenal function, the effect this has on growth and metabolism and the treatment options available.

The reader is encouraged to discuss any additional questions or areas of concern with the doctor after reading this booklet.

Serono Symposia Australasia is pleased to bring you ***Congenital Adrenal Hyperplasia (CAH)***, which is part of their "Hormones and Me" educational booklet series. We hope that you will find it a valuable and helpful resource.

We wish to express our gratitude to Serono Laboratories (UK) Ltd and the Child Growth Foundation for allowing the distribution of this booklet, which was updated and reproduced for Australian and New Zealand readers in 2000. Special thanks to the original authors and editors, Dr MDC Donaldson (Royal Hospital for Sick Children, UK), the late Dr DB Grant (Great Ormond Street, UK), Dr Richard Stanhope (Great Ormond Street Hospital for Children and the Middlesex Hospital, UK), Mrs Vreli Fry (Child Growth Foundation, UK) and the British Society of Paediatric Endocrinology (BSPE).

This booklet was reviewed and edited with the help of Associate Professor Garry Warne, (Royal Children's Hospital, VIC, Australia) - a Paediatric Endocrinologist specialising in childhood endocrine disorders and a member of the Australasian Paediatric Endocrinology Group (APEG).

Dr Margaret Zacharin, a Paediatric Endocrinologist (Royal Children's Hospital, VIC, Australia) has reviewed the booklet range on behalf of the Australasian Paediatric Endocrine Group (APEG).

Introduction

Congenital adrenal hyperplasia (CAH) is an inherited condition that affects the production of hormones from the cortex of the adrenal glands. The term describes what the adrenals look like in this disorder and can be translated as a thickening or overgrowth (hyperplasia) of the adrenal glands before birth (congenital).

"Congenital adrenal hyperplasia (CAH) is an inherited condition that affects the production of hormones from the cortex of the adrenal glands."

The adrenals are two small glands that lie close to the kidneys (see Diagram 1). Each gland consists of two parts – the medulla (inside part) and the cortex (outside part). The cortex produces three main hormones – cortisol, aldosterone and androgen (or male hormone). The main hormone to be affected in CAH is cortisol but sometimes the disease affects the production of aldosterone as well. While cortisol and aldosterone levels tend to be low, androgen levels tend to be high.

