Myasthenia Gravis Association

THE CONGENITAL MYASTHENIC SYNDROMES

Information for Children and Adults Diagnosed with Congenital Myasthenic Syndromes

Myasthenia Gravis Association
RESEARCH · CARE · EDUCATION

ABOUT ME

Name		
Date of Birth		
Type of Myasthenia		
Emergency Contacts	**1**	**2**
Home Phone Number		
Alternative Phone Number		
My GP		
My Local Paediatrician		
My Neuromuscular Specialist		

MY MEDICATIONS

Name of drug	Dose	Times taken	Effects/side-effects

CONTENTS

Due to the nature of this publication, many items and references are repeated throughout. Therefore the subjects listed below give only a general indication of where the topic may be found.

THE CONGENITAL MYASTHENIC SYNDROMES (CMS)

Who is this booklet for?

This booklet is for children and adults diagnosed with Congenital Myasthenic Syndromes. This is a complicated subject that has been simplified for everyone; not all of the facts apply to all children and adults diagnosed with this condition. Technical terms are explained at the back (page 21 GLOSSARY).

Pages 19 and 20 have been left blank for you to make your own notes.

The Authors

The booklet has been written and compiled by:-

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1. What is Congenital Myasthenia?

Congenital myasthenic syndromes (CMS) is the collective term for a group of inherited congenital disorders of '*neuromuscular transmission'* - the mechanism by which messages from the nerves are sent across to muscles to make them work. This causes weakness in the muscles (myasthenia) which tire easily when they are required to work (fatigue). It does **not** affect the 'autonomic' muscles in the heart, guts, bladder etc.

The Congenital Myasthenias cause clinical symptoms (muscle weakness and fatiguability) similar to the more common autoimmune disease myasthenia gravis (MG).

In Congenital Myasthenic Syndromes, symptoms usually start in the first years of life with varied disability ranging from mild to severe muscle weakness, which may in some cases involve the breathing muscles.

2. How are CMS diagnosed?

A diagnosis of CMS is made through a combination of the clinical history (see below), a reduced electrical response of muscles to repetitive stimulation (demonstrating fatigue) and by specialised genetic investigations using DNA from a blood sample. Blood tests and/or a muscle biopsy may be needed to exclude other causes of similar symptoms in specific cases.

3. How are CMS inherited?

With rare exceptions most CMS are inherited via '*autosomal recessive*' mutations ('spelling mistakes') in genes. This means the child inherits a faulty gene from each of his/her parents. As a result a child has two faulty genes resulting in CMS. Parents do not have any symptoms as they only carry one copy of the faulty gene. The faulty genes result in defects in the nerve-muscle triggering system causing the weakness. Sometimes a new genetic defect may arise when the baby is first being formed; if so, it will not be found in the parents.

