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PHYSIOLOGY - HAS IT COME FULL CIRCLE?

UP Drukkery

PROF J G VAN DER WALT

VOORSTELLING: PROF. J G VAN DER WALT

Johann George van der Walt is op 7 Februarie 1944 in Johannesburg gebore. Hy matrukeleer in 1961 aan die Afrikaans Hoër Hoër Skool te Johannesburg en begin met sy studie in die Biochemie aan die Universiteit van die Witwatersrand, waar hy die grade BSc Honors in 1966 en MSc in 1967 onderskeidelik behaal. Na voltooiing van die MSc-studie is hy as die Voorsitter, Kweekingsassistent in Ooriëntasieswetenskap by die Departement Biochemie aangestel.

Die DSc-graad in Fisiologiese Chemie is in 1977 deur die Universiteit van Pretoria aan hom toegeken met die verhandelings "Production of volatile fatty acids in the rumen and their contribution to the glucose pool".

Hy nagradeer teorieë van die metabolisme van die vetgewasse in 'n artikel in die *Journal of Biological Chemistry* (1978) deur met prof. E. N. Bergman op Cornell Universiteit, New York, waar die metabolisme van glukose in die rumen as gevolg van metaboliese ingewoens is. In 1985 word hy deur prof. R. P. Anderson van die Universiteit van Sydney, Australië aangestel as die hoof van 'n laboratorium in die Departement van Fisiologie en Skape te Sydney.

PHYSIOLOGY - HAS IT COME FULL CIRCLE?

PROF J G VAN DER WALT

Gedurende 1987, na 'n besoek na Australië, word prof. van der Walt aangestel as Hoof van die Departement van Fisiologie van die Universiteit van Pretoria. In 1987 sluit hy by die Universiteit van Pretoria as mede-voorsitter in die Departement Fisiologie.

Intreerede gelewer op 2 September 1993 by die aanvaarding van die Professoraat in Fisiologie.

Tydens sy loopbaan het hy vele reisreise by internasionale kongresse en simposiume, waar hy ook as voorleer van bepaalde sessies optree. Hy geleef ook die geleentheid om te verhoor Fisiologie en Biochemie Departemente in die Verenigde State van Amerika, die VSA en Australië besoek al te if.

Hy word weer eens aangestel in Sydney, Australië om 'n besoek te lewer tydens 'n onderskeidelike besoek in 1992, gevolg by aanvaarding van prof. Anderson se bydrae tot die wetenskap.

Prof. Van der Walt is lid van die Departement van Fisiologie, Departement van Biochemie en die Departement van Fisiologie en Biochemie van die Universiteit van Pretoria.

Hy is lid van verskeie verenigings, naamlik die SA Biochemical Society, Physiological Society of Southern Africa, Australian Nutrition Society, S. A. Wetenskap vir Verlede en in die Toekomst van die Wetenskap, Die Suid-Afrikaanse Wetenskap vir Verlede, Hy is ook 'n regeringsraadslid van verskeie departemente.

VOORSTELLING : PROF J G VAN DER WALT

Johann George van der Walt is op 6 Maart 1944 in Johannesburg gebore. Hy matrikuleer in 1961 aan die Athlone Boys High School te Johannesburg en begin met sy studie in die Biochemie-riktig aan die Universiteit van die Witwatersrand, waar hy die grade BSc(Hons) en MSc in 1966 en 1967 onderskeidelik behaal. Na voltooiing van die MSc-graad is hy na die Veterinêre Navorsingsinstituut te Onderstepoort waar hy by die Rumen Biochemie-seksie aansluit.

Die DSc-graad in Fisiologiese Chemie is in 1977 deur die Universiteit van Pretoria aan hom toegeken met die verhandeling: "Production of volatile fatty acids in the ruminant and their contribution to the glucose pool".

Sy nagraadse navorsingsondervinding sluit die volgende in: Hy bring een jaar (1979/80) deur met prof E N Bergman op Cornell Universiteit, New York, waar die metabolisme van glukose en laktaat in skape en melkkoeie nagevors is. In 1985 word hy deur prof E F Annison van die Universiteit te Sydney, Australië uitgenooi om die effek van groeihormoon op die metabolisme van melkkoeie en skape te ondersoek.

Gedurende 1982, met die aftrede van dr F M C Gilchrist, word prof Van der Walt aangestel as Hoof van die Rumen Biochemie-seksie. In Februarie 1987 sluit hy by die Universiteit van Pretoria as mede-professor in die Departement Fisiologie, Veeartsenykunde, aan en twee jaar later word hy as Hoof van hierdie Departement aangestel.