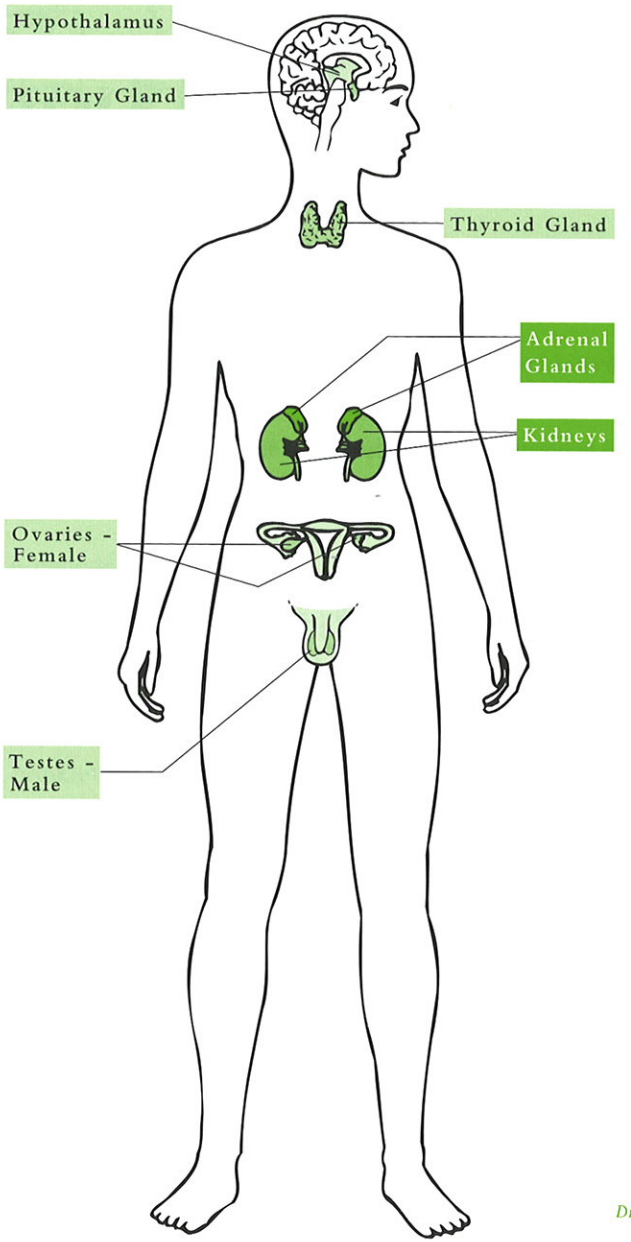

Diagram 1

What Does the Adrenal Cortex Normally Do?

The hormones produced by the adrenal cortex are called steroids and are essential for normal growth and metabolism. The three main hormones - cortisol, aldosterone and androgen (male hormone) are made from cholesterol (see Diagram 2), and their important functions are explained in the section that follows.

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Cortisol

Cortisol plays a vital role in regulating blood pressure, blood sugar levels and the immune system. Cortisol is particularly important in helping the body combat stress (such as an infection or injury) and in raising blood sugar levels when they are low. During these times the body must produce more cortisol to keep up with demand.

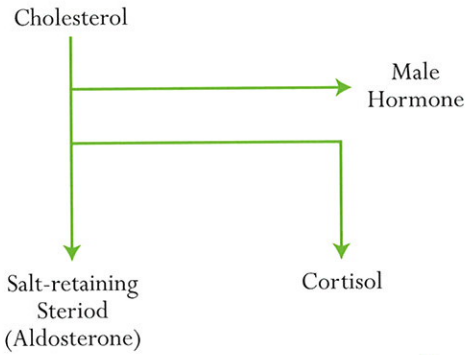

Diagram 2

Aldosterone

Aldosterone is a salt-retaining steroid that acts on the kidneys to help control the excretion of salt in the urine. It is important to prevent the accumulation of salt in the body (which can cause high blood pressure and fluid retention) while at the same time preventing excess salt loss (causing vomiting and dehydration). Aldosterone makes the kidneys retain salt when the body's salt levels are low. When the body's salt levels are high, the adrenal cortex reduces the amount of aldosterone produced, allowing the kidneys to excrete salt in the urine.

Androgen

Androgen is the male sex hormone that is produced by the adrenal cortex in both sexes and in the testes in males. In both males and females, adrenal androgens contribute to the formation of pubic hair during normal puberty.

The Control of Cortisol Production

The amount of cortisol produced by the adrenal cortex is controlled by a small gland at the base of the brain called the pituitary gland, which is connected to a part of the brain called the hypothalamus (see Diagram 1). When the body needs more cortisol, the hypothalamus stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH).

ACTH is released into the blood stream, reaches the adrenal cortex and stimulates the production of cortisol. As cortisol levels rise, the hypothalamus senses this and stops stimulating the pituitary gland to produce ACTH, which in turn slows the production of cortisol from the adrenal cortex.

What Goes Wrong in CAH?

The process of making steroid hormones from cholesterol in the adrenal cortex is very complicated. A protein called an enzyme brings about each step. In the common form of CAH, the enzyme 21-hydroxylase is not working. This interferes with the production of cortisol and aldosterone but not the production of androgen (see Diagram 3). The pituitary gland senses the low levels of cortisol, produces ACTH which over-stimulates the adrenal cortex causing it to increase in size. The result is a deficiency of cortisol and aldosterone and an excess of androgen.

