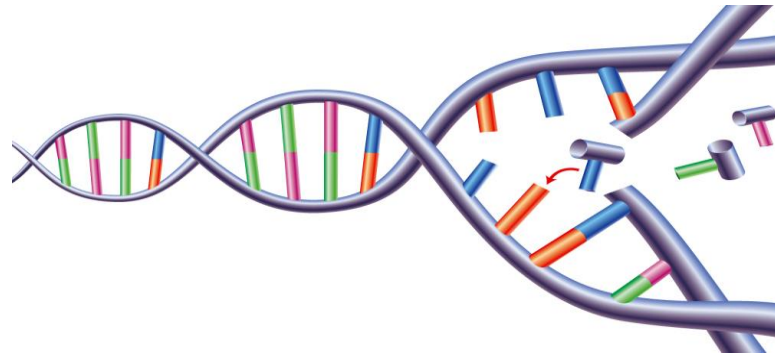


# Nucleotide nutrition

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## New horizons in the treatment of IBS



Robert Verkerk PhD

Consultant to ProBio Healthcare

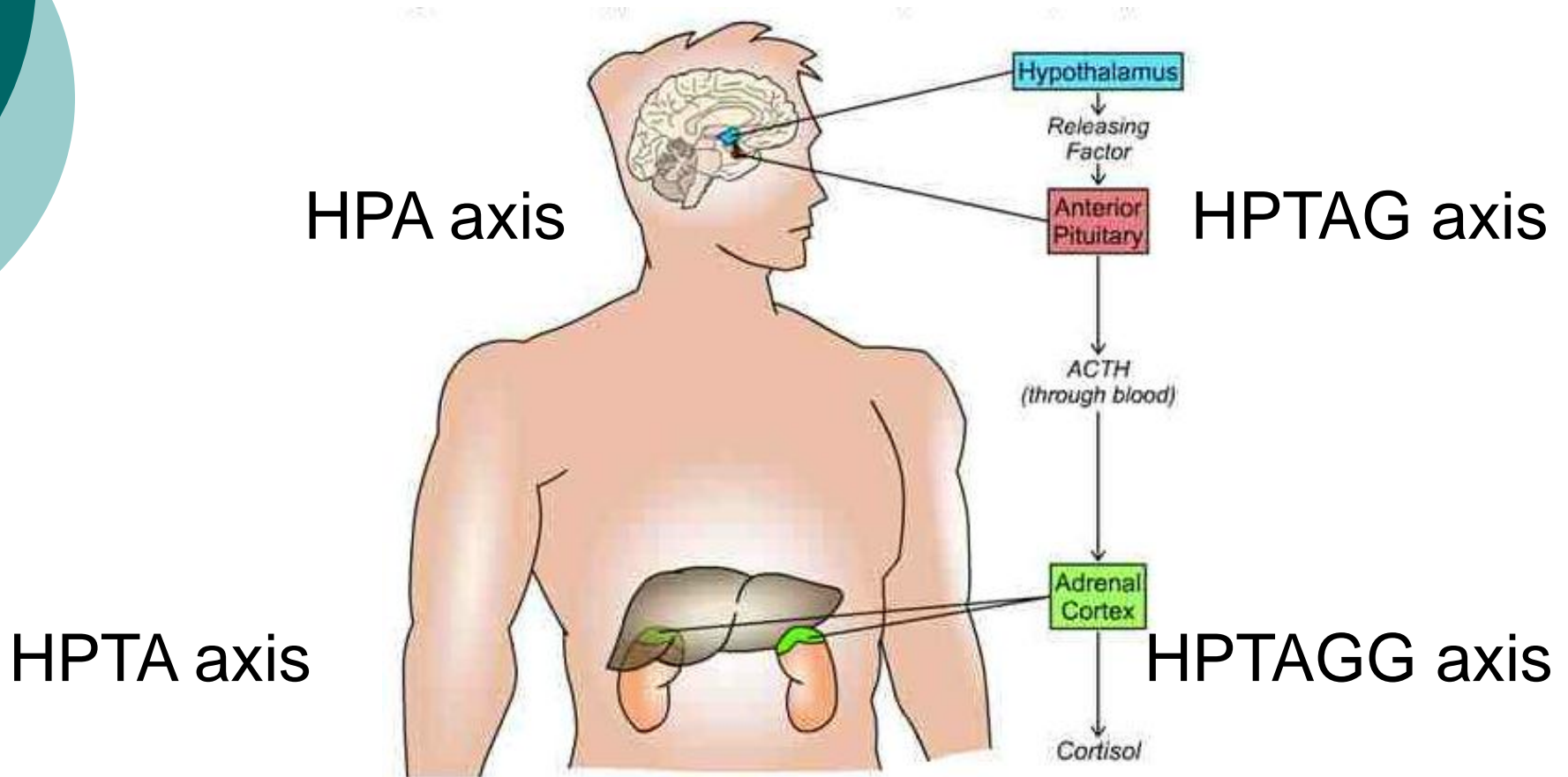
rob@anhconsultancy.com

[www.probiohealthcare.com](http://www.probiohealthcare.com)

[www.nucleotides4health.org](http://www.nucleotides4health.org)