Tydens sy loopbaan lewer hy talle referate by internasionale kongresse en simposia, waar hy ook as voorsitter van bepaalde sessies optree. Hy gebruik dan ook die geleenthede om by verskeie Fisiologie en Biochemie departemente in die Verenigde Koninkryk, die VSA en Australië besoek af te lê.

Hy word weer eens uitgenooi na Sydney, Australië om 'n oorsig te lewer tydens 'n uitsonderlike byeenkoms in 1992, gereël ter waardering van prof Annison se bydrae tot die wetenskap.

Prof Van der Walt is benewens 46 kort mededelings en plakkate, outeur en/of mede-outeur van 31 gekeurde publikasies in vooraanstaande wetenskaplike tydskrifte.

Hy is lid van verskeie verenigings, soos byvoorbeeld die SA Biochemical Society, Physiological Society of Southern Africa, Australian Nutrition Society, S A Vereniging vir Veekunde en is Redakteur van hulle tydskrif, **Die Suid-Afrikaanse Tydskrif vir Veekunde**. Hy is ook 'n geregistreerde natuurwetenskaplike.

Prof Van der Walt het die Nasionale Toekenning **BP Landboustudiebeurs (1979)** en die internasionale toekenning **Thomas Lawrance Pawlett Scholarship**, Sydney University (1985) ontvang.

Johnny van der Walt is getroud met Lia van Domselaar en die egpaar het twee seuns, Ian en Eric.

Op nie-akademiese vlak is Johnny een van die hoogste gekwalifiseerde SCUBA duikinstruktors en onderwaterfotografe in die land en elke vrye oomblik word benut om hierdie stokperdjie onder die water en onder die grond te beoefen. Verdere mylpale wat bereik is, sluit in die toekenning van Springbokkleure vir onderwaterhokkie in 1977 en 1979, die bereiking van die bodem van Sinoiagrot op 'n diepte van 109 m in 1972 en 'n uitnodiging om 'n mededeling tydens die Internasionale Onderwater Kongres in London in 1973 te lewer.

Prof P. SMIT
VISEKANSELIER EN REKTOR

**INTREEREDE: PROF J G VAN DER WALT AS PROFESSOR IN EN HOOF
VAN DIE DEPARTEMENT FISILOGIE,
FAKULTEIT VEEARTSENYKUNDE
UNIVERSITEIT VAN PRETORIA**

2 SEPTEMBER 1993

VERWELKOMING

Baie dankie vir die pragtige voorstelling!

Mnr die Rektor, Viserektor, Dekaan, kollegas en vriende

Dankie aan u almal dat u vanaand gekom het om na my te luister. Volgens die tradisie van Europese Universiteite moes voornemende Departemenshoofde eers hul filosofie, vaardigheid en vakkennis in die openbaar verdedig *voordat* hulle aangestel is. Hierdie voorwaarde het vervaag tot 'n tradisie waar almal teenwoordig uitgenooide gaste is en die rede eers *na* aanstelling plaasvind. Nietemin, ek kan u almal verseker dat die opdrag word nog net so ernstig opgeneem asof dit nog 'n voorwaarde is.

I would like to thank my family for providing the support and milieu that is vital for any academic. At the very centre of this family unit stands my wife Lia, without whom I am sure I would not have accomplished half as much.

Without any further ado, let me begin my speech.

PHYSIOLOGY - HAS IT COME FULL CIRCLE?

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Life

Logic

Study

PHYSIOLOGY

1. Introduction

"... I hold it equally impossible to know the parts without knowing the whole and to know the whole without knowing the parts in detail."

Blaise Pascal

Historically, the problem of understanding the biological mechanisms of an animal was approached by simply subdividing the complete organism into functional units, or organ systems. Such systems were then studied separately. This logical process was followed inexorably to molecular level, spawning many new and independent branches of biology such as biochemistry, biophysics and molecular biology. In the process, some fundamental mechanisms such as the genetic code have been elucidated. However, it is now becoming clear that the whole is more than simply the sum of its parts.