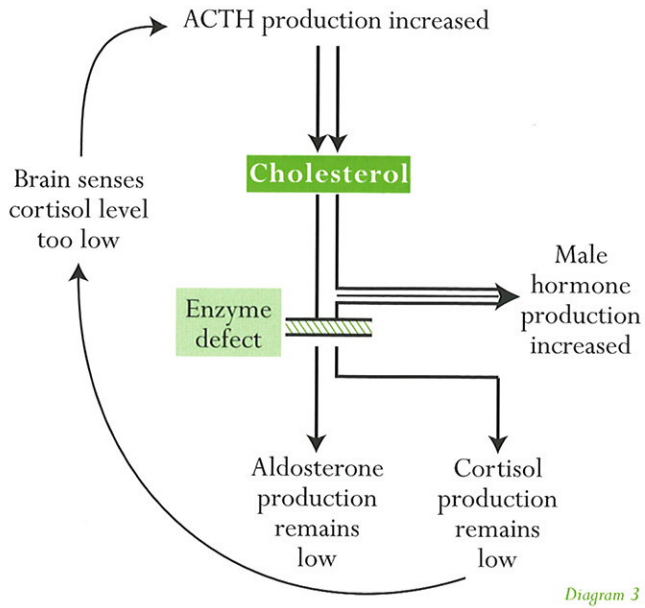

Diagram 3

Types of CAH

There are three main types of CAH: severe salt-losing CAH, severe non-salt-losing CAH and a milder form of CAH that may go undetected. The severe types of CAH are also known as 'classical CAH' while the milder form is known as 'non-classical CAH'. The type of CAH depends on the severity of the enzyme defect.

"There are three main types of CAH: severe salt-losing CAH, severe non-salt-losing CAH and a milder form of CAH that may go undetected."

Severe Salt-Losing CAH

This form of CAH results from a severe enzyme deficiency resulting in low levels of cortisol and aldosterone but high levels of androgen. Boys with this type of CAH will look normal at birth and the first signs of the disorder are usually poor feeding, weight-loss and vomiting occurring between the first and second weeks of life. This is due to salt and water loss in the urine due to low levels of aldosterone and requires urgent medical treatment.

Girls with severe salt-losing CAH are more easily diagnosed. They often have male-like genitalia (masculinisation) due to their high levels of androgen while developing in the womb. The outer lips of the vagina (the labia) tend to

be fused like a scrotum and the clitoris enlarged like a penis making it difficult to tell at first glance if the baby is a girl or a boy. The sex of the child can be confirmed with a blood test examining the sex chromosomes. If the diagnosis is delayed, girls are prone to the same salt-losing problems as boys.

Severe Non-Salt-Losing CAH

This form of CAH results from a milder enzyme defect resulting in low levels of cortisol, normal or slightly low levels of aldosterone and high levels of androgen. It does not generally cause severe illness in the newborn, although the genitalia of girls may be mildly masculinised. Because aldosterone levels are normal or only slightly low, these children do not have the same problem with salt-loss as children with severe salt-losing CAH.

Signs of the condition in early childhood include rapid growth and the early appearance of pubic hair. Boys may have enlargement of the penis and girls have enlargement of the clitoris. These effects are due to excess male hormones. Although these boys and girls tend to be tall for their age, if untreated they will be short adults as the male hormones cause the bones to mature rapidly and growth finishes earlier than normal.

Non-Classical CAH

"This form of CAH is so mild that there may be no symptoms in childhood at all."

This form of CAH is so mild that there may be no symptoms in childhood at all. Signs of mild CAH include rapid early growth, early appearance of pubic hair, acne, blood pressure problems and difficulty fighting infections. Women may have excess facial hair, irregular periods and difficulties becoming pregnant.

Who Gets CAH?

CAH is an inherited disorder and to understand how it is passed on it is necessary to know a little about chromosomes and genes. Chromosomes are thread-like structures contained in every cell of the body and genes are tiny areas on the chromosomes containing genetic information. Genes determine a person's characteristics from the moment of conception and the information contained in the genes is essential for development and normal body functioning.

Each cell contains 23 pairs of chromosomes, one of each of the pair coming from the mother and one from the father. CAH results when two defective genes for adrenal enzyme production, one from each parent, are inherited. The parents do not have CAH because they have one defective gene and one normal gene, which are dominant and overrides the faulty gene. These parents are called 'healthy carriers'.