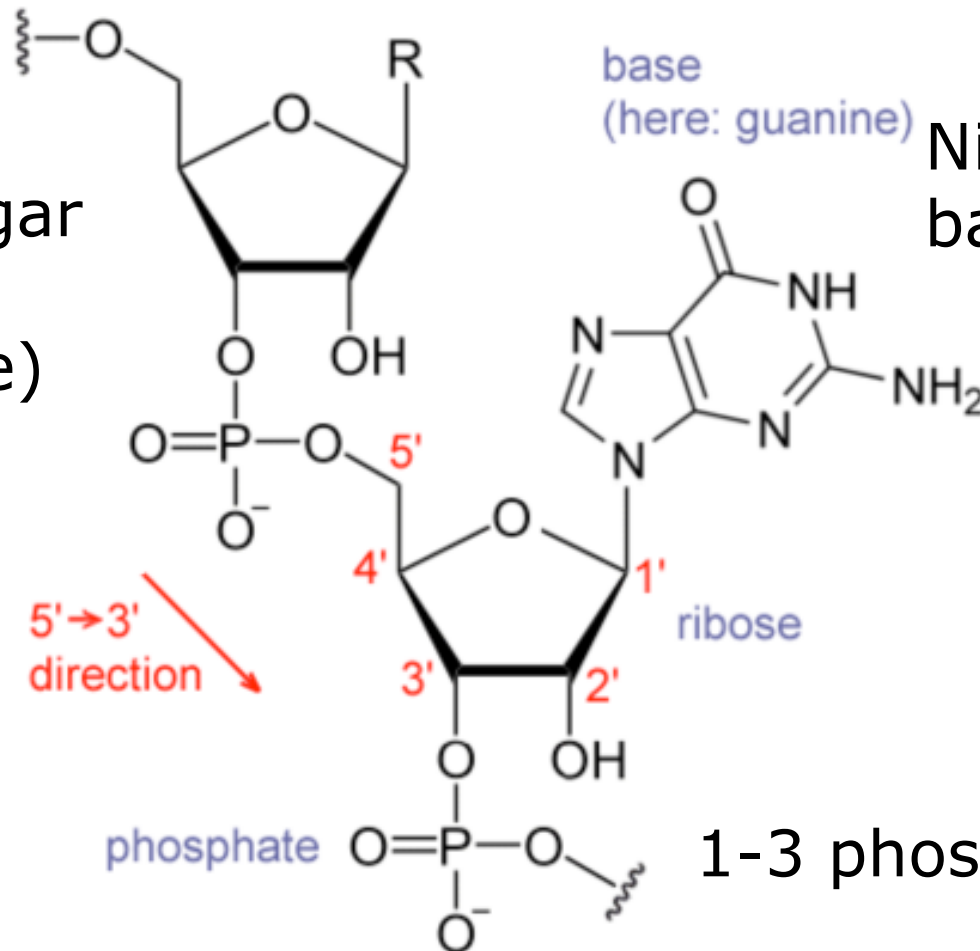
# Setting the scene: The gut / endocrine connection

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# What are nucleotides?

Pentose sugar  
(ribose or  
deoxyribose)



base  
(here: guanine)

Nitrogenous  
base

ribose

phosphate

1-3 phosphates



# Classification of nucleotides

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According to nitrogenous base...

## **Purine nucleotides:**

adenosine (A), guanine (G), inosine (I)

## **Pyrimidine nucleotides:**

cytosine (C), uracil (U), thymine (T)

# Where did nucleotides originate?

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- Possibly complex molecules to emerge in 'primordial soup'

Simmonds HA, van Gennip AH. Nucleotide degradation. *Encyclopedia of Life Sciences*. John Wiley & Sons, 2005. pp 1-9.

- As components of nucleoproteins, but also free
- Present in all foods, in highly variable quantities
- Particularly rich in colostrum / breast milk

Gil A. Modulation of the immune response mediated by dietary nucleotides. *Eur J Clin Nutr*. 2002; 56 Suppl 3: S1-4.

# Endogenous and exogenous sources

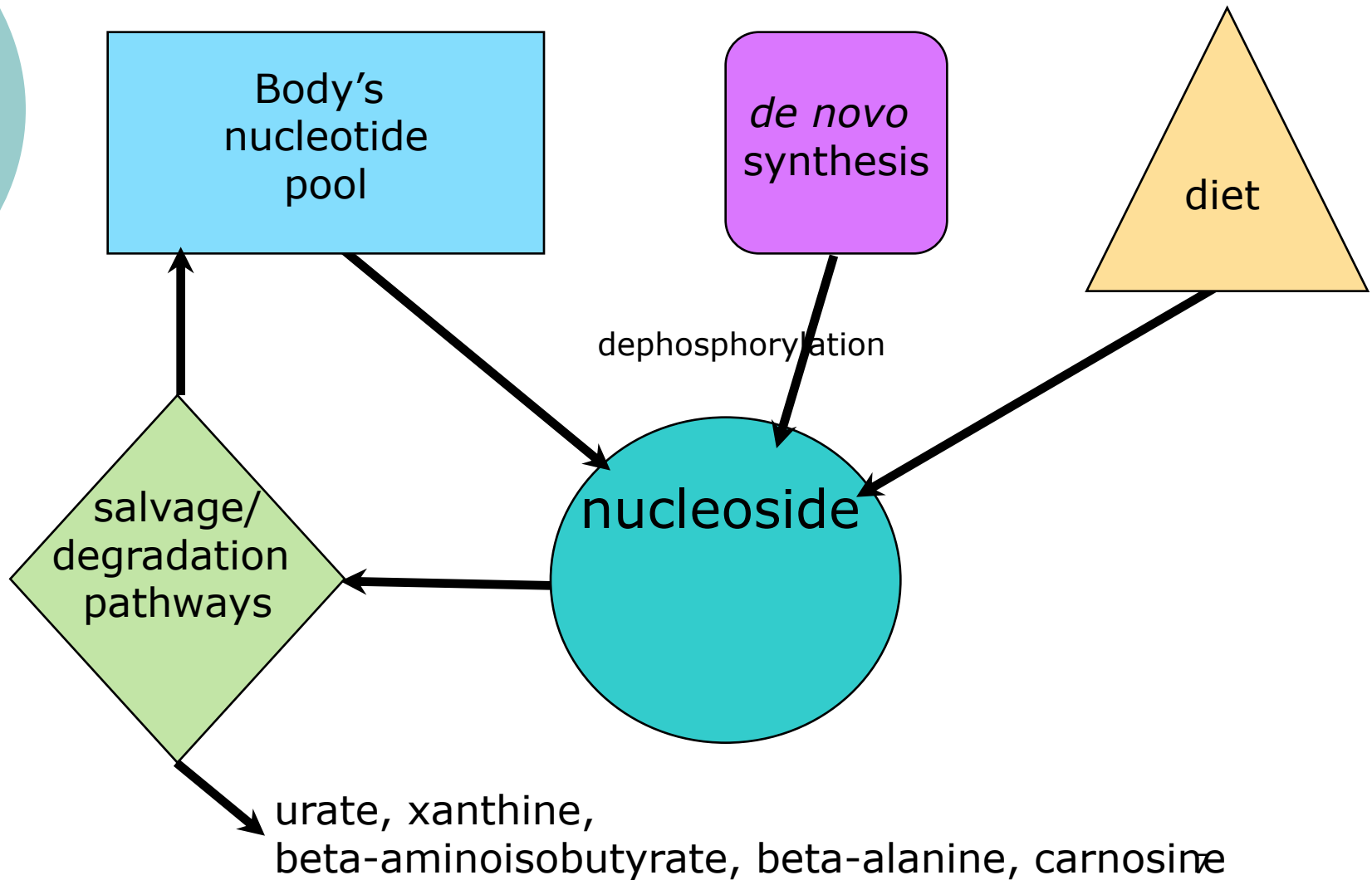
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- *De novo* synthesis from metabolites such as glutamine, aspartate and glycine, particularly in the liver
- Salvage pathways, from RNA/DNA degradation
- Exogenous intake from diet

