WHAT MAKES US TIC?

THESIS SUBMITTED FOR

THE DEGREE OF DOCTOR OF SCIENCE (Med)

IN THE UNIVERSITY OF CAPE TOWN

PROFESSOR MARY MAY ROBERTSON

MBChB, MD, DPM, FRCPCH, FRCP (UK), FRCPsych

PUBLISHED WORK 1971 – 2006

VOL. 1

TO THE MEMORY OF MY PARENTS

KATHLEEN FRANCES ROBERTSON (NEE HAYNES) 1909-1986

FORDYCE CENTLIVRES ROBERTSON 1917 – 1991

ACKNOWLEDGEMENTS

MY PATIENTS AND THEIR FAMILIES
FOR THEIR PATIENCE AND COOPERATION
FOR TEACHING ME SO MUCH

MY COLLEAGUES
FOR COLLABORATION AND FRIENDSHIP

PROFESSOR W A (ALWYN) LISHMAN
DR FD (MICK) PASCOE
DR RTC PRATT
FOR INSPIRATION

DR PETRA KAHLE
WITH ADMIRATION

JOHN McKAY LUDGATE
FOR HIS SUPPORT

ALBERT VAN DE SANDT CENTLIVRES
1887-1966

CHIEF JUSTICE OF SOUTH AFRICA
1950 – 1957

CHANCELLOR OF THE UNIVESITY OF CAPE TOWN
1950 – 1966

A CHAMPION OF ACADEMIC FREEDOM

MY GREAT UNCLE

Chief Justice
The Honourable Mr. Albert van de Sandt Centlivres'

INAUGURAL ADDRESS

Let me begin to-day by telling you how greatly I appreciate the great honour which the University has bestowed on me in conferring the honorary degree of doctor of laws and how I value the, if I may say so, even greater, honour which Convocation has thrust upon me by electing me to the office of Chancellor of this University. To me it is the greatest honour which has ever been conferred on me. For the honour of being elected to the highest office in this University is the greatest honour which it could have conferred on one of its past students. My indebtedness to the old S.A. College can never be discharged in full, but it pleases me to be able to think that, by the service which I shall endeavour to the best of my ability to render in the high office I now hold, I may possibly be able to discharge a small portion of that indebtedness. It is in this spirit that I assume my new duties.

It seems a far cry from 1904 to 1951. It was in 1904 that I, a callow youth, first entered the portals of the old S.A. College. In coming back to the University in another capacity after this long lapse of time I feel like the *vagabundus* who at long last returns to the intimacy of the family circle. The 40 odd years that I have spent in the wilderness have seen great changes in higher education in South Africa and more particularly in the South African College. Since the date when I first entered the College, it has blossomed into a leading University in the sub-continent—a University which, still possessing the vigour of youth, is growing from strength to strength.

To-day it is but natural that all of us should think of the great world figure who preceded me in the office I now have the honour to hold. Scorning many of the frivolities of this

world, he was a man of extraordinary vitality both in its physical and intellectual aspects. He was never happier than when he achieved something, whether after laboriously scaling the heights of his beloved Table Mountain he at length reached the summit and with zest inhaled the pure mountain air, or whether he succeeded in bringing to fruition some object on which he had set his heart. Those who love to scale the mountain tops obtain a broader vision of the world that lies at their feet than those who are content to abide in the plains and this broader vision of physical things inspires them to endeavour to obtain a broader intellectual and mental vision as well. General Smuts was one of those few mortals who habitually scaled the heights both physically and intellectually. Of the many addresses delivered by him during his long life none was more inspiring than the one he delivered at the unveiling in May 1923 of the memorial erected near Maclear's Beacon in memory of those who made the supreme sacrifice in the First World War. In a few memorable phrases he epitomized the Spirit of the Mountain. He said:—

> "The sons of the cities are remembered and recorded in the streets and squares of their cities and by memorials placed in their churches and cathedrals. But the mountaineers deserve a loftier pedestal and a more appropriate memorial. To them the true church where they worshipped was Table Mountain. Table Mountain was their cathedral where they heard a subtler music and saw wider visions and were inspired with a loftier spirit."

Those memorable words should serve as an inspiration to both those who have the privilege of teaching and those who have the privilege of learning at this University which, situate as it is on the heights overlooking the vast expanse of the Cape Flats, dominates the closely settled plains lying at its feet. It is in keeping with the lofty spirit referred to by your late Chancellor that those who founded this University should have chosen as its site a height of incomparable beauty, a height which affords a wide vision over the world lying below, a height which in its turn is dominated by the majestic beauty of Devil's Peak. It follows from the very situation of this

University that all those who come within its walls cannot fail to be inspired by the lofty spirit of idealism and by a desire to use the knowledge and training acquired by them for the benefit of those less fortunate members of the community who are unable, through various causes, to embark upon a University career.

What are the ideals which a University should strive to attain? First and foremost I would place the ideal of preserving the liberty of the individual. General Smuts in his striking rectorial address delivered at St. Andrews University in 1934 stated that individual freedom, individual independence of mind and individual participation in the difficult work of government seemed to him to be essential to all true progress. He defined liberty as meaning freedom of thought, speech, action and self expression and maintained that human government based on a negation of liberty was an anachronism in our western civilization.

There can, of course, be no freedom in the true sense of the word in a country where its Universities are in all their activities strictly controlled by the State. Fortunately for us in South Africa our Universities are in many respects free of State control and are to some extent able to work out their own destinies. It is true that all Universities in South Africa are dependent upon the State in the sense that a large part of their income is derived from State grants. This fact has caused the fear in some quarters that the State may claim the right to destroy the academic freedom which is so highly valued by every University worthy of the name. The late H. A. L. Fisher, the famous historian and the great warden of New College at Oxford—my old College—points out in his "Unfinished Autobiography" that there was at one time vehement opposition in the name of academic freedom to the acceptance by Oxford and Cambridge of parliamentary grants. Those Universities, which had in the past been sustained solely by private benefactions, were compelled by financial considerations to accept those grants but dictation from the government was never attempted. Mr. Fisher added that "the boon of academic freedom was fully understood and

widely valued. Even Universities which accepted grants from the State would have sacrificed their parliamentary monies without demur rather than submit to dictation from the Government". I am sure that no such dictation will be attempted in South Africa.

I cannot place too great an emphasis on the fact that academic freedom is the very life-blood of every University. To put it positively, academic freedom, as I understand it, means the unrestricted right on the part of a University to decide for itself what it shall teach, how it shall teach it and whom it shall admit to be taught, as well as the unrestricted right to select as its teachers the best men and women available, whether they happen to have been born in South Africa or elsewhere. In the old days, when university education in the true sense of the word was unobtainable in South Africa, we had to import the bulk of our professors and lecturers from overseas. To-day the position is very different and South Africa is able to supply most, if not all, of its own professors and lecturers. But, even although this is the position, there is no reason why appointments should not be made from outside South Africa when the persons appointed are men or women of exceptional ability and learning. It cannot be suggested that England, with its centuries of University education, is unable to fill all its professorial chairs with Englishmen. Yet Oxford and Cambridge, in the true University spirit, do not hesitate to appoint persons who are not Englishmen, when such persons will add lustre and fame to them. Good blood, which is fresh, no matter where it comes from, rejuvenates and re-invigorates the institutions into which it is introduced.