When two 'healthy carriers' have children, one in four will have CAH (inheriting two defective genes), one in four will be normal (inheriting two normal genes) and two in four will be 'healthy carriers' like their parents (inheriting one defective gene and one normal gene). This pattern of hereditary is known as autosomal recessive inheritance (see Diagram 4).

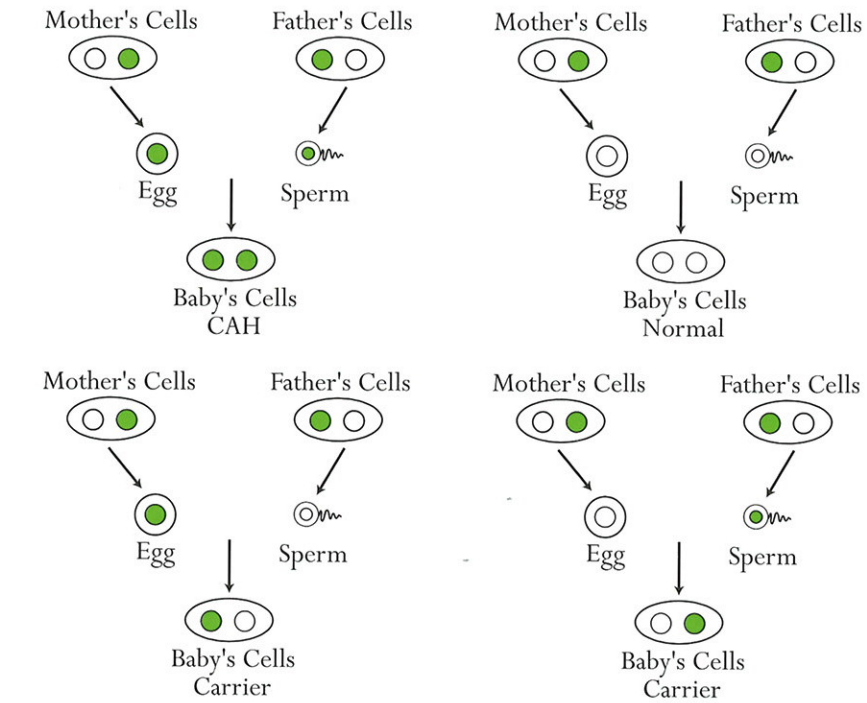

Diagram 4

The partners of people with CAH must be healthy carriers in order to produce children with CAH. The risk that a partner may be a healthy carrier is around 1 in 50 although this risk may be greater amongst certain racial groups or if the partner is a blood relation, such as a cousin.

A person with CAH whose partner is not a carrier will have children who are healthy carriers.

A person with CAH whose partner is a carrier has a one in two chance of having a child with CAH

Diagnosis of CAH

A doctor may notice CAH by physical appearance, symptoms or through a family history of the disease. To confirm the diagnosis, the doctor may take blood and urine tests measuring the levels of cortisol and the raw materials which make up cortisol. Measuring cortisol levels can also help families determine if they are carriers for CAH.

"Measuring cortisol levels can also help families determine if they are carriers for CAH."

It is known that the gene for CAH is located on chromosome 6, close to a well recognised gene for white blood cells, human leukocyte antigen (HLA). HLA testing and DNA analysis can determine if the normal gene for the 21-hydroxylase enzyme is present and can help in detecting carriers. Prenatal diagnosis is available to those with a family risk of CAH. This involves testing tissue or amniotic fluid from the unborn baby.

Available Treatment for CAH

The aim of treatment in CAH is to provide the body with the ability to maintain normal sugar levels, balance water and salt and undergo normal growth and sexual development. This means replacing the hormones that are deficient. Successful treatment is a lifelong undertaking and relies on close medical supervision with regular evaluations and dosage adjustments.

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Cortisol can be replaced by treatment with a number of synthetic steroids such as hydrocortisone, prednisolone or dexamethasone. All these medications are relatively cheap and available in oral form. Dosage must be tailored to each child's needs and is usually given 2 - 3 times a day. In times of stress such as infection, injury or surgery, the body's cortisol rises so extra hydrocortisone must be given. This is particularly important in preventing low blood sugar (hypoglycaemia). The doctor will advise of the dosage change necessary in a particular situation.