Grimble GK, Westwood OM. Nucleotides as immunomodulators in clinical nutrition. *Curr Opin Clin Nutr Metab Care*. 2001; 4(1):57-64. Review.

# Metabolism: summary

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# 4 main areas of research on exogenous sources

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## Colostrum/breastmilk

- immune and gastrointestinal effects on neonates [Review: Schlimme et al, 2000](#)

## Supplemental nucleotides

- Infant formulae, growth/development/immunity [Reviews: Carver, 1999 and Grimble and Westwood, 2001](#)
- Young children, immunity/GI infections [Reviews: Uauy et al, 1994; Cosgrove, 1998; and Schaller et al, 2007](#)
- Adult immunity, including in relation to transplant rejection [Review: van Buren et al, 1994](#)

# Key requirement: cell growth

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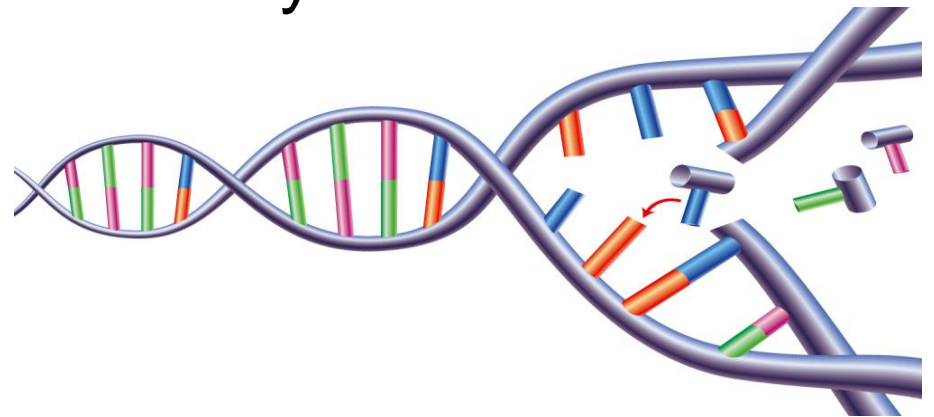
The body is constantly producing new cells,  
e.g.,

- **Gut lining:** cells turn over < 1 week
- **Lymphoid tissue:** average (healthy) human body contains c.  $10^{12}$  lymphoid cells = c. 2% of total body weight
- During disease, stress, rapid growth lymphoid production increases dramatically

# Nucleotides and cell generation

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- Every new cell requires 3 billion nucleotides to build its DNA
- Some cells and organs in the body lack the ability to produce nucleotides
- Endogenous production limited; endogenous sources may be limited and highly variable



## Dietary Nucleotides: A Conditional Requirement

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CHARLES T. VAN BUREN, MD, AND FREDERICK RUDOLPH, PHD

*From the Department of Surgery, University of Texas Health Science Center and Department of Biochemistry,  
Rice University, Houston, Texas, USA*

- Scientific consensus over conditional essentiality
- Peak requirements:
  - rapid growth
  - infection, disease
  - stress, trauma
- Sites of requirement at times of peak requirement:
  - immune system
  - GI systems

Deficiencies exacerbated by apparently  
decreasing nucleotide intakes

# EU levels for infant formulas

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Maximum levels of nucleotides permitted for use in infant formula and follow-on formula in the EU according to amending Directive 2006/141/EC

<b>Nucleotide</b>	<b>Maximum Level (total concentration of nucleotides will not exceed 1.2mg/100kJ [5mg/100kcal])</b>	
	<u>Cytidine 5'-monophosphate (CMP)</u>	0.6mg/100kJ
<u>Uridine 5'-monophosphate (UMP)</u>	0.42mg/100kJ	1.75mg/100kcal
<u>Adenosine 5'-monophosphate (AMP)</u>	0.36mg/100kJ	1.50mg/100kcal
<u>Guanosine 5'-monophosphate (GMP)</u>	0.12mg/100kJ	0.5mg/100kcal
<u>Inosine 5'-monophosphate (IMP)</u>	0.24mg/100kJ	1.0mg/100kcal

# EC levels vs TPAN levels

Infant age (months)	Infant mean body weight (kg) <sup>a</sup>	Infant energy requirement (kJ/day) <sup>a</sup>	Total nucleotide intake per day (mg/day) [mg/kg bw]	
			<u>EC Directive<sup>b</sup></u>	<u>TPAN<sup>c</sup></u>
1	4.47	500	6.00 [1.34]	8.55 [1.91]
3	6.05	420	5.04 [0.83]	7.18 [1.12]
6	7.64	355	4.26 [0.56]	6.07 [0.79]
9	8.60	340	4.08 [0.47]	5.81 [0.68]
12	9.31	340	4.08 [0.44]	5.81 [0.62]

<sup>a</sup> Data from Human Energy Requirements (2001). FAO Food And Nutrition Technical Report Series. Report of a Joint FAO/WHO/UNU Expert Consultation, 17–24 October 2001. FAO: Rome. (<ftp://ftp.fao.org/docrep/fao/007/y5686e/y5686e00.pdf>)

<sup>b</sup> Based on 1.2 mg/100 kJ total nucleotide intake according to EC Directive 2006/141/EC.