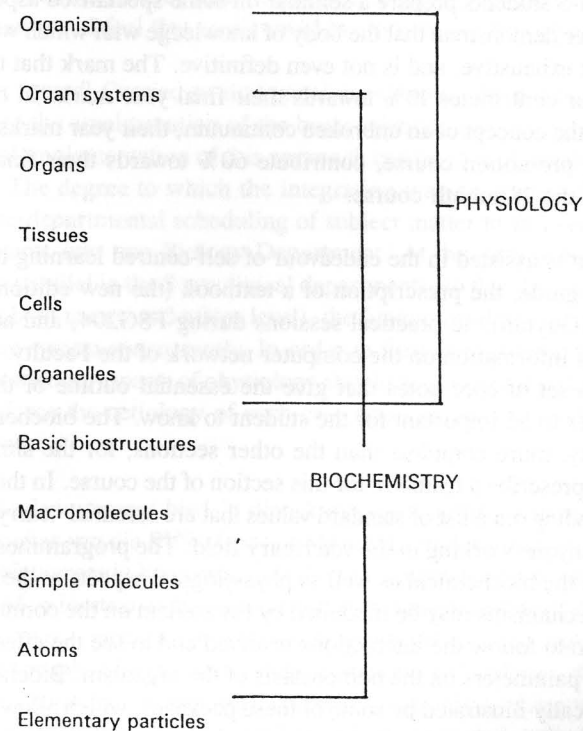
Research support in the USA, funded by the National Institutes of Health (NIH), has shifted over the past 2 decades from a preponderance of systems-orientated (90-95%) to highly specific molecular biology type projects (70%). Even more pronounced has been the shift in teaching curricula, wherein only 16% of both pre-and post-graduate medical students receive an integrated systems-based physiological education. This shift affects the future of physiology from both the research and teaching aspects. Traditionally, the separate disciplines of biochemistry and biophysics have maintained a two-way communication with physiology, deriving their problems from it and contributing to it by integrating new information into existing hypotheses. On the other hand, molecular biology serves as a highly valuable tool, contributing to physiology by opening up areas thus far inaccessible to research. However, it differs from the previous two disciplines in that it has a separate agenda in pursuing the minute building blocks of living systems without an apparent tendency to integrate these results into general physiology. A challenge for the future will be the ultimate integration of this information into our overall understanding of living organisms. For now, however, it is imperative that the trend to increasing specialisation be countered by integrative studies, for it is difficult to see how the next generation of teachers, many of whom have been brought up on isolated, detailed studies, can cope with instructing veterinary and medical students.

Since integrative physiology is the key to understanding the intact organism, something a veterinarian must be able to do, it is important that it be applied and taught in this way. As a result, the research programme reflects a whole body, integrated approach, as does the curriculum, for both undergraduate veterinary students as well as postgraduate students from all disciplines.

2. Teaching

Undergraduate: The Department teaches Physiology to both the veterinary students (BVSc) as well as the veterinary nurses (Dip Vet Verpl). The course for the BVSc students is given over 18 months during the third, fourth and fifth semesters and covers all basic aspects of physiology, including biochemistry. About a third of the formal contact time is devoted to biochemical aspects of the course, which are presented as an integrated part of physiology. The theme of the course revolves around the concept of homeostasis and the paradigm that form determines function. The students are given a view into the living organism that shows the continuum that stretches from a largely descriptive understanding of the interactions between various organ systems down to the chemical and physical forces underpinning these systems. The course offered to the nursing students covers the same fields that are given to the veterinary students, except at a more superficial level.

Fig. 1



Most of the lectures are given in the second year (FSG204 = 390 lectures during semesters 3 and 4), and are used to cover the course material. The small fraction of lectures that remain in the fifth semester (FSG314 = 60 lectures) are targeted for the important task of integrating all this information into a coherent body of knowledge. Over the past few years the department has systematically shifted more of the knowledge-based aspects from this semester back into the second year, to make room for these aspects. In line with this philosophy, that physiology must form an integrated body of working knowledge, several innovations have been introduced into the teaching philosophy of this department. The students are told at the beginning of the course that they must strive to overcome the piecemeal approach that must of necessity be followed in teaching, and that all information must be used to build a solid, three-dimensional model of an animal. In order to encourage this goal, and to promote long-term memory, the tests which take place every 10 weeks are given on an accumulative basis (about 30% of any test will refer back to older work). While this may seem onerous at first, the students have the assurance that those who cope with the system will receive encouragement in the form of exemption from the final examination. In their fifth semester, groups of 4-5 students prepare a seminar on some specialised aspect of physiology, to further demonstrate that the body of knowledge with which we have provided them is not exhaustive, and is not even definitive. The mark that they receive for this seminar contributes 10% towards their final year mark. In order to further encourage the concept of an unbroken continuum, their year marks from FSG204, which is a promotion course, contribute 60% towards their final year mark at the end of the 18 month course.