4. The Nerve-Muscle Junction

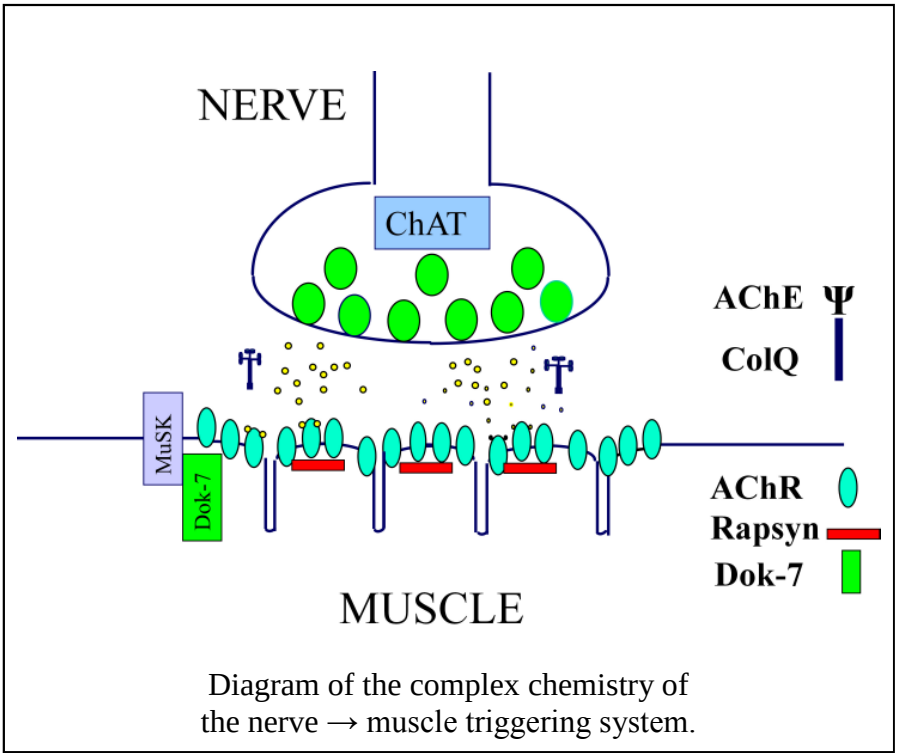

Diagram of the complex chemistry of
the nerve → muscle triggering system.

Normally, a special chemical called acetylcholine (ACh) is released from nerve endings into the gap between nerve and muscle called the synapse. This chemical attaches itself to tube-like '*channels*' running through special areas on the muscle surface called '*ACh receptors*'. When attached, the ACh opens the channels, and salts – sodium and potassium – move through them producing a small electrical current that activates muscles to work.

Each ACh receptor is made up of five specialised building blocks (named in Table 1, page 11). Other proteins (including Rapsyn and Dok-7) in the muscle are responsible for clustering them together so they can receive the maximum amount of ACh. Any ACh left over is broken down by an enzyme called acetylcholine-esterase (AChE) and taken back into the nerve ending and recycled by the enzyme ChAT.

One front-line treatment for most myasthenias is to make the ACh

last longer by blocking its break-down, using the drug Pyridostigmine or other anti-AChE drugs. Another drug called 3,4 DAP is used to boost ACh release from the nerve endings.

5. What is the difference between CMS and Myasthenia Gravis?

In most myasthenias, there are just not enough ACh receptors, so muscle triggering fails partly or completely. When most people talk about myasthenia they mean Myasthenia Gravis, an uncommon condition which affects children as well as adults. It is caused by antibodies, 'immune' proteins that block and destroy some ACh receptors resulting in less effective signalling from nerves to muscles (instead of attacking foreign germs). This is an 'auto-immune' condition like rheumatoid arthritis and is treated with steroids, immunosuppressive drugs and thymectomy (surgical removal of the thymus gland).

CMS on the other hand are genetic defects that cause problems with the way the receptors are built or the way they work. Some defects affect the way the messaging chemical is released or mopped up. They do **NOT** respond to steroids and the other treatments suitable for myasthenia gravis, which should be avoided in CMS patients.

6. Clinical features

Diagnosis is based on early recognition of the symptoms and signs of CMS. It is important to remember that although some clinical features might be considered characteristic of congenital myasthenic syndromes, not all symptoms are found/experienced by each patient; they can also vary significantly with the patient's age.

The clinical features of CMS include:

1. In infants

There is often a history of:-

- Decreased movements of the baby inside mother's womb before birth
- Polyhydramnios - too much amniotic fluid inside the womb
- Arthrogryposis - baby born with stiff joints
- Weak suck and cry
- Difficulties in feeding and swallowing
- Reduced movements after baby is born
- Breathing difficulties which may come in bouts [be episodic]

2. In children

They may experience the above plus:-

- Frequent chest infections, making the weakness worse, and often needing hospital admissions
- Droopy eyelids, particularly when the child is tired
- Reduced movements of the eyes in all directions of gaze, occasionally double vision
- Unclear or nasal speech
- Difficulty chewing and swallowing
- Late walking
- Waddling gait and tendency to fall easily
- Fatigue with exercise – can walk only short distances at a time, can't keep arms above head for long, and has difficulty climbing stairs
- Scoliosis (curvature of the spine)
- Sometimes distinctive facial features, such as prominent lower jaw, high arched palate and mal-occlusion or crowding of the teeth

3. In adults

Problems may be similar to those in children, but may have been recognised later on. Additional findings are:-

- Often describe poor sporting abilities at school
- Easily fatigued especially on climbing slopes and stairs
- Hard to straighten fingers and wrists

Many other conditions that affect muscle, nerve and brain function can cause similar symptoms.