In children with salt-losing CAH due to low aldosterone levels, replacement of both cortisol and aldosterone is necessary. A synthetic hormone similar to aldosterone (fludrocortisone) is given to prevent the loss of salts in the urine. Fludrocortisone is available in tablet form and is given once or twice a day. In the first year of life, children with salt-losing CAH will also require salt supplements, usually added to feeds. After the age of one however, the combination of fludrocortisone and dietary salt is enough to maintain salt balance.

Special Needs of Girls with CAH

Most girls with CAH will require some corrective surgery to their genitals, although the degree of masculinisation depends on the severity of their CAH. Surgery is usually performed as an infant but it may be necessary to have further procedures later in life. Surgery normally involves reducing the size of the clitoris while preserving sensation, separating fused labial folds and opening the vagina.

If the diagnosis of CAH is made during pregnancy it is possible to reduce the masculinisation of female babies by treating the mother with a synthetic hormone similar to cortisol, such as dexamethasone. This treatment must be undertaken by an endocrinologist and only after careful discussion. The dexamethasone crosses the placenta and enters the baby's blood stream where it suppresses the production of ACTH in the baby's pituitary gland. This helps prevent the excess production of male hormone that is responsible for masculinisation.

"Most girls with CAH will require some corrective surgery to their genitals, although the degree of masculinisation depends on the severity of their CAH."

Fertility

Fertility rates appear to be lower in women with CAH, especially in the severe types, despite the internal sex organs (ovaries, uterus and vagina) being normal. Even so, women with CAH should use appropriate contraception if having unprotected sex. If trying to become pregnant, fertility specialists can assist with fertility treatment if necessary. It is essential for women with CAH to consult an endocrinologist when trying to become pregnant to ensure their CAH control is optimal at the time of conception.

The best way to ensure future fertility in women with CAH is to maintain good control of androgen levels throughout childhood and adolescence. The key to this is careful monitoring through blood and urine tests and taking medications regularly. If hormonal balance is poor, the ovaries can be affected by a condition known as polycystic ovary disease. This problem may cause difficulties with fertility and necessitate special treatment to increase the chances of conception.

Some women with CAH may have difficulties with sexual intercourse (such as dryness or tightness of the vagina) as a result of the surgery carried out earlier in their lives. A gynaecologist can help with this problem.

Some Useful Tips

If a child with CAH becomes ill or suffers an injury it is important to contact his or her specialist for advice regarding the adjustment of their hydrocortisone dose. As a general guideline the following may be useful:

- If the child has a minor illness such as a mild cold but is otherwise well no increase in hydrocortisone dose is required.
- If the child has an illness such as a chest infection or tummy upset, severe enough to prevent normal activities or miss a few days of school, it is advisable to double the daily dose of hydrocortisone. This should be done in consultation with the local doctor.
- In severe illness, especially when associated with diarrhoea and vomiting, the child will need hydrocortisone urgently and may need to be given an injection of hydrocortisone. Children with CAH (particularly those with the severe salt-wasting form) can become critically unwell very quickly. An unnecessary dose of hydrocortisone is not dangerous but delaying the dose in a sick child can be disastrous. Always contact the doctor in this situation for advice.
- In an emergency where the child is shocked (pale, clammy, drowsy or unconscious) a hydrocortisone injection should be given immediately and an ambulance called.

- Any surgical procedures requiring general anaesthetic are likely to require additional hydrocortisone therapy. Consult the specialist for advice. Dental extractions under local anaesthetic do not usually necessitate special treatment but the dentist should be advised of the child's condition.
- Children with CAH should wear a medical alert bracelet stating that they have the disorder so appropriate treatment can be given in an emergency. It is also wise for them to carry a letter from their specialist when travelling overseas explaining the condition and any medications they may have with them.
- It is advisable to tell all treating doctors that the child has congenital adrenal hyperplasia rather than using the acronym CAH. The acronym CAH can also mean chronic active hepatitis and it is extremely important that any treating doctor is very clear that the child has congenital adrenal hyperplasia NOT chronic active hepatitis.