The student is assisted in the endeavour of self-centred learning by the provision of a study guide, the prescription of a textbook (the new edition of the smaller version of Guyton), 12 practical sessions during FSG204, and access to a large database of information on the computer network of the Faculty. In addition, we hand out a set of core notes that give the essential outline of the material that we consider to be important for the student to know. The biochemical notes are, of necessity, more complete than the other sections, for the simple reason that we do not prescribe a textbook for this section of the course. In the future, we will also be handing out a list of standard values that are essential "carry around" knowledge for anyone working in the veterinary field. The programmes on the network cover both the biochemical as well as physiological aspects of the course. Processes and mechanisms may be modelled by the student on the computer, thereby allowing him to follow the interactions involved and to see the effect of varying the important parameters on the homeostasis of the organism. Biochemical pathways are graphically illustrated by some of these packages, which allow the modern-day student to more easily visualise these sometimes complicated series of reactions.

There is also a database of short form questions in biochemistry available, which enables the student to self-evaluate his standard of knowledge. Unfortunately, we do not live in Paradise, and some problems have arisen from this student-centred approach. Students come to University burdened with 12 years of inappropriate education. Not only are they taught incorrect facts (water vapour = steam = water droplets), but they are indoctrinated into a technique of learning that is counter-productive to the development of higher cognitive function. Physiology by its very nature demands a high degree of insight, and a well-developed ability to visualise objects in three dimensions. In addition, a high degree of curiosity is required; I look for the student who was always in trouble for dismantling items such as the alarm clock it see how they worked. Unfortunately, children are categorised by teachers and parents early on as being either "mathematically inclined" or else "biologically inclined". The inference here is that biology does not require the same precision of thought normally associated with the physical sciences, and that students who operate on "fuzzy logic" are best suited to the biological sciences. In fact, in my experience it is people with an engineering background who experience the least difficulty with physiological and biochemical mechanisms. Teleological thinking is entrenched at school, and is an extremely persistent weed that is difficult to root out. I feel that more could be done in the first year to counter this mind set.

What about the future? Carried to its logical conclusion, the philosophy of integration leads to the amalgamation of the basic sciences into one course; Biology. The practical implementation of this approach can be seen at several universities in Europe. The degree to which the integration may be applied may stretch from simple interdepartmental scheduling of subject matter to full scale integration of departments into one Biology Department. At the very least, curricula should be run in parallel in the 3 preclinical departments, so that the student learns the structure (at both macro and micro level), the function and the energy requirement of an organ system concurrently. In order to further re-inforce the concept of integrated knowledge, aspects of physiology should be given in the clinical years, in order to reinforce the aetiology of each case so as to provide a rational basis for the treatment.

Nagraads: Die departement bied 'n dienskursus aan in die vorm van FSG700, wat aan die behoeftes van die BVSc(Hon) of MMedVet student voldoen. Weereens word 'n breë, geïntegreerde benadering tot die vak aangemoedig, en druk om die kursus aan te bied in losstaande brokkies word weerstaan. Inteendeel, die FSG700 kursus word nou in die vorm van 'n reeks modules aangebied, waarvan 5 die kern van die kursus uitmaak. Hierdie sluit velde in soos neurofisiologie, die opname en gebruik van suurstof, energiemetabolisme, liggaamsvloeistowwe en endokrinologie. Die kernmodules word oor 2 namiddae aangebied; tydens die eerste

word basiese begrippe hersien en tydens die tweede word praktiese probleme opgelos en bespreek. 'n Verdere 6 modules, wat meer gespesialiseerde vakrigtings dek, word aangebied, soos bv. oefeningsfisiologie, metaboliese afwykings, voëlfisiologie, geslagskunde en die patofisiologie van bloedparasiete. Dit word ook van die studente verwag om 'n spesifieke opdrag na te gaan in die literatuur, en 'n volwaardige seminaar daarvoor aan te bied en skriftelik voor te lê aan die klas. Die inhoud van die seminaar kan die belangstellingsveld van die student weerspieël, en kan sy kliniese of navorsingsveld ondersteun. Verbasend, het studentgetalle afgeneem sedert hierdie aanpassings gemaak is. Ek is egter oortuig dat hierdie verskynsel net 'n tydelike statistiese afwyking verteenwoordig; enige ander vertolking is seker nie moontlik nie.