A specialist is therefore often required to confirm a clinical diagnosis of CMS. Various other tests are often required before a diagnosis can be made. These include:-

- Testing muscle stamina using standardised timed tests
- 'Electromyogram' (EMG), testing muscle responses to electrical nerve stimulation
- Edrophonium or Tensilon® test (injecting a drug into a vein to check for instant improvement in power)
- Muscle biopsy (to exclude other causes of muscle weakness)
- DNA testing (from a blood sample)

7. What are the different types of CMS?

There are many types of CMS. Depending on the exact fault(s), the problem may be at the nerve ending in the production and release of the ACh (pre-synaptic), in the synapse (the gap between the nerve and muscle-synaptic), or on the muscle surface (post-synaptic), with defects in the ACh receptors, their numbers or their clustering.

Many of these defects result from known gene faults, which we can identify in the patient's and parents' DNA. Some require a muscle biopsy to test the actual function of the nerve-muscle junction. There are yet other forms of CMS where we have not yet found any faults, but we are still searching. Progress is rapid; the most recent 'find' was of Dok-7 (2006).

We are also trying to find out exactly how these gene defects affect function, as this will lead us to better and more definitive

treatments. Some of the CMS identified so far are shown in Table 1 below along with treatment options for each type.

Types of Congenital myasthenic syndrome

Table1

CMS Type	Inheritance	Treatment (Not all registered for use in CMS)
Acetylcholine receptor deficiency ***CHRNE, CHRNA, CHRND and CHRNB genes***	AR	Pyridostigmine, 3,4 DAP
Rapsyn deficiency ***RAPSN gene***	AR	Pyridostigmine, 3,4 DAP
Dok-7 CMS ***DOK7 gene***	AR	Ephedrine, salbutamol, 3,4 DAP. May get worse with Pyridostigmine
ChAT deficiency CMS with episodic apnoea' ***CHAT gene***	AR	Pyridostigmine, 3,4 DAP
Acetylcholinesterase deficiency ***COLQ gene***	AR	Ephedrine May get worse with Pyridostigmine
Slow channel syndrome ***CHRNA, CHRNB, CHRND and CHRNE***	AD	Quinidine, Fluoxetine
Fast channel syndrome ***CHRNA, CHRNB, CHRND and CHRNE***	AR	Pyridostigmine, 3,4 DAP

8. How is CMS treated?

The key to treatment is to choose drugs suitable for each patient's type of CMS. The main drug treatments available are shown in Table 2 with their main side effects (*not comprehensive*).

Table 2

Drug	Type of CMS	Possible side effects
Pyridostigmine (Mestinon^{R})	ChAT, Fast channel, RAPSN, ACh Receptor deficiency	Diarrhoea, abdominal cramps, breathing difficulty, sweating, slow heart rate, increased weakness (uncommon)
Ephedrine or Salbutamol	Dok-7, Acetylcholinesterase (ACHE) deficiency	Anxiety, high blood pressure, fast heart rate, chest pain, (uncommon) difficulty passing urine, tremor, breathing difficulty, confusion
3,4 DAP	Dok-7, ACh Receptor deficiency Fast Channel	Tingling in hands and around mouth (common)
Fluoxetine	Slow channel syndrome	Low blood pressure, sleep disturbance, urinary frequency, suicidal thoughts or self-harm (uncommon)
Quinidine	Slow channel syndrome	Heart rhythm disturbances, blood disorders, behaviour changes (uncommon)

9. What are the genetic implications for CMS?

Almost all CMS are inherited as '*autosomal recessive*' disorders. This usually implies that both parents carry one faulty gene copy,

and their affected child has inherited one fault from each parent. This couple will have a 1 in 4 (25%) chance during every pregnancy of having another child with the same disorder. Children who have inherited an autosomal recessive type of CMS will pass on one copy of the faulty gene to their child. They themselves are unlikely to have affected children, as the chances of their partner also carrying a faulty gene are very small, unless he/she is a blood relative (e.g. first cousin).

Currently only the slow channel CMS is known to be inherited as an '*autosomal dominant*' disorder. This means that the condition can be passed on from just one parent to their child. These can also arise from a new gene fault that occurs while the baby is being formed, which means that neither parent carries a gene defect and is therefore unaffected. If, instead, one parent does carry the fault, he/ she has a 1 in 2 chance of any further child being affected, and so does any affected patient.