To put it negatively there can be no academic freedom when doctrinal uniformity is insisted on and when frank and free discussion and criticism and the toleration of divergent opinions are not permitted. That position arose under the Hitler régime in Germany and, as a result of the short-sighted policy adopted by that régime, the Universities in that country lost many of their most eminent professors and teachers, some of whom were fortunate in escaping the horrors of concentration camps and were eagerly sought after by the great

Universities of those countries which still cherished academic freedom.

In the university domain and in the academic field generally there was much in common between General Smuts and the late J. H. Hofmeyr whose untimely death came as a great shock to South Africa in general and more particularly to this University which had the proud honour of claiming him as its most brilliant and most gifted alumnus. Mr. Hofmeyr in his inspiring address in 1939 on the occasion of his installation as Chancellor of our sister University of the Witwatersrand reminded his audience of "the University's high calling to guarantee the fundamental principles of freedom" and proceeded to say that "academic freedom—freedom of thought and freedom of expression—is the University's own most cherished possession. When it surrenders that, it loses the the very justification of its existence. The University's primary function is the making of man. It can best serve the cause of freedom by giving to the community men and women with the qualities of mind, of spirit and of character which will fit them to be its very doughty champions."

I feel sure that the sentiments so ably and lucidly expressed by the late Mr. Hofmeyr will be endorsed by all who are listening to me to-day.

To achieve and maintain the freedom which General Smuts and Mr. Hofmeyr had in mind, the true function of a University must never be lost sight of. The imparting of knowledge is an important function but a far more important function is to discipline the mind and train it to make the best use of its own powers. The mass of mankind are either too busy about their own daily affairs or too indolent to think for themselves: they are far too apt to accept the views of others and are led astray by those who designedly make use of some plausible slogan or catch-phrase. Another device is to appeal to prejudice or emotion or passion. I doubt whether any person is entirely free of prejudice but the seeker after truth must, as far as is humanly possible to do so, divest himself of all prejudice, for prejudice is nothing but the child of ignorance. A further device is to indulge in personalities. There is nothing

more nauseating than when questions are discussed not on their merits but on the demerits of the person who proposes a solution. The only effect of such a device is to cloud the issue and to divert the minds of others from enquiring whether the solution suggested is sound or not. Let it always be borne in mind that unless a University succeeds in banishing from the minds of its students all irrelevancies and succeeds in making them think for themselves it fails in its main object. A moment's reflection will show that when one is confronted with a problem the first step to take is to ascertain the true facts. Many people assume that they know the facts: that assumption is often false. To find the true facts may entail a great deal of intelligent research. Ruskin put the matter very clearly when he said:—

"Without seeking, truth cannot be known at all. It can neither be—set down in articles, nor in any wise prepared and sold in packages ready for use. Truth must be ground for every man by himself out of its husk, with such help as he can get, indeed, but not without stern labour of his own."

You cannot be intellectually honest unless you ascertain the true facts of any problem that is claiming your attention and unless the answer you give to that problem is an answer which you honestly believe to be correct. As Sydney Smith put it, truth is the hand maiden of justice and freedom is its child. Having ascertained the true facts of any problem the next step is to think out some solution and as regards the steps I have mentioned a trained mind is required. The training and disciplining of the mind is therefore the highest function of every University.

A properly trained mind is an invaluable asset to the community, more especially as such a mind will not resent fair criticism nor will it tolerate intolerance towards others. The possession of a trained mind is of the utmost importance in a country such as ours where there is such a diversity of races, colours, languages, religions and traditions. Our country is full of complex problems which can only be satisfactorily dealt with—I will not say finally solved, for that,

with the constant permutations of human relationships, is impossible—if they are approached in the proper manner, viz. with an open mind—a mind eager to find the true facts and hear the views of others and willing to adopt a solution which will neither offend the deep rooted susceptibilities of those affected by such a solution nor infringe their fundamental rights as human beings. We must realize, whether we like it or not, that we are not a homogeneous community and that whatever is detrimental to one section of the community must in the long run have a disastrous effect upon the rest of the community.

In this connection we must constantly bear in mind that the solution some may suggest may not be the solution favoured by others. For different minds function in different ways and even in the highest court of every country you will find differences of opinion. These differences of judicial opinion, it is almost unnecessary to say, are honestly arrived at and are due to the complexity of the problems which are considered. And it does not follow that the majority views are always correct, even in the case of judicial opinions, however carefully they are arrived at. For after all is said and done there may be more answers than one to a problem which is not of a purely mathematical or scientific nature. In a certain sense, differences of opinion are not to be deplored, for such differences not only show that those who are grappling with a problem think for themselves and are not mere rubber stamps for the opinions of others but they also whet the intellectual appetite and act as a spur to thorough investigation. This world of ours would be a dull world if everyone thought alike. The experiment of making all people think alike has been tried in some countries and has never succeeded. Every country which has tried the experiment has found to its cost that it has caused itself irreparable damage. No self-respecting individual will submit to being intellectually dishonest by slavishly pretending to accept opinions which are foisted on him by others and in which he himself does not believe. Rather than do this, he will leave his native land as happened in the case of France when the revocation of the Edict of Nantes

led to the exodus of its best citizens, the Huguenots, who, preferring exile to the serfdom of the soul, enriched the culture of the countries to which they emigrated. To-day, alas, a large part of the world has almost succeeded in hermetically sealing its borders and thus preventing those of its citizens who value freedom of thought from escaping from the mental and physical prison house in which they find themselves. History teaches us that however homogeneous a country is, there is ample room for differences of opinion among its citizens and that any attempt to force them into one common intellectual or religious mould can never succeed. History also shows that virtue is not the exclusive property of any particular nation and that each nation has its good and bad men and women. One is sometimes apt to view with aversion all manners and customs different from those with which one is familiar. This feeling is a sure sign that one's education has been at fault and that one has not progressed very far from a state of barbarism. The primitive savage, terrified of the unknown, often put strangers to death. To-day we do not put strangers to death, excepting when we are at war with them. We have made considerable progress in our relation to human beings who live a different mode of life and it is as well to recognize quite frankly that the human family is one, especially in these modern times, when science has very largely succeeded in annihilating distances and has provided man with the means of destroying himself.

We should all remember what the late Lord Balfour said in opening the great Hebrew University of Jerusalem in 1925: "Learning is a bond which unites all mankind, all men of adequate instruction in all parts of the world."

It may be asked: how can University life foster the spirit of tolerance? In the first place those who have been properly trained to teach have, through experience, learnt how necessary it is to tolerate the views and feelings of others and their experience will colour their whole method of teaching. Secondly the University through its playing-fields and student societies provides ample opportunities to its students to get to know one another and to learn how to bear with one another!

It is a fallacy to imagine that the sum-total of University education is to attend lectures, burn midnight oil over text books and write examinations. University education means much more than that; otherwise the product of Universities would be mere book-worms or blue-stockings incapable of leadership in the practical affairs of life. A University will fail in its true purpose unless it produces men and women who will take a leading part in the community when they leave its portals. As I have already indicated, ample opportunities are provided by the University to enable its students to be leaders of men and women. In mixing with their fellow students on the playing fields and in taking an active part in some student society they rub off their own rough corners and learn to co-operate with one another. Experience teaches one how much tact and thoughtfulness and above all infinite patience are required in order to be able to achieve anything in this world.

The modern world is far more complex in its organization than the old city states of ancient Greece and owing to the ever-increasing tendency all over the world to-day on the part of every State to regulate, if not in some instances to abolish, private enterprise, there is a much greater demand for able administrators who will be capable of directing the activities of the large staffs under their control This requires a deep knowledge of your fellow men, a spirit of co-operation and a capacity to handle others in such a manner that you will get the best out of them.