Die departement het tans 3 MSc en 4 PhD studente, wie se navorsing 'n wye verskeidenheid velde dek. Al ons studente is deelyds, insluitend een personeelid, en benader gewoonlik die departement met 'n bestaande doelwit wat deel vorm van hul werksopdrag. In die verlede was baie van ons studente vanuit die landbounavorsingsopset afkomstig. Met die nuwe beleid van die Landbounavorsingsraad voorsien ek 'n dramatiese afname in nagraadse studente vanuit hierdie instansie. Die eerste aanduiding daarvan was die onlangse kanselering van 'n PhD student se inskrywing as gevolg van werkslading en betrokkenheid met kontraknavorsing. Dit is nie net 'n probleem wat my departement raak nie maar sal seer sekerlik wyer uitkring. Miskien is dit 'n probleem wat nou al die aandag van die Rektoraat moet geniet. Die Departement se fasiliteite is nou van so 'n hoë gehalte dat ons voltydse nagraadse studente kan huisves. Ons het nie net 'n opgeknapte gebou nie, maar ook nuwe apparaat wat ons sal toelaat om ons navorsingspoging deur te druk vir die volgende 5 tot 10 jaar. Hierdie fasiliteite behoort meer nagraadse studente, wat onontbeerlik is vir die toekomstige groei van enige departement, na ons toe te lok. Die belangrikheid van sulke studente is duidelik uitgewys deur die verlies van 'n navorsingsassistenskap twee jaar gelede. Die student het haar PhD voltooi waaruit daar nou 6 publikasies verskyn het. In die proses het sy nie net die getal publikasies van 'n klein Departement soos die van Fisiologie aansienlik vergroot nie, maar het ook 'n klimaat van akademiese bedrywigheid aangemoedig deur haar voltydse toewyding aan navorsing. Die teenwoordigheid van sulke voltydse navorsingspersoneel wat hulle volle aandag aan navorsing kan toewy, genereer die opwinding van oorspronklike ontdekking en bemoedig die nodige kultuur en werksetiek binne die raamwerk van 'n andersins pedantiese omgewing. Tans word die dosente binne die Departement hoofsaaklik met doseerwerk besig gehou, en dit word duidelik in die onlangse publikasiegeskiedenis van die departement getoon.

Tussengevoegde Graad: Die noodsaaklikheid van so 'n graad vir die toekomstige ontwikkeling en moontlike uitbreiding van die Departement Fisiologie word

duidelik uitgelig deur die vorige gegewens. Kortliks, lewer die Departement groterdeels 'n diens aan die kliniese departemente deur om voorgraadse studente op tweede- en derdejaarsvlak vir 'n kliniese omgewing voor te berei. Dit beteken dat ons as Departement feitlik nooit hierdie studente weer terugkry as nagraadse navorsingsstudente nie, anders as by suiwer wetenskaplike fakulteite. Ons lyn van onderrig word onderbreek met 2.5 jaar intensiewe kliniese opleiding wat die student uitstekend toerus vir sy toekomstige loopbaan as praktiserende veearts, maar hom geen insig tot navorsing gee nie. My gedagte van so 'n tussengevoegde graad, verkieslik op honneursvlak, word ook voorgestel deur die veeartsenykomitee van die Stigting vir Navorsing en Ontwikkeling, wat ook die gedagte ondersteun dat hierdie graad vir die uitmuntende studente bedoel is sodat hulle as toekomstige navorsers en akademiese leiers kan ontwikkel. Voortvloeiend uit hierdie opset sal daar 'n bron van navorsingsgerigte granduandi beskikbaar wees, wat verder op nagraadse vlak sal wil studeer. Kortliks wil ek graag 'n oorsig gee van die moontlike stuktuur van hierdie BSc(Hon)-graad. Die BSc(Hons) Vet. Fis. kursus sal aangebied word deur die Departement Fisiologie en sal een akademiese jaar heeltyds duur. Studente sal op akademiese prestasie geselekteer word. Afgesien van die gewone toelatingsvereistes, sal ons graag enige student wat volgens algemene regulasie G.19 vir 'n honneursgraad mag inskryf, toelaat om aansoek te doen, alhoewel die klem op studente wat die derde jaar van die BVSc-grad voltooi het en wel 65% of meer vir Fisiologie behaal het sal val. Die doelwit sal wees om studente bekend te stel aan die filosofiese benadering van veeartsenykundige fisiologie, en om hulle in die benadering en tegnieke van meer gevorderde fisiologie en fisiologiese navorsing op te lei.

Ek sal graag wil sien dat die kursusinhoud die volgende belangrike punte moet toelig. 'n Navorsingsprojek sal onder toesig van 'n studieleier voltooi moet word, en sal as mondelinge referaat aangebied word en ook as 'n geskrewe joernaalartikel ingehandig word teen die einde van die tweede semester. Die doel hiervan is om die student te leer om onafhanklik te werk en om bekwaamhede soos formulering van hipotese en doelwitidentifisering, gebruik van gevorderde toerusting, versameling en analiese van volledige data, ensovoorts te laat ontwikkel. Die keuse van projek moet inskakel met die doserende personeel se navorsingsveld, en studente sal in oorleg met die Departementshoof een projek kies. Die projek sal dan onder toesig van die betrokke studieleier uitgevoer word. Alle studente sal die UP-simposium oor navorsingmetodiek vroeg in die eerste semester moet bywoon. Projekbeplanning sal saam met die studieleier uitgevoer word, met inagneming van die voorbereiding van 'n protokol wat teen einde Februarie voorgelê moet word. Daar sal ook 'n literatuuroorsig vroegtydig voorberei moet word. 'n Projekverslag sal ook voorgelê moet word wat die versamelde data in publikasievorm uiteensit. Die dokument moet dus as volwaardige publikasie

voorberei word en slegs literatuur pertinent tot die bevindinge behoort te verskyn, soos in die formaat van 'n erkende joernaal (bv. Journal of Physiology).