Once a diagnosis of CMS is made, families should be referred to their specialist genetics centre for a full discussion of the genetic implications of the diagnosis. Prenatal diagnosis can be offered in a future pregnancy if the genetic mutation has been identified.

10. What is the progress of CMS?

Often CMS will start with weakness, fatigue, difficulties in feeding and/ or breathing in infancy and early childhood. These, if diagnosed early, can be treated and prevented to some extent with medication. The use of AChE inhibitors can prevent some of the 'apnoeic' attacks (when breathing stops), but some infants may require tracheostomy and intermittent ventilation. Almost all children with CMS will be able to walk independently. CMS does not affect intellect in any way.

Breathing support, physiotherapy, speech and language therapy may be needed to help with breathing and feeding. Lung function tests are monitored regularly. Correct diagnosis of the type of CMS is important for predicting both the the most suitable treatment(s) and

the long-term outcome. Most CMS patients find that their muscle strength improves with time and the need for medication reduces. Some others will need life-long medication to maintain muscle strength, or, rarely, a wheelchair will be required even in adulthood.

Sometimes the weakness of the eyelids and eye movements do not improve with treatment although body muscle strength improves. Unfortunately, in some rare cases no treatment helps. On the other hand, some CMS are so mild that they are only diagnosed in late childhood, adolescence or even adulthood. Supportive treatment is offered in all cases where it is needed.

11. Exercise

Whilst this is limited by the muscle weakness and fatigue, we advise taking as much exercise as can be tolerated. Physiotherapy should be continued as this prevents complications, such as joint contractures (stiffness). Use of a wheelchair for distances may help to conserve strength.

12. Guidelines for anaesthesia/operation

If you need an operation, you must tell your surgeon and anaesthetist, about your myasthenia, as it may demand special treatment.

The anaesthetist will need to juggle your drugs before and after the operation with your current weakness; also the surgeon's needs for muscle relaxants with your anti-cholinesterase medication. Afterwards, you will also need close monitoring of your breathing, swallowing and also oxygen levels in your blood. This may mean you staying in hospital for a few days. If you have breathing difficulties or swallowing problems before your operation, then you will probably need a general anaesthetic.

If expectant mums with CMS need a Caesarean section, a planned spinal anaesthetic is preferable – discuss this with your midwife and

obstetrician as soon as possible. Again close monitoring of your respiratory function and oxygen levels are required; we need to be watchful as problems can arise up to three weeks after delivery.

13. Guidelines for drugs to avoid

Certain drugs should be avoided by people with CMS because they interfere with normal neuromuscular function.

Drugs to be avoided or used with caution include:

- Many types of antibiotics
- Some drugs used for blood pressure or the heart (especially beta blockers)
- Some drugs used in psychiatric conditions

Many other drugs may worsen symptoms as well, so patients should **always check with the doctor who treats their CMS before taking any new drugs**.

It is very dangerous to start a new drug without consultation with your doctor as you may become extremely weak.

A Medic-Alert card or bracelet provides important information to emergency carers about the special situation of a person with CMS. They are available from health care providers.

14. Some general advice for families and schools

Here are some simple measures to help children with CMS at home and within the school environment. You may wish to discuss these with the school teacher.

- Using a chair of suitable height. Avoid sitting on the floor and having to get up and sit down frequently.
- Having extra time for completing work and for tests.
- Using computers and laptops instead of writing.

- Discussing how much to join in PE and sport. Being able to stay indoors during playtime.
- Allowing for starting late and leaving early.
- Not having to stand in queues.
- Not being required to raise a hand in classroom to be noticed, not having to shout aloud or raise voice to be heard.
- Explaining to the school and friends about myasthenia and the difficulties associated with it.
- Need to take medication precisely on time in school without fail.
- Taking time to eat a meal and drink slowly. Same applies to feeding babies at home.
- Droopy eyes, squint, slurred speech and low speech volume may incur teasing and criticism.
- Symptoms of myasthenia typically vary from day to day and time to time. Children are therefore not "making things up" at certain times or on some days.
- A statement of special education needs is often needed to get extra assistance in the school or help with transport.
- Referral to the community paediatricians and community paediatric nursing teams as important sources of advice and support.
- In addition to routine vaccinations, children and adults with CMS should have flu vaccine every year and Prevnar® (pneumococcal vaccine), if they have not had it as part of routine immunisation schedule.
- Your child should be encouraged and helped to lead as normal a life as far as they can. Sensible precautions and interventions should be adopted try not to go over-board.