All this can be learnt at the University, if the student is only willing to exert himself in this direction. It is in this respect that a wholly residential University is such an aid: for when the students live within a reasonable distance of one another it is far easier for them to lead a corporate life than when they are scattered through a large area. From the nature of things it is unlikely that our University will become wholly residential within our life-times but it is satisfactory to be able to record that one of the most important features of the development scheme, which is now under way, is the provision of additional large residential blocks for men and

women students and the establishment of a student community within easy access of public transport. It is earnestly to be hoped that sufficient funds will be forthcoming to enable the University to provide these further facilities for its students —facilities which are badly needed and which, when provided, will enable a larger proportion of the students, than is at present the case, to avail themselves of the opportunities afforded to equip themselves adequately for the battle of life.

This University is a replica upon a small scale of South Africa as a whole. It is fitting that this should be so, for the function of a University is to prepare its students for life in the larger world outside its gates. This University opens its portals to men and women from all walks of life and thus affords those, who have the privilege of continuing their studies within its bosom, a unique opportunity of getting to know South Africa in miniature as it were, and of acquiring what may be described as a broad South African outlook. In this respect the University is faithfully carrying out the great tradition built up by the old S.A. College. If you examine the records of that College you will find that it was an unfailing reservoir which supplied South Africa with many of its most eminent men in diverse walks of life. The policy adopted by the University in this respect will stand its students in good stead when they leave the University and enter the larger world outside and are confronted with problems which are peculiar to a country which we are proud to call our own.

I have stressed that the function of a University is to discipline and train the mind and to broaden the vision of its students in order to equip them for the battle of life. In the old days the main function of a University was the teaching of the Humanities; nobody was considered to have a sound education unless he had a good grounding in the Humanities. To-day the position seems to be very different. There is too great a tendency to specialise at too early an age both in the Universities and in the schools. The danger of the Universities becoming mere higher-grade technical colleges must be avoided. I do not want to be misunderstood and I want to make it clear that to-day, owing to the spectacular advance

that has taken place in science and other fields of knowledge, specialisation is an urgent necessity and such specialisation is now one of the main functions of a University education. And coupled with specialisation is the need for research opportunities. But specialisation based on an insecure foundation has its dangers, for without a good general education as a basis to work on, specialisation is apt to lead to narrowness of outlook. In this connection I cannot do better than quote from the rectorial address delivered by the late Mr. Asquith (as he then was) at Aberdeen in 1910. He said:—

> "A University which is content to perform the office of a factory of specialists is losing sight of some of its highest functions. Nobody but an impostor can in these days assume to take all knowledge for his province—Genius apart, there is much to be said for the old University ideal of the "all-round" man—not the superficial smatterer who knows something about everything and much about nothing, but one who has not sacrificed to the pursuit of a single dominating interest his breadth of outlook, the zest and range of his intellectual curiosity, his eagerness to know and to assimilate the best that has been and is being thought and written and said about all things that either contribute to the knowledge or enrich the life of men."

I have in the course of this brief address endeavoured to let you know what my views are in relation to University matters and University education, for it is not without importance to yourselves that you should know the views of your new Chancellor. If I have overlooked anything which you may think I should have mentioned or if I have not sufficiently stressed one or other aspect of University training or if I am perhaps mistaken in some of my views I ask for the indulgence which I hope you will be willing to accord to one who has still to learn by trial and error what is required of him in an office which is so different from any other office which he has hitherto held.

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&
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Genetics & Neuroimmunology

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SECTION 1

CORRESPONDENCE

A STATEMENT AFFIRMING THAT THE WORK IS
THE ORIGINAL WORK OF THE APPLICANT AND DETAILS OF COLLABORATION

A STATEMENT THAT THE WORK HAS NOT BEEN SUBMITTED
FOR CONSIDERATION FOR AN EQUIVALENT DEGREE
AT THE UNIVERSITY OF CAPE TOWN OR ANY OTHER UNIVERSITY

A STATEMENT AFFIRMING THAT THE APPLICANT HAS MADE
A SIGNIFICANT INTERNATIONAL CONTRIBUTION TO THE FIELD
OVER A SIGNIFICANT PERIOD OF TIME

ROYAL FREE AND UNIVERSITY COLLEGE MEDICAL SCHOOL DEPARTMENT OF MENTAL HEALTH SCIENCES
BLOOMSBURY CAMPUS

8th August 2006

Ms Adri Winckler
Manager Postgraduate Administration
Faculty of Health Sciences
University of Cape Town
Room N2.19.1
Wernher & Beit Building North
Anzio Road
OBSERVATORY
Cape 7925
South Africa

Dear Ms Winckler

Re: Application for the award of the DSc (Med) degree

Thank you for your letter of the 21st July 2006, inviting me to register for the degree and also to submit selected works for the degree.

I have submitted my work primarily in the field of Neuropsychiatry with special reference to depression in people with epilepsy and the Gilles de la Tourette Syndrome (GTS; the majority of the thesis).

Please find, as requested, enclosed:

1. The completed application form
2. Three copies of the bound thesis for examination
3. Four books which I have co-authored, also for examination
    - i Psychiatry at a Glance (Katona C & Robertson M 20005: 3RD ED)
    - ii Tourette Syndrome: The Facts. Oxford University Press, Oxford. Robertson MM, Baron-Cohen S (1998)
    - iii Tourette Syndrome. A Practical Guide for Teachers, Parents and Carers Carroll A, Robertson MM (2000)
    - iv Why Do You Do That? (A book about Tourette Syndrome for Children and Young People). Chowdhury U, Robertson MM (2006)
4. A CD made and distributed by the USA Tourette Syndrome Association – as two of my review articles are included on it.

With regard to the thesis, it has a Table of Contents and is clearly divided into sections, divided by coloured numbered "dividers". When there are subsections (Sections 8 and 10) there are blue divider pages between the subsections.

Prior to the Table of Contents are the Dedication and Acknowledgements, and I am proud to be able to include the Inaugural Address of Albert Van De Sandt Centlivres, 3rd Chancellor of UCT, a champion of academic freedom, and my great uncle.

Dept of Mental Health Sciences
University College London, Wolfson Building, 48 Riding House Street, London W1W 7EY
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http://www.ucl.ac.uk/mental-health-sciences/

One entire section is devoted to a 32 page detailed synopsis. As you are aware the University requested a synopsis.

Another section is devoted an updated Curriculum Vitae.

Under "Correspondence" are the following:

i. A copy of this submission letter
ii. A statement that I have not submitted the work for another degree
iii. A statement of the nature and value of my international contribution
iv. A statement of my personal contribution to the research
v. A statement signed by M Trimble about my personal contribution
vi. A statement signed by V Eapen about my personal contribution
vii. A statement signed by D Pauls about my contribution to the Consortium
viii. A copy of the statement signed by V Eapen about my contribution (in her PhD)
viiii. A copy of the statement signed by P Brett about my contribution (in his PhD)

Under "Collateral Evidence" are the following:

i. A letter of support from Ms Judit Ungar, President USA Tourette Syndrome Assoc.
ii. A letter of support from Dr J Stern, Chair, UK Tourette Syndrome Association
iii. A copy of my award from the UK GTS Association
iv. As my FRCP (elected) is rare, I have enclosed correspondence from the Royal College of Physicians, as well a citation from my election (Dr O Hill)
v. As my FRCPCH (elected) is extremely rare, I have enclosed correspondence from the Royal College of Paediatrics and Child Health
vi. I have enclosed an invitation from the USA Attorney General inviting me to be an expert witness (unusual, I suspect, for a non American)
vii. As I have not been eligible for teaching awards since 2003, I have enclosed the end of year (Summer 2005) feedback from the Undergraduate administrator, indicating that my student lectures are still considered to be excellent.