Alle eksperimentele werk sal teen die laaste dag van die eerste semester voltooi moet wees, waarna die projekverslag teen middel Augustus voltooi moet wees. Ek verwag dat elke student sy resultate by 'n kongres sal voordra in die vorm van 'n referaat. Die 20 minute voordrag sal deel vorm van die eksamen gedurende November. Die paneel eksaminatore sal daarna kans kry om vir 15 minute vrae te stel aan die kandidaat.

Elke student sal verwag word om 5 modules tydens die tweede semester te voltooi. Elke module duur twee weke, en bevat 'n selfstudiekomponent en geleentheid om vertrouwd te raak met fisiologiese instrumente en hul gebruike. Die studente sal verwag word om 'n aantal seminare om toegepaste fisiologie en patofisiologie te skryf. Die seminare moet heeltemal onafhanklik saamgestel en aangebied word. Die student sal alle beskikbare inligting deur of van die biblioteek moet bekom. Aanbiedings sal ook mondelings aangebied moet word. Studente moet ook kursusse in Statistiek 110 en Fisiologie 700 bevredigend voltooi.

Die eindeksamen behoort uit drie komponente te bestaan, naamlik die navorsingsprojek (geskrewe voorlegging, studieleier se evaluering en mondelinge voordrag), seminare (geskrewe artikel en mondelinge voordrag) en die eksamen self (skriftelik en mondeling).

Die daarstelling van so 'n tussengraad behoort dus die sirkel vir die Departement Fisiologie te voltooi; daar behoort 'n terugvloei van studente te wees na die nagraadse program.

3. Research

When Jan van Riebeeck landed at the Cape to establish a provisioning station for the Dutch East India Company, he obtained most of his animal products from the indigenous Koi peoples. As the settlement grew, and as people pushed into the hinterland, so the perception grew that the "superior" breeds from Europe should be brought into "improve" the local stock belonging to the local people, who were after all ignorant of the theory and advantages of breeding programmes. This perception grew into an entrenched paradigm, that led to the virtual extinction of many local breeds of sheep and cattle. At the same time, vast herds of wild herbivores thrived on the same grasslands of Southern Africa despite regular periods of low rainfall. Most of the total land area of Southern Africa (102 272 323 and 17 192 709 hectares for the RSA and the homeland areas, respectively) is taken up by farms (83 064 408 and 16 111 523 hectares, respectively). However, only a small fraction of this farmland is arable (15 927 198 and 2 034 648 respectively), leaving vast tracts suitable only for grazing ruminants.

Many grasses translocate protein to their roots during winter, which corresponds to the driest period of the year. As a result, grazing herbivores often have to contend with a protein content (crude protein or CP) of less than 3% ('t Mannetje, 1984). The grazing ruminant may remain in a positive nitrogen balance at CP levels above 6%, in contrast to most monogastric mammals which require about 12% CP or more.

Although the evolutionary history of the local domestic stock was not comparable to that of the indigenous wildlife, it was long enough to ensure some adaptation to the climate and plants. The wheel has turned full circle, as current interest in these indigenous breeds has grown tremendously, and one of the aspects that is enjoying attention is protein metabolism and water homeostasis.

Water homeostasis

In this, as in other areas of physiology, many of the key processes are circular in nature. The major nitrogenous excretion product, urea, is produced in the liver via the urea cycle, elucidated by H.A. Krebs & K. Henseleit in 1932, 5 years before the Citric Acid Cycle was described. The complete urea cycle occurs only in the liver, and consists of 5 sequential reactions, the first 2 of which take place inside the mitochondrion, and the remaining 3 in the cytoplasm. In the first reaction, toxic ammonia is coupled to another waste product, bicarbonate, to form carbamoyl phosphate, using 2 molecules of ATP in the process. This compound is then attached to an amino acid carrier, ornithine, to form citrulline, which is exported across the mitochondrial membrane. The second amine group is contributed by aspartate. After the carbon skeleton of aspartate is removed as fumarate, leaving arginine, urea is excised, thereby returning ornithine to the beginning of the cycle.