<sup>c</sup> ‘Total Potentially Available Nucleosides’ (TPAN) after Leach *et al*, 1995.

# Nucleotide profiles

Reference Content/dose	AMP	CMP	GMP	UMP	IMP	Total	Upper Limit
<i>Content in mature human breast milk (Gil &amp; Sanchez-Medina, 1982)</i>							
µm/L (mg/L)*	20 (7.8)	19 (7.0)	3 (1.2)	13 (4.8)	-	55 (20.8)	n/a
<i>TPAN (after Leach et al, 1995)</i>							
µm/L (mg/L)*	32 (12.5)	88 (32.4)	31 (12.4)	38 (14.0)	-	189 (71.5)	n/a
<i>European Commission Directive (1996)</i>							
mg/100kcal (mg/L)*	1.50 (10.4)	2.50 (17.3)	0.50 (3.5)	1.75 (12.1)	1.00 (6.9)	7.25 (50.2)	5 (35)
<i>Pickering et al (1998)</i>							
mg/L	9.8	31.2	14.4	17.7	- †	73.1	- †
<i>Schlimme &amp; Martin (1999)</i>							
mg/100kcal (mg/L)*	1.8 (12.5)	4.7 (32.3)	1.8 (12.6)	2.0 (14.0)	- Ψ	10.3 (71.4)	- Ψ

Where AMP = adenosine 5'-phosphoric acid, CMP = cytidine 5'-monophosphoric acid, GMP = guanosine 5'-phosphoric acid, UMP = uridine 5'-phosphoric acid and IMP = inosine 5'-phosphoric acid.

\* The conversion on mg nucleotide/L infant formula was calculated under the assumption that the infant formula used is isocaloric with human milk (69 kcal/100 g milk according to Souci *et al.* 1994); nucleotide values are given as disodium salt.

† Without addition of 5'-IMP.

# Nucleotide supplementation in infants

From the SMA HP website....

## Nucleotides

### Helping to build an infant's immunity

- Without the right nutrients to help develop the immune system, infants may become susceptible to infection.
- For this reason, SMA Gold contains nucleotides – which naturally occur in breast milk – to help develop the immune system.<sup>13, 14</sup>
- Nucleotides are also important for a healthy gut. They promote the growth of 'good' bacteria in the gastrointestinal system, and the development of healthy gastrointestinal cells.

	<u>Unit of measures</u>	<u>Per 100 ml</u>	<u>Per 100 g</u>	<u>Per 100kcal</u>
Taurine	mg	4.7	37.2	7
Choline	mg	6.7	53.0	10
<b>NUCLEOTIDES</b>	<b>mg</b>	<b>3</b>	<b>23.3</b>	<b>4.5</b>

# Infant formula market - 2007

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- The top 4 major brands of infant formula are nucleotide-supplemented
- 6.4% sales growth



# Nucleotide supplementation in adults - What's the supporting case?

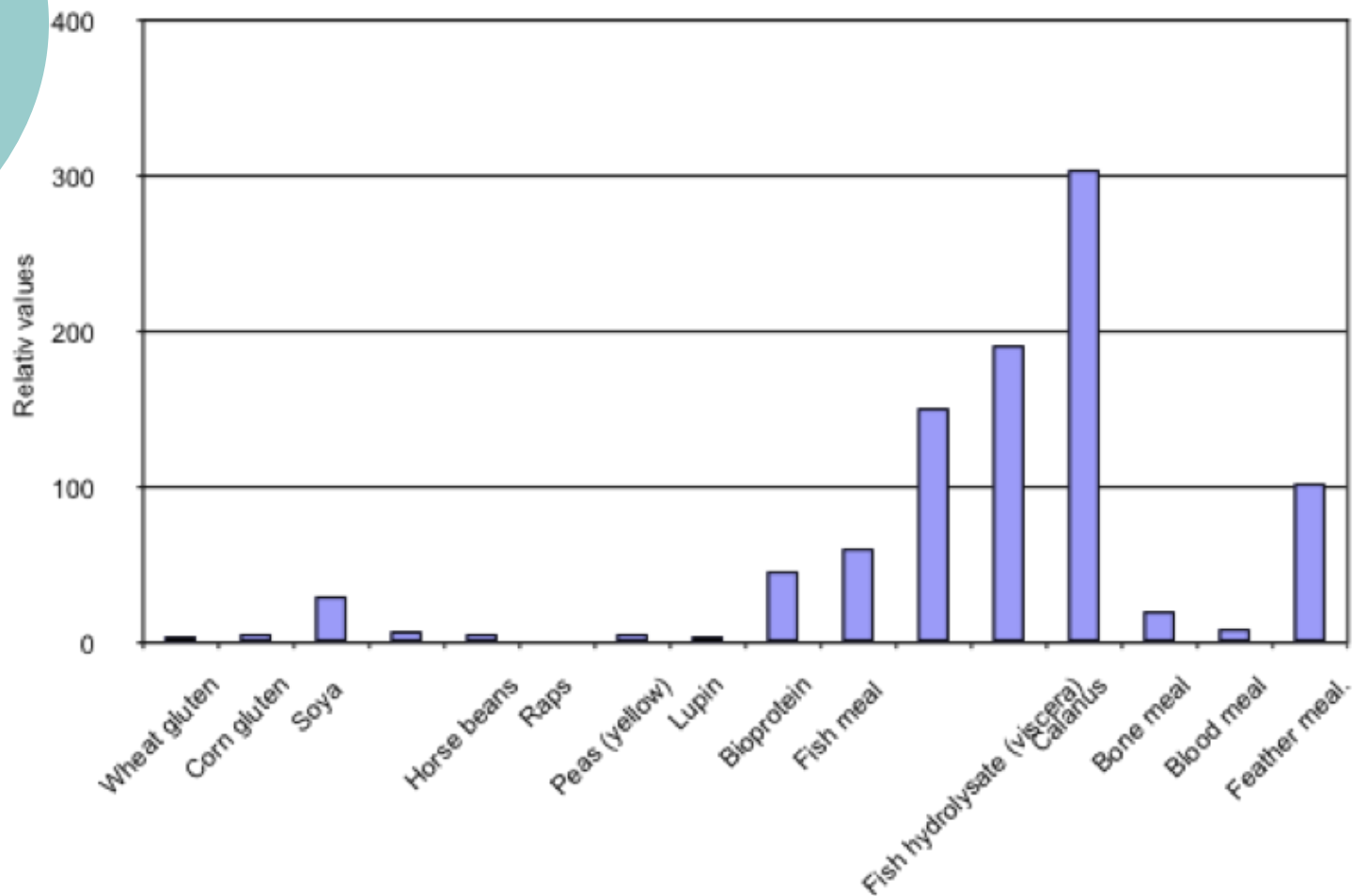
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## Is it a problem when nucleotides are deficient?