I look forward to hearing from you

Yours sincerely

Signed by candidate

Mary M Robertson MBChB, MD, DPM, FRCPCH, FRCP, FRCPsych
Emeritus Professor of Neuropsychiatry, University College London
Visiting Professor, Honorary Consultant, St George's Medical School & Hospital
Senior Visiting Fellow, Institute of Neurology, University College London

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South Africa

Dear Ms Winckler

Re: Statement of not having submitted my work before for the award of the DSc (Med) degree

I declare that I have not submitted this work to the University of Cape Town nor any other University for consideration of the degree of Doctor of Science (Med) nor for any other equivalent degree.

I submitted my work on Depression in People with Epilepsy to the University of Cape Town for an MD degree, which was awarded in 1983.

Yours sincerely

Signed by candidate

Mary M Robertson MBChB, MD, DPM, FRCPCH, FRCP, FRCPsych
Emeritus Professor of Neuropsychiatry, University College London
Visiting Professor, Honorary Consultant, St George's Medical School & Hospital
Senior Visiting Fellow, Institute of Neurology, University College London

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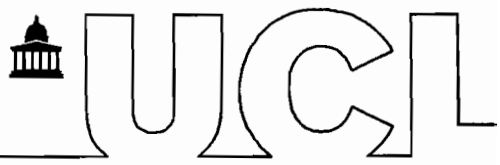

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Dear Ms Winckler

Re: Statement of the value, nature and international impact of the contribution - submission for consideration for the award of the DSc (Med) degree – Mary M Robertson

As required for the DSc (Med) degree at the University of Cape Town, I submit this Statement of the value, nature and international impact of my contribution to Neuropsychiatry as a discipline.

In this submission I am aware that this award is given for work of international standing which is regarded as seminal. In this regard, I believe that I have contributed internationally to the discipline of Neuropsychiatry for over two decades, in that I was an acknowledged international expert in the field of depression in people with epilepsy for many years. With regards to the Gilles de la Tourette Syndrome, I have been an acknowledged expert since the late 1980s, and I continue to be an international leader. I have also contributed to the field of depression.

In the field of depression in people with epilepsy, in which I undertook research for my MD, I described the clinical characteristics of the depression and also challenged previous ideas about the right side of the brain being primarily involved in the depression, and also showed that the depression was not associated with epilepsy variables. Mine was also one of the earliest studies to show that carbamazepine was significantly associated with less depression and less anxiety; in other words an anticonvulsant drug was psychotropic. These early studies in epilepsy, as well as some in depressive illness paved the way for the use of anticonvulsants in affective disorders, in particular bipolar affective disorder; this is common practice today. I also showed that phenobarbitone was associated with depressed mood; this and other early studies (together with the findings on carbamazepine) paved the way for, if possible, anticonvulsant monotherapy with an agent which improved mood as well as reduced seizures. I also conducted the only double blind placebo controlled antidepressant

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medication trial in the patient group, which gave new insights into treatment options and also reported the pharmacokinetics between anticonvulsants and antidepressants. Other pharmacokinetic studies have been conducted, but to the best of my knowledge, no further treatment studies. I also showed that a particular test which was in vogue at the time was not useful in people with epilepsy (the Dexamethasone suppression test).

I was also invited to write many review articles and numerous book chapters on the subject (see CV). For the sake of clarity and to cross-reference with my CV, I have numbered these publications. The book chapters have been included in three major American Epilepsy Textbooks (eg Robertson 1988 [bc 9]; Robertson 1997 [bc 26]; Robertson 1998 [bc 28]).

With regard to the Gilles de la Tourette Syndrome (GTS), in the early 1980s (when I began my interest) the condition was almost unknown in the UK, and indeed internationally, apart from a few certain centres in the USA. It was thought to be very rare indeed, a bizarre curiosity, and to consist mainly of motor tics, noises and coprolalia (involuntary swearing). Most doctors did not know about GTS. I set up and ran a GTS dedicated clinic and either personally conducted the research, supervised, inspired or collaborated, to provide a body of work which has resulted in a profound change in the knowledge of GTS in the UK and internationally.

The work, over the years, has shown that GTS is quite common (affecting 1% of youngsters), that the clinical presentation varies enormously, that coprolalia only occurs in less than a third of clinic patients and in very few GTS individuals identified in the community. I have also shown that people with GTS have more psychopathology than healthy people. We have described, in detail, certain types of psychopathologies such as depression and obsessionality, and what particular features of GTS are related to these. We have shown that GTS is not the unitary condition as suggested by international bodies who recommend the diagnostic criteria. We have demonstrated that GTS affects both the individual's quality of life and also that of the patients' carers. We have demonstrated that is of no use to undertake certain investigations routinely (eg brain CT scans) in these patients, and that GTS has a genetic basis which is complex, and that other disorders may be genetically linked to it. The work has also identified other factors, such as some infections and pre- and peri natal events, which may be of some relevance in its genesis or development. Studies using sophisticated imaging of the brain (MRI, SPECT, PET scans) have shown differences between patients with GTS and healthy control volunteers. I have devised assessment schedules to aid the diagnosis of GTS. We have undertaken neuropsychological studies indicating subtle deficits in particular areas, differences between GTS and other groups, and have tested several hypotheses including the theory of mind within GTS. The work has also shown that there is effective treatment, but that this is far from simple. We have investigated a range of treatments, from a variety of medications, to injections in the vocal cords, to repetitive transcranial magnetic stimulation, and even to psychosurgery in a few patients. I have personally seen the majority of the cohort of over 1200 GTS patients reported on in the various publications and initiated much of the collaboration.

I am also the only British member of the Tourette Syndrome Association International Consortium for Genetics, since the late 1980s, and the Consortium performed the first genome scan in GTS. I have also represented the Consortium twice; first in South Africa and then in Japan, formally visiting colleagues and clinics, and, in South Africa, undertaking research. In other words, my work and initiatives have changed the profile, understanding of the cause and treatment of GTS.

I have published widely in the discipline of neuropsychiatry from the early 1980s to 2006 (283 publications including 158 peer reviewed publications, 20 invited reviews and editorials and 41 book chapters [61 single author publications – 3 papers, 55 reviews

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and/or chapters, 3 abstracts]). I have published many original research papers that are widely cited and have appeared in high Impact Factor journals such as Brain, The Archives of General Psychiatry, The American Journal of Psychiatry, Biological Psychiatry, The British Journal of Psychiatry, The Journal of Child Psychiatry and Psychology, The Journal of Affective Disorders, The Journal of Neurology, Neurosurgery and Psychiatry, Movement Disorders, Epilepsia and several high Impact Factor genetic journals and psychiatric genetic journals (see CV).

In addition to the original research I have been invited to write numerous review articles and book chapters on GTS. The majority of these are as a single author. These include those in high impact factor journals such as Nature, Brain, the Journal of Child Psychology and Psychiatry, and the British Journal of Psychiatry. Relatively recently I have had reviews on the epidemiology of GTS the behavioural treatments available for GTS affective disorders, with particular reference to depression, and GTS and GTS and comorbid ADHD and its treatment published. Many other reviews have been published (see CV). I have also been invited to contribute on GTS to major American spearheaded textbooks devoted to neuropsychiatry, movement disorders, and neurology. I have been invited to contribute to four American books devoted to GTS. In order not to duplicate, the details of these are both in the synopsis and CV.