In ruminants, as in most animals, water turnover is proportional to metabolic rate, and varies between 5-30% of the total pool per day. In terms of water intake, this can range from 2.74 l/100kg/day in Thompson's gazelle (*Gazella thomsoni*) to 6.42 l in *Bos taurus*, all dehydrated to 85% of initial body weight. Additions to the pool may come from drinking (cattle 347 ± 12 , sheep 197 ± 29 ml/kg^{0.82}, the record being held by a camel who took in 200l in 3 minutes), feed moisture (0.2% of body weight in summer in the Dorcas gazelle), and metabolic (starch=0.556, fat=1.07l, protein=0.396 g/g feed). Water is lost via the urine (10-15% of total), faeces (33%) and insensible routes (remainder). Dehydration reduces these losses from urine by between 27% to 75%, from faeces by 17% to 37% and via insensible routes by very little. The reduced urine output is achieved by concentrating the urine, up to 8-fold more than blood in the case of the camel.

One of the major functions of the mammalian kidney is the conservation of water, metabolites and electrolytes. In general, cattle and sheep can produce urine

(17-45 and 10-40 ml/kg per day for cattle and sheep, respectively) that is about 4 and 7 times, respectively more concentrated than plasma compared to the maximum of 4 fold for man. At this point, another cycle plays a key role in conserving water via the kidney. Major factors that contribute to this ability include a relatively deep medullary region, a high proportion of juxta-medullary nephron loops that extend throughout the medulla, and the counter-current mechanism involving the vasa recta and the recirculation of urea. Of the urea filtered at the glomerulus, 50% is reabsorbed in the proximal tubule. Some urea (about 60% of the amount filtered) moves back into the nephron via the Loop of Henle. Of the amount reaching the collecting duct, about 85% is reabsorbed. This circular movement of urea leads to an accumulation of urea in the medulla, aided by the retarding action of the vasa recta and its counter-current mechanism.

Nitrogen metabolism

The resulting increase in blood urea concentration leads to an increase in enterohepatic recycling, either via the saliva (linear) or transruminally (hyperbolic). The ratio of salivary secretion to diffusion through the rumen wall was calculated to be 2:1 and 5:1, when serum urea was 172 and 360 mg N/litre, respectively. As a result, more ammonia is available in the rumen for microbial protein synthesis, thereby improving the efficiency of nitrogen retention. The metabolism of urea might therefore provide the link between the adaptation of ruminants to drought and their ability to utilise feed with a low crude protein content. Only by examining the role of urea in a holistic fashion will it be possible to elucidate the possible interaction between water and nitrogen retention in ruminants.

In order to understand the role of urea in ruminants, it is necessary to briefly review the protein metabolism of the splanchnic bed. The presence of a fermentation vat at the front of the digestive tract leads to the proteolysis of feed protein before it can reach the site of absorption in the small intestine. The efficiency of this process is proportional to the vulnerability of the protein to microbial attack. This fraction (bypass protein) may supply essential amino acids to the animal when it is digested in the small intestine. Once again, a cycle in the rumen plays a role in the nitrogen economy of the animal. Dietary protein (60-90%) and non-protein nitrogen (*ca* 100%) are both degraded to ammonia, which is incorporated into microbial protein (50-70% derived from ammonia). The recycling of nitrogen through this pool in the rumen may be minimised by defaunating the animal, thereby removing the protozoal component which is responsible for much of this. The composition and amount of microbial protein is relatively constant and independent of the intake and composition of feed protein.

Although the splanchnic bed only constitutes 7-13% of total body mass, it uses 40-60% of total oxygen demand. In general, splanchnic blood flow is proportional

to the intake of energy. A large amount of ammonia, proportional to nitrogen intake and between 0.4 and 6.5 times higher than all the α -amino linked acids taken up by the portal-drained viscera, may be absorbed from the rumen. Of the total nitrogen that flows from the abomasum to the small intestine, between 30%-60% represents α -linked amino acids. The increase above basal values largely represents unfermented feed protein, which may be as high as 60% of non-ammonia nitrogen entering the small intestine. Amino acids and small peptides are absorbed mainly from mid to lower ileum. Most amino acids appear to be at least partially metabolised in passage through the gut wall (about 60% in sheep). Of the total nitrogen entering the caecum, between 40% and 60% enters as amino acids, 15% as urea and 1% to 13% as ammonia. Urea may also diffuse into the lumen from the blood. Increasing the energy supply to hindgut fermentation will increase faecal excretion of nitrogen, while decreasing the concentration of urinary urea. Nitrogen is absorbed in net amounts, mainly as ammonia, from the hindgut. Net flux of ammonia, urea and the α -linked amino acids appears to be proportional to nitrogen intake.