- **Scientific reviews** of nucleotide research data are exposing a deficiency in certain circumstances.
- **The intensive care trials** using the Impact enteral formula (includes micronutrients, nucleotides, Omega 3, etc.).  
In clinical trials, patients who received Impact formula developed fewer infections and had shorter hospital stays than those patients fed standard enthal
- **Supplemented infant formula** Many paediatric studies show the benefits of supplementing nucleotides to formula milk, which is why all the leading brands do.
- **Animal studies** with different nucleotide content of feeds.  
Commonly used ingredients show low levels. Adding nucleotides increased surface area of the gut lining leading to improved nutrient uptake, health and development.

# Ingredients are not all equal when it comes to nucleotide content

Sum Free Nucleotides in feed ingredients



# Why not just eat more nucleotide rich foods?

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## Nucleotide rich foods

- Liver
- Offal
- Yeast extract
- Mushrooms
- Lean meat
- Fish

In the 21<sup>st</sup> Century we either **don't** or **won't** eat these foods in sufficient quantities to meet 1-2 g requirement for healthy people, more for diseased...



# Nucleotide supplementation: Animal data

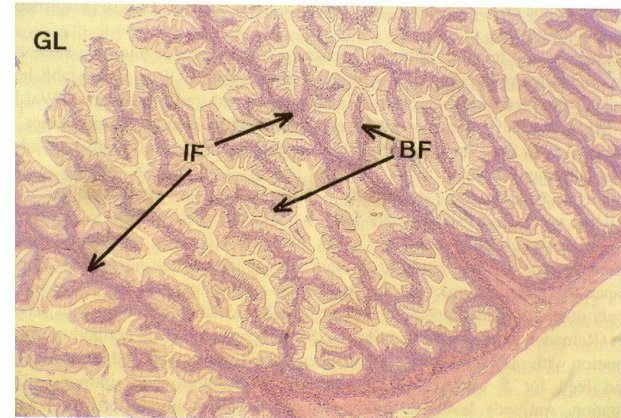
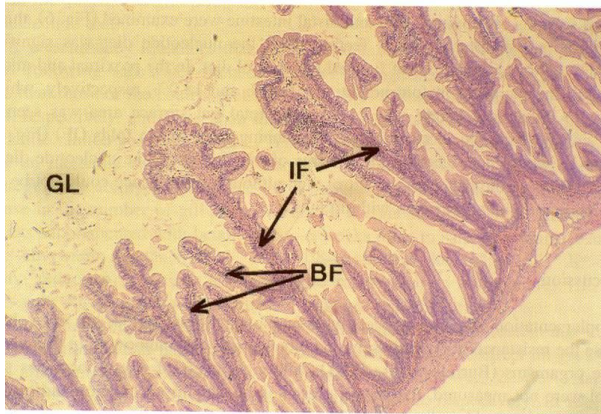
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- Conventional poultry, pig and salmon feeds did not contain supplementary nucleotides
- Trials where feeds supplemented with nucleotides have been given have shown increased villi development and nutrient uptake and subsequent improvements in health and growth

# Dietary nucleotides: A novel ingredient in fish feeds

Burrells et al, Aquaculture 2001

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- 25% higher villi
- Increases in mucosal surface area of gut
- Enhanced vaccination efficacy
- Improved growth through improved nutrient absorption



# Nucleotide supplementation in animal feed: established benefits

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- A credible alternative to antibiotic growth promoters - reduced antibiotic use to reduce impact on resistance in humans (EC Regulation 178/2002)
- Improved animal welfare – helping to replace the health benefits that antibiotics gave
- Reduced colouring agents due to improved nutrient absorption
- Nucleotide supplementation in both commercial and domestic animal feeds is now becoming mainstream practice



# Nucleotide supplementation: Human data

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- **Bower et al.** ICU enteral trial
- **Dancey et al.** IBS trial
- Davidson et al. Colds trial
- McNaughton et al. Immunity and stress
- McNaughton et al. Cholesterol

# Enteral nutrition with nucleotides

Krenitsky, J (2006). Immunonutrition — fact, fancy or folly? Practical Gastroenterology, May 2006.