I have co-authored 4 books which have been translated into 10 languages (Hungarian, Japanese, Italian, Greek, Chinese [Taiwan]. Korean, Chinese [Complex Character], Danish, Polish and Icelandic). One of these was an undergraduate textbook in psychiatry and four were on GTS.

I have received 11 awards, including national competitions (epilepsy) as well as international awards. I have reviewed grant applications and promotions from the United Kingdom, Canada, the United Arab Emirates, and South Africa. I have been invited to deliver 57 lectures at major international meetings, including 12 keynote or opening lectures. I have been awarded 18 competitive grants supporting staff (including 10 from the United States of America). I have more invitations this year, including keynote or opening addresses.

I worked collaboratively with a colleague at the World Psychiatric Association. I have been an advisor to the World Health Organisation twice (on both epilepsy and the Gilles de la Tourette Syndrome), and have served on the committees of the International Neuropsychiatric Association and European Society for the Study of Tourette Syndrome (ESSTS). With regards ESSTS, it was founded with myself as Foundation Chair (elected at the European Federation of Neurology Meeting, Copenhagen, 2000). The other Co-Chair who took a less active role, was Dr A Korsgaard, a Neurologist from Copenhagen, Denmark). The first British ESSTS one-day meeting was organised and hosted by me on 20th September 2002. It was well attended by UK delegates as well as others from several European countries. Due to my illness, ESSTS fell fallow for a while, but another meeting is planned for 2007, in Norway. I was invited to serve as a member of the International Narcotics Control Board as an Expert panel member at the United Nations. I was appointed in October 2002 and was also invited to advise for a third time, at the World Health Organisation in May 2003, but had to decline because of cancer.

I am an advisor to the following national Tourette Syndrome Associations: United Kingdom, Canada, Ireland, Germany and Italy. With regards the Tourette Syndrome Associations, I have had a substantial influence on the practices of many. I have attended and spoken at meetings in Germany. I was a foundation member and vice chair of the United Kingdom Association, chaired and sat on many committee meetings over the years, as well as almost all the Annual General Meetings (AGMs) in the 26 years of its existence, either speaking, hosting speakers, or being on the panel of

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experts (for the predominantly lay audiences). I have written and then co-authored most of the association booklets. With regards to Ireland and Italy, I have been to and spoken at many association meetings (lay audiences), but have also spoken at many of the scientific meetings, often as keynote speaker. I am in regular e-mail contact with the Canadian association (Foundation) and have commented on publications. In September 2006 I have been invited as Keynote speaker at the Canadian Foundation international meeting. Between October 2005 and October 2006, I will have addressed as Keynote speaker or equivalent, the following Tourette Syndrome Associations: Canada, Italy, Ireland and Australia, and I will have presided over the UK Association's Annual General meeting.

With regards the USA Tourette Syndrome Association, I participated at its first conference and was thereafter an invited speaker twice, and chair-person once; I was also on the Scientific Organising Committee of their last (2004) meeting.

I have also had major national appointments in the United Kingdom including being the Foundation Treasurer of the British Neuropsychiatry Association, between the years 1987-1999. I was an Elected Fellow on Council and also Sub-Dean for Examinations, of The Royal College of Psychiatrists (London). I chaired Women in Psychiatry special interest group (WIPSIG).

In recognition of my contribution to the field of Medicine as a discipline, I was elected a Member of the Royal College of Physicians, followed by the Fellowship. In recognition of my contribution to care and health of children and adolescents, I was elected a Member of the Royal College of Paediatrics and Child Health followed by the Fellowship, this year. Election to Fellowships of Colleges outside one's specialist field in the UK, is, I am told, exceptional. I have always been an all-rounder and was elected a Fellow of the Royal Geographical Society for a circumnavigation and extensive "anthropological travelling" (solo) in 1976. I have published photographs and poetry.

Yours sincerely

Signed by candidate

Mary M Robertson MBChB, MD, DPM, FRCPCH, FRCP, FRCPsych
Emeritus Professor of Neuropsychiatry, University College London
Visiting Professor, Honorary Consultant, St George's Medical School & Hospital
Senior Visiting Fellow, Institute of Neurology, University College London

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ROYAL FREE AND UNIVERSITY COLLEGE MEDICAL SCHOOL DEPARTMENT OF MENTAL HEALTH SCIENCES
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8th August 2006

Ms Adri Winckler
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Dear Ms Winckler

Re: Statement regarding Personal Contribution to the publications

The time period covers for this thesis the progression of my career as a medical student (1971), registrar (resident [1973 – 1979]), Research Fellow (1980-1983), senior registrar (1984-1986), Senior Lecturer in Neuropsychiatry (1987 - 1995), Reader in Neuropsychiatry (1995-1998) and Professor of Neuropsychiatry [personal chair] 1998 - onwards).

The publications that I have selected to submit in fulfilment of the requirements for award of a Doctor of Science (Medicine) at the University of Cape Town are predominantly conjoint work, except for 61 publications, which include my first three data containing publications (Robertson 1971 [1]), Robertson (1975 a, b [correspondence 1;2]), 3 abstracts and 55 single author peer reviewed reviews, editorials and book chapters. In this submission, I will include the majority of my peer reviewed publications, but only some of reviews, editorials and chapters, due to space constraints. I am also submitting 4 authored books and a USA Tourette Syndrome Association CD (which includes 2 of my review articles).

The work I submitted for my MD thesis and which was awarded by the University of Cape Town in 1983, resulted in the following publications: (Robertson and Trimble 1985 [16]; Robertson et al 1986; 1987 [17, 20]);this was my own work.

Over the years I have supervised many PhD and MSc students, research fellows, residents, medical students and psychologists, as well as having collaborated with local, national and international peers and colleagues. The names of individuals whom I have supervised and with whom I have collaborated are detailed in my Curriculum Vitae. In this statement I will outline my contribution to the groups of studies and also some individual studies. I will also single out a few individuals with whom I have published many times (eg M Trimble, V Eapen, P Brett) or juniors who have collaborated, held joint grants or who have initiated their own research (eg A Muenchau, M Orth).

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of it, assessing > 200 GTS patients using it, and the Diagnostic Confidence Index (Robertson et al 1999 [96]) was published. All GTS patients at the clinic at the National Hospital Queen Square and St Georges Hospital have thus also been assessed using that instrument since the early 1990s'. Patients have also been interviewed using DSM criteria for ADHD, OCD, CD, ODD, all at my initiative in a standardised format.

I initiated all the studies in this section. From the research I conducted for my MD degree I realised the need to assess psychopathology using standardised published assessment schedules and so I chose all the rating scales which have been used on the GTS cohort in discussion with colleagues including M Trimble. Thus, from about 1980 to 2006 (even after I left the clinic at NHNN) the same instruments have been used as a basis with a new ones being added and old ones discontinued, all at my initiative, testing specific hypotheses. I updated the scales and interviews, and chose new ones, depending on the study (eg the special SCID 11 interview and Dowson self-report scale, specifically to assess personality disorders).

All GTS subjects fulfilled the appropriate DSM and WHO criteria to be included in any study. I have changed the requirements for diagnosis, along with the DSM changes (apart from DSM-IV with which I did not agree). I have personally assessed the majority of the cohort of over 1200 patients in the clinic at NHNN and supervised the assessments of the rest, with my various research fellows, residents and PhD and other students, with myself making all final diagnoses of both patients and their first degree relatives. When was on holiday, there were no assessment clinics at NHNN. There were two brief gaps in this: when my parents in South Africa died (1986 and 1991) and a longer gap when I was ill with cancer, although then I discussed the cases and all difficult cases at that time regularly with my locum, M Orth, who I had trained up clinically (he was my research Fellow). He and I met regularly throughout my illness.