CAH is a rare condition in the community. Many doctors have never seen or treated a patient with this problem. It is very sensible to always carry a letter from the specialist, explaining the nature of the condition and how to manage an emergency situation. This is particularly important when travelling away from the child's home area to a place where a doctor would not be familiar with the child.

More information about management of acute stress, illness, hypoglycaemia etc., is available in the booklet, ***Management of Emergency or 'Stress' Situations where Hypoglycaemia or Cortisol Deficiency Occur***, which is also part of the Serono Symposia Australasia "Hormones and Me" series.

Questions and Answers

Q *Will a child with CAH reach a normal adult height?*

A With careful treatment it should be possible for children with CAH to achieve an adult height within the normal range. However, even with the very best treatment it is not always possible to achieve perfect growth and some children with CAH do not reach their potential adult height.

Q *Is steroid therapy harmful?*

A Steroid treatment is vital in CAH to ensure normal growth and development. If the correct dose is used, there should be no side effects as the treatment is replacing natural hormones that are deficient. However, if too much hydrocortisone is given over a long period of time it can result in slowing of growth and weight gain. Too much fludrocortisone can cause high blood pressure, but this is usually temporary and responds to dose reduction.

Q *How is the dosage of steroid determined?*

A The dose of treatment varies between individuals. In general, non-salt losers will require lower doses than salt-losers. As the child grows, the dose will be increased and may rise quite steeply at puberty. Each child should be monitored closely by their paediatric endocrinologist and doses adjusted to their individual needs. Growth rate is the most reliable marker for determining hydrocortisone dose although blood tests may also be necessary. Blood pressure monitoring as well as blood and urine tests are used to determine the correct fludrocortisone dose.

Q *At what time of day should treatment be given?*

A Opinions vary on the best time to give hydrocortisone. It should usually be given in 2 - 3 doses throughout the day. The child's paediatric endocrinologist will advise the exact type of treatment that suits the child.

Q *Can the child receive live vaccinations while on steroids?*

A Yes. The dose of steroids in CAH is equivalent to the amount produced naturally by the body and will not interfere with the body's response to vaccination. Children with CAH should receive all the recommended vaccinations. The situation may be very different for children on high dose steroids for other medical conditions.

Q *How often should the child be medically assessed?*

A Regular medical assessment and monitoring of treatment is the key to the successful management of CAH. Regular assessment of growth, bone maturation, blood pressure as well as blood and urine tests help the paediatric endocrinologist decide on the best treatment plan. Generally a visit to the paediatric endocrinologist or clinic 3 - 4 times a year will be necessary. It is also important to have a local doctor who is easily accessible and familiar with the child's condition.

Q *Can the child live a normal life?*

A Yes. Although not curable, CAH is a treatable condition. With careful treatment, children with CAH can lead normal lives and should have a normal life expectancy. There are however, many issues that a person with CAH may face and there are people who can help. Paediatric and adult endocrinologists, gynaecologists, fertility specialists, psychologists and counsellors can all play vital roles in helping children and adults with CAH live healthy lives.

Further Reading

Warne GL
Your Child with Congenital Adrenal Hyperplasia
www.rch.unimelb.edu.au/publications/cah_book

Androgen Insensitivity Syndrome Support Group (AISSG)
www.medhelp.org/www/ais

Australasian Paediatric Endocrine Group (APEG)
www.racp.edu.au/apeg

The Endocrine Society
www.endo-society.org

Intersex Society of North America
www.genetic.isna.org

Hawkridge C
The Menopause, HRT and You
1999

John Hopkins Children's Centre
www.med.jhu.edu/pedendo

The Hormone Foundation
www.hormone.org

National Centre for Biotechnology Information
www.ncbi.nlm.nib.gov/htbin-post/Omim/getmim?search-CAH

UK Society for Endocrinology
www.endocrinology.org

Glossary

Adolescence

The period in development between the onset of puberty and adulthood.