**Table 1.**  
**Immunonutrition Products and Comparison (per 1000 kcal)**

<i>Product</i>	<i>Kcal/mL</i>	<i>Arginine (gm)</i>	<i>EPA/DHA (gm)</i>	<i>Glutamine (gm)</i>	<i>Nucleotides (gm)</i>
AlitraQ <sup>a</sup>	1.0	4.4	0	15.5	0
Crucial <sup>c</sup>	1.5	10	3.6	0	0
Immun-Aid <sup>d</sup>	1.0	14	0	12	1.0
Impact <sup>b</sup>	1.0	12.5	1.7	0	1.2
Impact 1.5 <sup>b</sup>	1.5	12.5	1.5	0	1.2
Optimental <sup>a</sup>	1.0	5.5	3.26	0	0
Perative <sup>a</sup>	1.3	6	0	0	0
Pivot 1.5 <sup>a</sup>	1.5	8.6	2.6	0	0
Stresson Multi-fibre <sup>c</sup>	1.25	7.12	0.88	10.4	0

<sup>a</sup>Ross Products 800-227-5767 [www.ross.com](http://www.ross.com)

<sup>b</sup>Novartis Nutrition 800-333-3785 [www.novartisnutrition.com/us/home](http://www.novartisnutrition.com/us/home)

<sup>c</sup>Nestle Clinical Nutrition 800-422-2752 [www.nestleclinicalnutrition.com](http://www.nestleclinicalnutrition.com)

<sup>d</sup>Product discontinued

(Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus.)

# Nucleotide supplementation: exploring benefits for people with diagnosed IBS

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- **Pilot study** undertaken in 2003 by KGK Inc., University of Guelph, London, Ontario, Canada  
**Aim:** to determine whether in a group of 15 patients with diarrhea-predominant IBS whether dietary supplementation with IntestaidIB could alter IBS symptoms and/or quality of life.
- **Results:** IntestaidIB supplementation decreased straining, hard stool and incomplete evacuation in individuals with IBS without causing any adverse effects

# Nucleotide supplementation: exploring benefits for people with diagnosed IBS

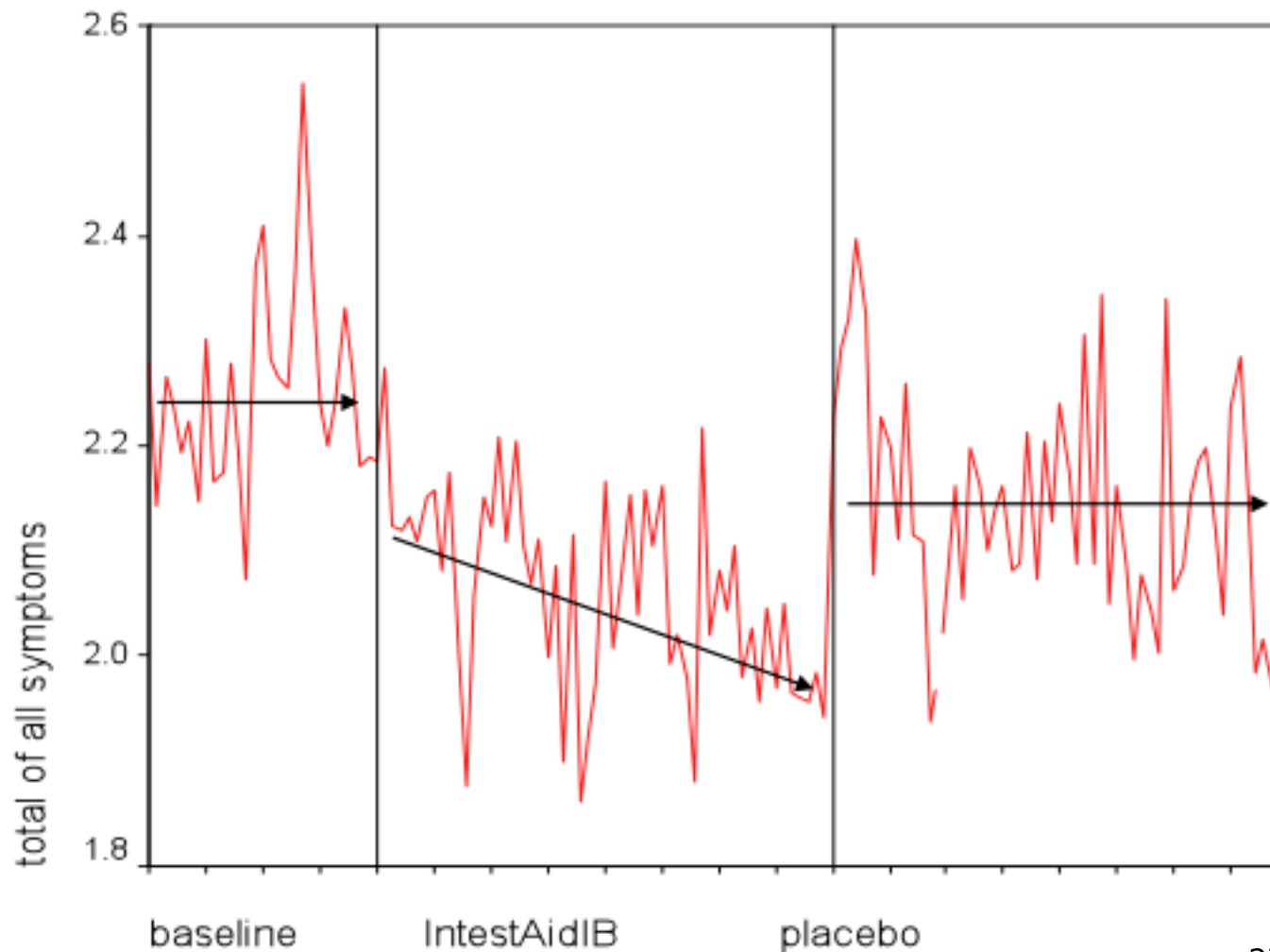
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Double-blind, randomised, placebo controlled, cross-over trial with 37 diagnosed IBS sufferers.