For other studies some assessment schedules were initiated because of previous results, leading to further studies. New collaborators also added new assessment techniques or schedules.

When H Critchley was appointed to the post in 2005, which I had vacated when I retired, he asked me to collaborate with him. He continued to employ the majority of the interview schedules and rating scales which I had either devised or chosen as part of an assessment battery. He added two new scales, one for schizotypy and one for catatonia (Cavanna et al [2 papers submitted and 2 abstracts published [22,23]). I then invited A Cavanna to join me in other projects.

<u>The effect of GTS on the patient and the family</u>

Quality of Life (QOL).

In this study I initiated the collaboration with C Selai who had worked with M Trimble on QOL in epilepsy, as I realised that no such study had been undertaken in GTS, hence the initiation. I had assessed and diagnosed all patients who participated in the study and I then supervised the whole study. K Elstner who undertook the research and was first author, was my medical student [100].

Care-giver burden and parental difficulties in having youngsters with Tourette Syndrome.

I initiated the study with G Livingston (an old age psychiatrist working with patients with dementia and also their care-givers), hence the initiation as the study, once again, had not been undertaken in GTS patients and their carers. I had assessed diagnosed all patients in the study and supervised the whole study. G Livingston and I supervised C Cooper for her MSc project examining the topic. In that study I diagnosed most of the GTS patients and diagnosed their comorbid psychopathology [117].

U Chowdhury and I have collaborated in another study. Some patients and carers were from another clinic for the Chowdhury study.

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Prevalence of Gilles de la Tourette Syndrome

Seeing the families of patients in the clinic where 42% had a family history of tics or GTS (Robertson et al 1988 [21]) and having noted in a large pedigree that 50/85 family members had undiagnosed tics or GTS (Robertson and Gourdie 1990 [27]), it was decided to undertake prevalence studies. The first study was Robertson et al (1994 [48]) in New Zealand and then the UK pilot and definitive mainstream school studies followed (Mason et al 1998 [85], Hornsey et al 2001 [101]) in which I collaborated with H Zeitlin (Hornsey was my PhD student); thereafter we undertook another study, Eapen et al 1997 ([78] a learning disability study [collaborating with R Kurlan], and the studies in youngsters with autistic spectrum disorder, in which I collaborated with S Baron-Cohen (Baron-Cohen et al 1999 [93]; Baron Cohen et al 1999 [94]). I initiated and supervised the prevalence study of GTS and tics in general adult psychiatry wards (Eapen et al 2001 [102]) in which I supervised all my junior staff from wards and V Eapen.

I was joint grant holder for both the Mason et al and Hornsey et al studies (see CV) and in the Hornsey et al paper, in addition, (i) she and I together examined a group of 20 GTS patients in order to establish inter-rater reliability for the study and then (ii) I also examined all the GTS-possible cases identified in the study. Prof Zeitlin and I supervised H Hornsey for the large West Essex study for her PhD which was awarded in November 2002. In the Eapen et al (1997 [78]) study, V Eapen, R Kurlan and I conducted all assessments and interviews in the schools.

Aetiology

Genetics and Family Studies of Tourette syndrome

Between the mid 1980's and 2006, I have been involved with genetic studies of both consecutive GTS patients, and both consecutive and opportunistic GTS extended families of clinic probands who have GTS. The genetic studies have been four-fold and some case reports have also been published, which may add to the understanding of the complex genetics of GTS.

1. The first was initiated in the early 1980s (reported in 1993; Robertson and Trimble [42]). In this M Trimble and I initiated the study because of a GTS+ XYY patient having been reported. I collaborated with D Hughes the cytogeneticist and essentially wrote the paper. D Hughes undertook the cytogenetics and commented on the paper (see acknowledgements in paper).

2. The second group of studies was collaborating with H Gurling (supervising P Brett's PhD thesis – see below); all the laboratory studies followed the publication of a large GTS pedigree (Robertson and Gourdie 1990 [27]) eg all the Brett et al, and Curtis et al papers, one Eapen et al (genomic imprinting [75]) and Kurlan et al (bilineality [54]).

3. The third section was supervising the PhD thesis of V Eapen (see below).

4. The fourth section includes the work of the Tourette Syndrome Association (USA) International Consortium for Genetics, of which I have also been a member since the mid 1980s and have collaborated in all aspects. I was the Principle Investigator, and indeed only investigator in the UK, and at the UCL/NHNN site. I have contributed in devising schedules, assessing patients, doing web-based diagnoses, attending meetings, contributing to regular conference calls, involved in grant applications and have represented the Consortium twice (in Japan and South Africa); several papers have been published, and I have contributed to all, although to differing degrees [95, 104, 105, 116]. Please see letter from PI D Pauls in this section confirming my Consortium activities.

5. Finally, we have identified interesting patients who have well defined chromosomal abnormalities, such as GTS and the chromosome 22q11 deletion syndrome occurring in two members of one family, and we have suggested hypotheses as to the possible genetic basis of GTS (eg Robertson et al 2006 [138]).

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Neuro-immunology and PANDAS

I initiated these studies in the UK, initially planning to work in collaboration with L Kiessling of Rhode Island USA, but this did not materialise as, although I had Ethics Permission (IRB approval), I was already undertaking two international research projects with no dedicated staff. I latterly, therefore collaborated with G Giovannoni (Neuroimunologist) and we supervised R Dale for his PhD (awarded 2005). We have had collaborative grants from the USA TSA (see CV). Two papers have been published [112, 128]. With G Giovannoni we are currently involved with a longitudinal study, funded by the USA TSA (continuing) and we have been awarded a further grant, with A Schrag taking the lead in that (see CV). I also collaborate with R Rizzo of Catania University, Sicily, Italy and I made a significant contribution to the Italian PANDAS paper (Rizzo et al 2006 [136]; in press). We (Giovannoni, Rizzo, Martino, myself and others) are currently setting up an Italian/UK collaborative project.

Neuroimaging Studies

I initiated the neuroimaging studies, as evidenced by the fact that I was the only member of the clinic on the first neuroimaging publication (Hall et al 1990 [cp 8] and a second Hall et al abstract [a 25]. I also obtained specific funding from the Gateposts Foundation for the MRI study. In recognition of this I was invited to write an Editorial in the European Journal of Nuclear Medicine, published in 1990 (Robertson 1990 [ir 3]). Collaboration was initially with P Ell and his team (DC Costa, M Hall), but later with M Trimble, and R Dolan.

The Neuropsychology of GTS

I have always been interested and neuropsychology (co-authoring one of my first publications with a psychologist (Robertson and Hamburger 1975 [6]). I have therefore fostered collaborations researching the neuropsychological aspects of GTS and have collaborated with psychologists S Baron Cohen (Cambridge UK), B Sahakian and T Robbins (Cambridge UK) and S Channon (UCL, Department of Psychology). We have examined and published on many and various aspects of psychological functioning and projects include Executive Functioning, Theory of Mind, the Intention Editor, attentional problems, social problems, aspects of childhood developmental functioning; treatment studies are envisaged. S Channon is currently applying for an Honorary Contract to join me in my new position and Hospital.