Aldosterone

A steroid hormone produced by the adrenal gland that helps regulate salt concentration in the body.

Amniotic Fluid

The liquid surrounding a baby in the womb.

Cholesterol

A steroid found in animal fats and oils.

Chromosome

A thread like structure that carries genetic information in the form of genes composed of DNA. Normally, each human cell contains 23 pairs of chromosomes, and one pair of these are the sex chromosomes. Genes and chromosomes are like blueprints for the body's development, and so play a large part in determining a person's characteristics.

Clitoris

Part of the external female genitalia.

Congenital

A feature or condition that is present from birth, but not necessarily hereditary.

Corticosteroids

Steroid hormones produced by either the adrenal gland or synthetic process. Examples include cortisone, hydrocortisone and prednisolone.

Cortisol

A steroid hormone produced by the adrenal cortex. There are a number of hormones made by the adrenal gland and they are called corticosteroids.

DNA

Stands for Deoxyribonucleic Acid and is the chemical that forms the genetic code.

Endocrine Gland

A gland that makes hormones and releases them into the blood. The pituitary, thyroid, adrenal, testes (testicles) and ovaries are all endocrine glands. All of the glands together make up what is termed the endocrine system.

Endocrinologist

A doctor who specialises in the disorders of the endocrine glands.

Enzyme

A protein that triggers a biochemical reaction (changing one substance into another) but is not used up in the process.

Genes

Substances that convey hereditary characteristics, consisting primarily of DNA and proteins and occurring at specific points on the chromosome.

Gynaecologist

A doctor who specialises in the disorders of the female reproductive system.

Hormones

Blood chemicals that stimulate growth and sexual development and help to regulate the body's metabolism. Normally the body carefully controls the release of hormones as too much or too little may disrupt the body's delicate balance. They are produced by endocrine glands and carry messages from one cell to another via the bloodstream.

Hypoglycaemia

A less than normal amount of glucose in the blood.

Hypothalamus

Part of the base of the brain that controls the release of hormones from the pituitary gland.

Ovaries

Females have two ovaries, which produce the reproductive cells, i.e. eggs.

Paediatric Endocrinologist

A doctor who specialises in the disorders of endocrine glands in children.

Pituitary gland

A pea-sized gland at the base of the brain, which releases a number of important hormones related to normal growth, development and fertility, including growth hormone.

Placenta

The organ which connects the foetus to the wall of the uterus. The placenta provides the foetus with nourishment and eliminates wastes.

Scrotum

The bag of skin and thin muscles that holds the testes.

Testes

The male reproductive glands, which produce sperm, the male reproductive cells.

Uterus

Womb.

Organisations

CAH Support Group Australia Inc
PO Box 6036
Highton VIC 3216 Australia
Tel: 03 5227 8405
Website: www.rch.unimelb.edu.au / CAH

Congenital Adrenal Support Group New Zealand
15 Parkham Drive
Burnside Christchurch 5 New Zealand
Tel: 03 3584 505
Email: bmann@netaccess.co.nz

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Serono Symposia Australasia are proud to bring you this booklet from their "Hormones and Me" educational booklet series. We aim to provide readers with a healthy understanding of the issues relating to endocrine disorders particularly in children. We hope that you find it a valuable and helpful resource.

Please ask your doctor or nurse for further information on the resources available to you.

We wish to express our gratitude to Serono Laboratories (UK) Inc for allowing the distribution of this booklet, which was reproduced in Australia in 2000. We would also like to especially thank the Paediatric and Adult Endocrinologists who gave their time and experience to review and edit the booklets for Australian and New Zealand readers. Special thanks to all those involved in this process.

The views expressed in the "Hormones and Me" booklet series are not necessarily Serono Symposia Australasia's, but those of the qualified clinicians working in the field of paediatric and adult endocrinology.

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HORMONES AND ME

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THIS BOOKLET IS ESSENTIAL READING FOR ANYONE WITH CONGENITAL ADRENAL HYPERPLASIA. IT IS ALSO RECOMMENDED READING FOR THEIR FAMILIES AND FRIENDS.

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