Dancey et al 2006, *Nutrition Journal*, 5  
University of East London

- Double-blind, randomised, placebo controlled cross-over Symptom rated from 1 to 7 every day via questionnaire
- Symptoms assessed: abdominal pain, diarrhoea, urgency, incomplete evacuation, flatulence, bloating, constipation 4 weeks baseline
- 8 weeks IntestAid®IB /placebo, 4 weeks washout Main analysis: time-series

# Nucleotide supplementation: exploring benefits for people with diagnosed IBS



# Results

Nutr J. 2006; 5: 16.  
Published online 2006 June 8. doi: 10.1186/1475-2891-5-16.

Copyright © 2006 Dancey et al; licensee BioMed Central Ltd.

## Nucleotide supplementation: a randomised d placebo controlled trial of IntestAidIB in peop Bowel Syndrome [ISRCTN67764449]

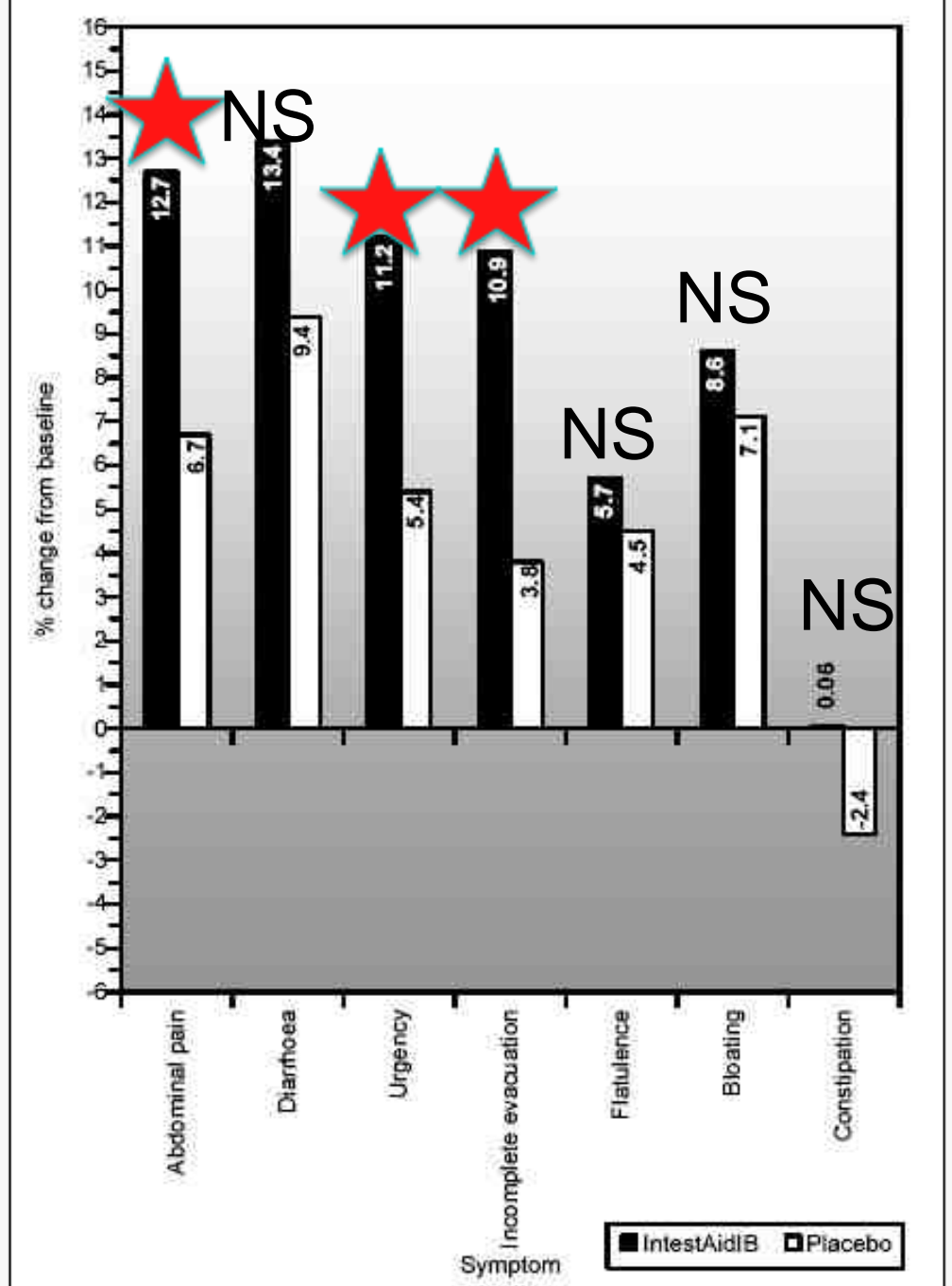
CP Dancey,<sup>1</sup> EA Attree,<sup>1</sup> and KF Brown<sup>1</sup>

<sup>1</sup>University of East London, UK

✉ Corresponding author.

CP Dancey: [C.P.Dancey@uel.ac.uk](mailto:C.P.Dancey@uel.ac.uk); EA Attree: [E.A.Atree@uel.ac.uk](mailto:E.A.Atree@uel.ac.uk); KF Brown: [K.f](mailto:K.f)

Received February 23, 2006; Accepted June 8, 2006.