I personally assessed all the GTS patients included, and made the diagnoses of GTS and the comorbid disorders and psychopathology. I completed mental state examinations as well as the scales and schedules, such as the Diagnostic Confidence Index, National Hospital Interview Schedule, Yale Global Tic Severity Rating Scale on all the patients involved in all studies. I had discussions with my senior collaborators, and have been a joint grant holder with 2 (Baron Cohen and Channon), see CV.

The psychologists undertook all the neuro-cognitive assessments and procedures for the studies. When a junior psychologist undertook these (eg Watkins [127] and Crawford [129]) they were supervised by B Sahakian and S Channon respectively.

Special investigations (copper, kynenurine metabolism, visual field defects, and neurophysiology (including event related potentials)

Copper studies were commenced as GTS was a movement disorder, and abnormal copper was characteristic of Wilson's disease, another movement disorder. Those patients which had abnormal results were investigated more fully by P Lascelles, chemical pathologist. I had assessed all patients and made a significant contribution to the study (Robertson et al 1987 [19]).

As I had experience in GTS and ran a large dedicated clinic, J Corbett and S Handley approached me to collaborate. H Rickards undertook the research for his MD thesis in my clinic.

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I initiated collaboration with opthalmologists, L Whitefield and D Brazier and one publication ensued on visual fields in GTS (Whitefield et al 1995 [c 10]).

G Barrett and I initiated the neurophysiological collaborative studies early on, and, with M Gobel and Z Pirtosek, we published (with me as the only GTS clinician) on event related potentials in GTS (Gobel et al 1992 [12]).

M Orth joined me as my Research Fellow to undertake an rTMS study (for which I was joint grant-holder; see CV). He became interested in GTS, and so I trained him clinically so that he could assess patients as well as complete our study, being supervised by myself. When I became ill with cancer, he did my locum, but returned to his native Germany after a substantive appointment was made (see later, H Critchley appointed). M Orth conducted and initiated several further neurophysiological studies, but I gave hands on assistance (eg with assessing patients, funding and/or undertaking the blind video ratings of response to challenges or treatment).

Treatment of Gilles de la Tourette Syndrome

I initiated the majority of treatment studies namely, Robertson et al (1990 [29]) a sulpiride study, Eapen et al (1993 [43]; side effects of sulpiride), Robertson et al (1996 [73]) the risperidone study and Davies et al (2006 [137]), the aripiprazole paper, where, as last author I drafted most of the various manuscripts of the paper and organized the final submitted paper. The Robertson et al (1990 [28]) limbic leucotomy was a collaborative effort. The rTMS studies were funded, and I was a joint grant-holder, although my research fellows carried out the studies, while I had assessed by far the majority of the patients and also took part in the video ratings of the responses (Muenchau et al 2002 [108]; Snijders et al 2005 [c 14]; Orth et al 2005 [124]).

Obsessive-compulsive disorders (OCD) in England and the UAE.

Stimulated by phenomenological and pedigree studies in GTS, I conducted a study investigating the phenomenology and genetics of primary OCD patients. This was in collaboration with D Pauls of Harvard University (he and I were awarded a grant of dedicated OCD money to investigate the area) and we had collected data from OCD families in the UK. I supervised A McGowan (a nurse) in the pilot study. The work continued with V Eapen in the UAE and the paper has just been accepted for publication (Eapen et al 2006 – see later [143]).

Contributions with specific colleagues with whom I have had many publications

M Trimble

We have co-authored 34 peer reviewed papers (Pubmed) as well as other publications.

When I was a resident to M Trimble, he initiated a study examining the antidepressant action of flupenthixol. I assessed all the patients and took all the bloods at all times during the day and evenings, longitudinally for the study. He wrote the first drafts of the clinical study papers. With regards the neuroleptics/major tranquillisers as antidepressants review papers, I undertook the basic research, collecting and reading the papers, and writing the first draft of all the papers ([7, 8, 10, 12]).

I undertook my 3 year MD research doctoral thesis (available to medical graduates and somewhat similar to PhD in USA and Europe) with M Trimble as my supervisor, in the subject of depression in people with epilepsy (PWE). In this study I personally assessed all consecutive PWE to the unit, including those who fulfilled the necessary criteria for the studies and excluding those who failed to fulfil criteria for depressive illness. I interviewed all PWE whom I had diagnosed with a depressive illness (and thus included) using the Hamilton Depression Rating Scale and other scales/schedules. I personally conducted the Double-Blind Trial, and assessed all the patients before the trial and regularly throughout the trial, to assess their response to the medications or placebo. I initiated the dexamethasone suppression test (DST) study and organised collaboration with A Coppen. In the DST study, I prescribed the dexamethasone and took the bloods from the patients at the required

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times. I then rated and scored all the rating scales and interviews, analysed the data, performed all the statistical analysis and wrote the first draft of all the papers from the studies and thesis (eg Robertson and Trimble 1985 [16]; Robertson et al 1986; 1987 [17, 20]).

In all the other papers in PWE, I helped clinically and earned authorship; the first author took the lead (eg Roberts [11, 13], Allen [14]), while Trimble took senior authorship as the Consultant.

I then developed my interest in GTS and devoted the rest of my academic life to the subject. As said previously, I personally assessed almost all (and supervised the rest), of the GTS patients in the clinic from 1980 onwards until I took early retirement in 2004 (over 1200). In addition, for the first papers (Robertson et al 1988 [21, psychopathology] and Robertson et al (1989) self-injurious behaviours [SIB], [24]), I collected the data, rated and scored all the scales, completed the statistical analysis and wrote the first and subsequent drafts of the papers.

In the papers Robertson et al (1987; copper abnormalities, [19]) I also drafted the paper. In the Robertson and Trimble (1988; [23], personality variables) I saw the additional patients, scored the scales and performed the statistics.

In Robertson et al (1990 [24]), Robertson and Trimble (1991 [26], Middle East cohort), Robertson and Trimble 1993 [chromosomes, 42]), I took a significant part in the study (that is apart from having seen patients and family members [not necessarily in the GTS clinic]) with either writing the first drafts and/or initiating the studies. In the Frankel et al (1986 [18]) paper, I assessed the patients and administered the instruments. Trimble et al (1998 [88]) botulinum toxin into vocal cords was initiated by M Trimble. The George et al [40] GTS+OCD study and paper was jointly initiated through discussions, as a result of the Frankel et al [18] results, with which I had been intimately involved.

I initiated the neuroimaging studies, as evidenced by the fact that I was the only member of the clinic on the first neuroimaging publications (Hall et al 1990 [cp 8; a 25 (not chronological but correct)) and I obtained specific extra funding from the Gateposts Foundation for the MRI study. M George was research fellow to M Trimble and took the lead in several studies [39; 40; 46; 57]; similarly J Moriarty was lecturer to M Trimble and took the lead in other papers [64; 74; 80] as did Serra Mestres [118] doing the scanning and drug trials, although I had assessed all the patients and was the main supervisor/initiator in many (having initiated the neuroimaging link with P Ell).

Please see letter from M Trimble stating that he has seen this statement and agrees with the contents of this statement.

V Eapen

I have co-authored 17 peer reviewed papers with V Eapen (Pubmed), as well as other publications.

She was my PhD student. The Co-Supervisor was D Pauls. I was her primary supervisor throughout the studies and she continued working with me afterwards.

Apart from supervising her thesis, I provided "hands-on" assistance in data collection. Thus, in all papers in her thesis, I assisted in the diagnostic process by providing consensus diagnosis on all GTS probands and their first degree relatives (FDRs) involved in all the studies.