As a result, most feed protein (as well as any non-protein nitrogen) is recycled through the ammonia pool in the rumen to microbial protein, which is largely digested in the small intestine. Any remaining protein entering the large intestine is again subjected to microbial fermentation, leading to a net uptake of ammonia from this end of the digestive tract. This ammonia, together with that from the rumen, is taken up into the portal circulation and is incorporated into urea in the liver (about 2 and 16 gN/day from ruminal NH_3 and from deamination, respectively).

The next circle to play a key role in nitrogen metabolism is the recycling of urea back to the rumen. The amount that flows to the rumen, via saliva or directly by diffusion through the rumen wall, is proportional to the plasma concentration. Any production of urea that raises the plasma concentration above 4 mMol may be taken up by the postruminal tract. The exact amount remains controversial, with one school (Weston & Hogan) claiming that urea transfer into the rumen is directly proportional to the concentration in plasma, and that no further transfer occurs above a concentration of 16-18 mgN/100ml. Nolan & Leng, on the other hand, have shown that less than 1 gN/day is transferred to the rumen as urea, and that the transfer rate is inversely proportional to the ruminal NH_3 concentration. Regardless of the actual mechanism controlling the amount transferred, the flow ranged from 10 to 42% of N intake (20 gN/day, or about 50% of the amount synthesised in the liver). When diets contain less than 13-15% CP, then the amount of digesta nitrogen entering the duodenum is more than that of dietary nitrogen, while diets containing more than this level cause the balance to be negative. This suggests that the reticulo-rumen complex traps recycled nitrogen at low dietary intake levels.

The role of urea in recycling nitrogen in ruminants, as described above, is well established, although there remains some contention over the quantitative importance of this pathway. This does not exclude the possibility that other mechanisms to recycle nitrogen may have evolved in ruminants. Certainly, such mechanisms exist in other animals that do not have the benefit of a foregut fermentation process. Results obtained from hibernating polar bears show that nitrogen stores are recycled during a 7 month hibernation, so as to minimise the amount of nitrogen lost via urine (Ramsay *et al.* 1991). Their results suggest that urea may be utilised in this process. Ponies (Prior *et al.* 1974) and rabbits (Hoover & Heitmann, 1975), have been shown to recycle large amounts of urea, and to retain nitrogen in the process. Due to urease in the hindgut, most of the urea entering this organ will be hydrolysed to ammonia. Although there is some evidence of amino acid uptake from the hindgut (actively in pigs, (James & Smith, 1976); passively in rats, (Binder, 1970)), it is generally accepted that the major flow of nitrogen from this region is in the form of ammonia, while the carbon skeletons are actively absorbed from the caecum of rats (Fordtran *et al.* 1964). There is considerable evidence that not all the urea taken up by the digestive tract passes through to the lumen, but is degraded somewhere at a juxtamucosal site (Malmlöf & Nunes, 1992). The fact that the resulting ammonia does not appear in the circulation may be explained by the fact that the small intestine is a major site for the synthesis of citrulline from ammonia, bicarbonate and ornithine (Morris, 1992). The citrulline may then represent an important form of nitrogen transfer to the liver.

Thus is the circle closed once again; the urea that is made as an excretion product assists in the retention of water, and is itself retained and recycled back to the protein metabolism of the animal. Our current research programme reflects this integration between nitrogen metabolism and water homeostasis in ruminants. Recent work has, in fact, demonstrated that limiting water intake may improve nitrogen retention (by about 8 g crude protein per day) in sheep fed a diet low in nitrogen (7% crude protein). The mechanism by which this occurs forms the basis of our immediate research programme.

4. Conclusion

I hope that my brief journey through the physiology curriculum, with a detour via an intercalated degree, leading on to research, will have given you some sense of the challenges that lie ahead. The need to integrate our extensive knowledge is now more urgent than ever, and it comes at a time that is ripe for a major paradigm shift. The limitation that discontinuous thinking placed on our understanding of the world around us, is now being replaced by an ever-increasing

sense of continuity, reinforcing our place within the context of Nature, and not above it.

Pursuit of Knowledge

The ancients who wished to illustrate illustrious virtue throughout the Kingdom first ordered well their own states. Wishing to order well their own states, they first regulated their families. Wishing to regulate their families, they first cultivated their persons. Wishing to cultivate their persons, they first rectified their hearts. Wishing to rectify their hearts, they first sought to be sincere in their thoughts. Wishing to be sincere in their thoughts, they first extended to the utmost their knowledge. Such extension of knowledge lay in the investigation of things.

Confucius

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