# Nucleotide supplementation: exploring benefits for people with diagnosed IBS

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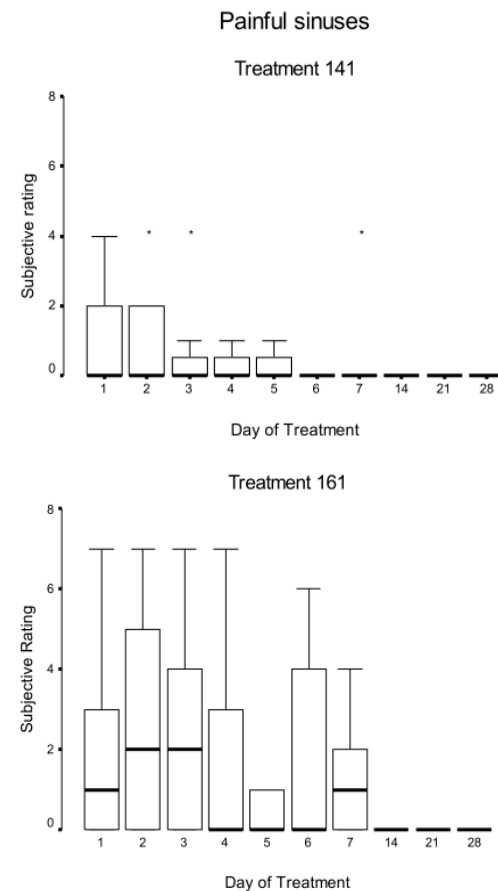
- Benefits of IntestAid®IB over placebo for all parameters  
Variability between patients
- Abdominal pain, feeling of urgency and feeling of incomplete evacuation were most pronounced  
No exclusion policy in baseline means probably underestimating benefits
- Small numbers probably reduced significance
- Longer supplementation could have increased effects  
General pattern of results all in same direction  
Implications of severity of symptoms decreasing over time

# Effect of Nucell® on Attenuation of Cold Related Symptoms

## A Double Blind Randomised Placebo Controlled Trial

Davidson et al

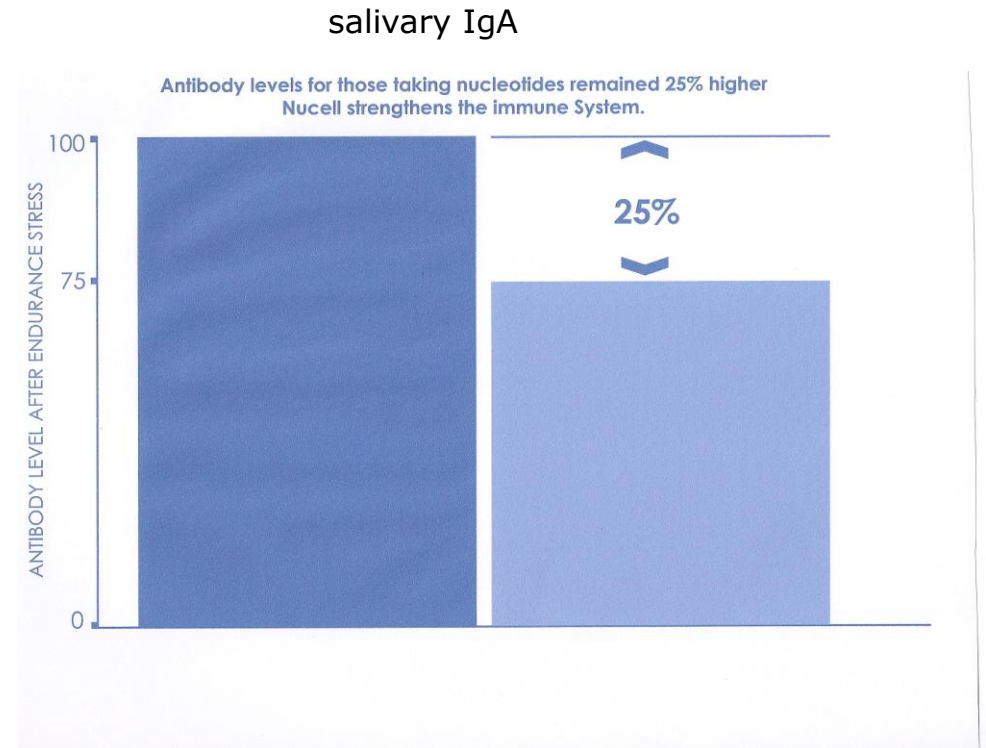
- Davidson's team looked at 36 cold sufferers in a RCT symptom reporting trial.
- Subjects who's diet were supplemented with nucleotides recovered significantly **faster**, and **suffered less** than those who had not received the supplementary nucleotides.



# The effects of a nucleotide supplement on the immune and metabolic response to short term, high intensity exercise

A Double Blind Randomised Placebo Controlled Trial  
McNaughton et al.

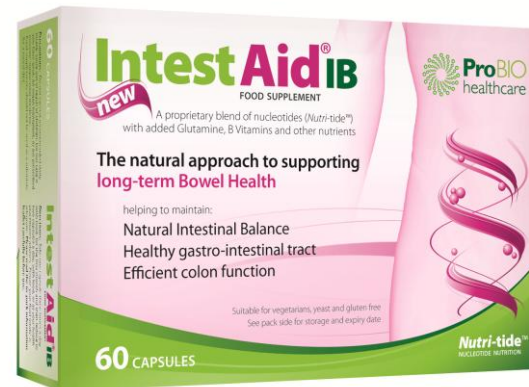
- Reduced immune suppression following intensive exercise
- Seen by SIgA levels for the nucleotide supplemented athletes remaining 25% higher than the placebo group after exercise



# Nucleotides: Emerging products

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- Specialist food or supplement products with ingredients for particular nutritional or medical purposes (PARNUTS)
- Food supplement products that support a proper/normal function





# Nucleotide supplementation: What now?

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- Case studies
- Dose-response studies
- Further clinical trials
- Patient feedback
- Health professional feedback

# Conclusion

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- The 'new' conditionally essential building block nutrient
- Formulation available today
- Promising results for GI and immune support
- The greater the stress on systems, the greater the need
- Further clinical experience required
- Further research required

Thank you.