15. Important advice in the event of illness – the care pathway

- Watch out for illness and infections. These can make weakness and any breathing or swallowing difficulties acutely and dramatically worse.
- Know in advance whom you should contact for advice in the event of you/your child developing an illness or worsening weakness.
- Make sure that you/anyone caring for your child (including nursery or school) has a list of numbers to contact in an emergency.
- Your GP is the first point of contact for minor illness. For more serious concerns you should contact your physician or paediatrician, or **in an emergency dial 999 for an ambulance.**
- Your child should have in place a rapid access agreement (often called a 'Passport' or 'Open Access') to the paediatric service at the local hospital, to avoid having to wait unnecessarily to be seen if they are unwell.
- Adults or children who have had or are prone to breathing difficulties should be under the care of a specialist respiratory centre. Parents and carers should be trained in cardiopulmonary resuscitation.
- If a child or adult with CMS has breathing difficulties **this is an emergency**, call 999 and get them to the nearest hospital. It is life-threatening.
- **If you need advice, get it sooner rather than later.**

16. Is there any other help available for patients with CMS?

Apart from your doctor and hospital specialist, there are specialist nurses at six centres throughout the UK and Ireland who will offer help, advice and support to a family. Ask your GP or hospital specialist whether such a service exists in your area.

The Myasthenia Gravis Association has information and advice about Myasthenia.

You can contact them through their website www.mga-charity.org, or telephone: 01332 290219, or free phone 0800 919922 or email: mg@mga-charity.org. You will get to know parent and patient groups through the MGA.

The MGA has formed a National Children's Branch, for parents and children with CMS, their website is www.myasthenickids.org

The Dubowitz Neuromuscular Centre

A leaflet giving more information about caring for children with CMS is available on the website of the Dubowitz Neuromuscular Centre, Great Ormond Street Hospital for Sick Children at:
http://www.ich.ucl.ac.uk/ich/academicunits/dubowitz_neuromuscular_centre/Homepage

You may also be entitled to the following:

Disability Living Allowance:
http://www.direct.gov.uk/en/DisabledPeople/FinancialSupport/DG_10011731

Blue Badge Parking scheme:
Contact your local authority

Carer's allowance:
Contact your local benefits office

Further information can be found in the MGA Information Booklet Volume 4

Occupational therapy advice regarding adaptations to your home and Local Authority Grants:
This is obtained via your local Social Services Department. For children, a referral can be made by your GP or health visitor to the Children with Disabilities Team at your local Social Services Department.

Your regional Muscle Centre may have a Family Care Advisor who can provide additional information and advice about benefits, adaptations and funding for powered wheelchairs.

The MGA supports specialist nurses at 6 centres throughout the UK and Ireland. (Dublin, Glasgow, Liverpool, London (Queen Square and Great Ormond St), Newcastle (we're pretty sure) Oxford and Southampton).

Additional Notes

Additional Notes

GLOSSARY

Acetylcholine (ACh) is a chemical transmitter released from nerve endings [see Diagram, page 7].

Acetylcholine Receptors (AChR) are tailor-made for the ACh to latch-into on the nearby muscle surface [see Diagram, page 7]. That then opens up channels into the muscles, allowing salt (sodium and calcium ions) to enter and trigger the muscle into action.

Acetylcholinesterase (AChE) is a protein near the AChRs that destroys any spare ACh [see Diagram, page 7].

Anti-cholinesterases are drugs that block AChE, so that any ACh lasts longer/has a better chance of triggering [see Diagram, page 7]. These drugs include Pyridostigmine (Mestinon®, long-acting), Neostigmine (medium-acting) and Edrophonium (Tensilon®, short-acting).

Antibodies are immune proteins tailor-made to destroy germs or block toxins. They travel around in the blood and tissue fluids.

Apnoea/apnoeic attack is the sudden stopping of breathing.

Arthrogryposis is stiff joints caused by failure to stretch them properly as babies develop.

Autoimmune diseases are caused by cells or antibodies that can attack our own tissues or cell products.

Autosomal is used for genes **not** on the sex chromosomes (X or Y).

Biopsy is a small sample of muscle used in microscopic or electrical diagnostic testing.

Bulbar applies to the movements of the face, chewing, swallowing, speech and breathing controlled by the lower brain stem.

ChAT is the enzyme that puts ACh back together (choline acetyl transferase).

ColQ is the stalk that anchors the AChE in the synapse.

Congenital myasthenic syndrome (CMS) strictly means that the weakness can be seen at birth. In fact, a few of these inherited faults in nerve → muscle triggering can start even in the teens.

Contracture is stiffness and decreased range of movement in joints caused by weakness and lack of stretching as babies first develop.

3,4 DAP (3,4 diamino-pyridine) is a drug used to boost ACh release from nerve endings in some congenital myasthenias.

Diplopia is double or blurred vision, especially when looking to the sides or up and down.

Dominant means when a **single** copy of a faulty gene is enough to cause problems.

Dysarthria is difficulty in pronouncing words – i.e. in the **movements** of speech (rather than in finding the right word in your brain).

Dysphagia is difficulty in chewing and swallowing.

Dyspnoea is difficulty in breathing.

Edrophonium (Tensilon®) is a very short acting anti-choline esterase drug (see section on Diagnosis).

EMG = electromyography is where nerves are stimulated electrically, and the resulting (electrical) impulses are measured in the muscles they supply. EMG helps Neurologists to sort out different congenital myasthenias and 'immune' MG.

Endo-tracheal tube is a tube put into the wind-pipe (trachea) so that the lungs can be ventilated mechanically.

Enzyme is a protein that helps to convert one chemical into another.

Ephedrine is a drug used for Dok-7 CMS and acetylcholinesterase deficiency CMS, which seems to build-up their muscles. At higher doses it can cause a 'fright/flight/fight' response like adrenalin does.

Fluoxetine is a drug used to treat the Slow Channel Syndrome.

Intubation when an endo-tracheal tube (see above) is put into the wind-pipe so the lungs can be ventilated mechanically.

Mal-occlusion is when the teeth do not meet exactly opposite each other when the jaw closes.

Mestinon® is the trade name for Pyridostigmine, a long-lasting anti-cholinesterase.

Mutation is an inherited fault in any gene.

Myasthenia is any form of muscle weakness, especially if caused by faults in nerve → muscle triggering.

'Neonatal MG' is the term used when autoimmune MG in a newborn baby is caused by antibodies from its mum: her MG should be the key to the diagnosis.

Neostigmine is another (medium-lasting) anti-cholinesterase.

Nerves relay electrical impulses from sense organs (e.g. eyes and skin) to the brain and spinal cord or from there to muscles and glands. They relay the signals to other nerves or muscles at special junctions (synapses), and switch them either on or off. Sometimes, they act more like dimmer switches, telling things to work harder or slower.

Ocular MG is MG affecting only the eyelids and/or eye movements, and not other muscles (nor eye focussing).

Polyhydramnios is too much amniotic fluid inside the womb that the baby has failed to swallow.

Prenatal diagnosis means testing – early in pregnancy – a sample of the baby's fluids or membranes for faults already identified in its family.

Propantheline is a drug like atropine that cuts down the side-effects of Mestinon® on the guts and other 'automatic' functions.

Pyridostigmine is a long-acting anti-ACh esterase drug that blocks breakdown of spare ACh (also called Mestinon®).

Quinidine is a drug used to treat the Slow Channel Syndrome. As it partly blocks the AChR, it can make other myasthenias worse.

Recessive is used for faults that only cause trouble when inherited from each parent.

Salbutamol is a drug usually used to treat asthma, but appears to have a similar effect to Ephedrine in Dok-7 patients.

Scoliosis is curvature of the spine (which can lead to a hunched back if not corrected).

Strabismus is a squint.

Synapse is any junction between a nerve and another nerve, a muscle or a gland. Signals can be passed either by chemical transmitters like ACh, or by direct electrical triggering.

Tensilon® (Edrophonium) is a short-acting anti-AChE drug; for diagnosing myasthenia, it is injected into a vein and any resulting increase in muscle strength is measured.

Vaccine is a germ (or germ product) made harmless. Still recognisable by 'immune cells', it can be injected in advance, so stimulating these cells to multiply and forearm us before the real menace comes along.

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