Specifically, in the autosomal dominant paper (Eapen et al 1993 [38]) and ADHD paper (Eapen and Robertson 1996 [68]), I assessed all consecutive clinic GTS patients and their FDRs. In the "genomic imprinting" paper (Eapen et al 1997 [75]), I assessed all GTS probands in the clinic, and also either personally assessed the many relatives in the large pedigrees (all seen in the community) or supervised the assessments of the relatives which were undertaken by V Eapen, J Stern (my research assistant) or A Gourdie, V Schneiden, G Jackson (my residents). The Robertson and Gourdie (1990) pedigree [27] was included in this study, and I had initiated that study and personally assessed all 85 individuals in the pedigree.

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In the GTS-OCD phenomenology paper (Eapen et al 1997 [81]) I had initiated the study and was co-grant holder with D Pauls (see CV) for the pilot study and I supervised A McGowan in the pilot study.

While she was undertaking her PhD, V Eapen also completed other several first author studies and case reports under my supervision of my patients, including those whom I had diagnosed on my general psychiatric ward [35], families of my patients who I thought were worth documenting [60], and a patient taking sulpiride with tardive dyskinesia, on whom I performed the AIMS interview [43], and finally, a treatment study (69). I initiated the large psychopathology study [121] and also assessed and provided consensus diagnoses on all patients, chose and scored rating scales, and punched data onto computer friendly anonymised cards.

I realised, as said above, in the early 1980s that a self-report questionnaire was insufficient for assessing patients with GTS. Therefore, I devised the fore-runner(s) to the National Hospital Interview Schedule (NHIS; Robertson and Eapen 1996 [70]) which has been used to assess over 1200 GTS patients in the clinic ever since (ie from ca 1982 to 2006). This includes also a tic history, tics present at interview, as well as tics and direct tic and associated behaviours examination of FDRs. V Eapen joined me in the layout of the final interview schedule and undertook the reliability and validity study (comparing it with the Yale Schedule; Pauls & Hurst, unpublished).

Some reports [56]; stimulus tics) were undertaken in collaboration. In the Mason et al (1998 [85]) pilot epidemiological study, V Eapen was a joint initiator and grant holder (see CV).

Please see a copy of The Statement from her PhD thesis of work that I contributed to her thesis. Please also see letter from V Eapen stating that she has seen this statement and agrees with the contents.

P Brett and H Gurling

H Gurling jointly supervised the PhD of P Brett. I was a supervisor throughout the studies.

Apart from supervising his thesis, I provided "hands-on" assistance in data collection, and to quote from his thesis: I "carried out most of the clinical interviewing on the collection of the Tourette Syndrome families"; I had also supervised A Gourdie, V Schneiden, G Jackson (my residents), and J Stern (my research assistant), which was not mentioned. Once again, all these assessments were undertaken in the community. Thus, in all papers in his thesis, I made (the majority) or supervised the diagnostic processes by providing diagnosis on all GTS probands and their FDRs involved in the studies both from my clinic and also in the community. In addition, I assessed the proband and family of the patient and relatives with and those without the 3 to 8 translocation who were not from my clinic.

I was also joint grant-holder with H Gurling on the 4 grants from The Medical Research Council (1), the Middlesex Hospital Trustees (1), and USA Tourette Syndrome Association (2) which supported P Brett and these genetic studies (see CV).

Brett was first author on all studies. As they were predominantly genetic studies, I was not last author on any of them. Please see a copy of The Acknowledgement from P Brett's PhD thesis of the work that I contributed to his PhD thesis.

6. Miscellaneous publications & non-medical publications

a) All these medical publications were collaborative. I played a significant part in all in the original work.

When the reviews are with a junior as first author, the medical student or junior doctor or research fellow wrote the review under my supervision [91, 131].

Several papers about academic psychiatry were published, in which G Livingston [87] and H Killaspy [111] took the lead, and I played a significant part. C Katona and I published on CV predictors of success which was initiated by him, but we undertook the study and wrote the paper together [37].

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With regards to the paper "Treating the homeless mentally ill" H Killaspy et al [123], I was the Consultant in charge of an acute psychiatric ward dedicated to treating the homeless - for many years. H Killaspy was my resident and E Greer was the senior psychiatric nurse allocated to the community psychiatric team. I examined all the patients in the study and H Killaspy used my diagnoses and assessments as part of the patients' profiles in the study.

b) All the poems were written by me and I took all the photographs.

AUTHORED BOOKS

1. Psychiatry at a Glance and C Katona

We jointly initiated Psychiatry at a Glance, undertook the research as to the niche in the market for an undergraduate psychiatric textbook, and we jointly both wrote the entire text and also drew the illustrations. We jointly revised the book for the first reprint, second and third editions. He and I have also edited a book (Depression and Physical Illness: A Practical Guide) in which we jointly initiated the project, but I took the lead, as it was my chosen subject.

2. Robertson MM, Baron-Cohen S (1998) Tourette Syndrome: The Facts

In this book I was the acknowledged GTS expert, and the book was a joint effort.

3. Carroll A, Robertson M (2000) Tourette Syndrome. A Practical Guide for Teachers, Parents and Carers.

I initiated the book, and A Carroll is a senior county educationalist advisor. We wrote our respective sections of the book, but always collaborated and touched base, so that the book gelled.

4. Chowdhury U, Robertson MM (2006) Why Do You Do That? A book about Tourette Syndrome for Children and Young People.

This was initiated by U Chowdhury, and he asked me because of my expertise in GTS to join in his venture. We chose the format of the book together, including illustrations and jointly wrote the book. I wrote all the poems for the book. I invited Tim Howard to write the forward.

5. The USA Tourette Syndrome Association CD

I was asked by the USA TSA if they could use my articles [99, ir 14] on their CD, particularly the review (Robertson 2000 [99]) in Brain. I facilitated the organisation of their being allowed to use the article in Brain

Yours sincerely

Signed by candidate

Mary M Robertson MBChB, MD, DPM, FRCPCH, FRCP, FRCPsych
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28 June 2006

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South Africa

Dear Ms Winkler

Re: Professor Mary M Robertson, Submission for DSc (Med)

This is to confirm that I have read and agree with the contents of the statement regarding her contribution to the work.

Yours sincerely

Signed by candidate

M R TRIMBLE MD, CP, FRCPsych
Professor of Behavioural Neurology
and Consultant Physician of Psychological Medicine

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1st July 2006

Dear Ms Winkler

RE: Statement regarding Personal Contribution to the publications towards the DSc (Med) Degree submission: Professor Mary May Robertson

I have had sight of the statement which I have read and confirm that the contents are true and represent Professor Robertson's contribution to the work.

I am visiting London, and thus do not have my correct headed notepaper.

Yours sincerely

Signed by candidate

Valsamma Eapen DPM, PhD, FRCPsych

STATEMENT

The collection, collation and analysis of the data presented in this thesis were carried out by the author herself, except in the following areas.

The data for the section on "genomic imprinting" was collected by the author along with five other investigators (Dr Mary M Robertson; Dr Jeremy Stern; Dr Allison Gourdie; Dr Vivienne Schneiden; Dr Gary Jackson) as part of another study on clinical phenomenology and linkage analysis. However, the data used in the analysis reported in this thesis was collated solely by the author. Support for statistical analysis was provided by Dr Jane O'Neill and Dr Hugh Gurling.

For the section on Single Photon Emission Tomography, the author herself carried out the direct clinical examination and collated the data. Dr J Moriarty performed the SPET scanning and Dr DC Costa provided the blind rating.

Dr Mary M Robertson helped in the diagnostic process by providing consensus diagnosis on the GTS probands and First Degree Relatives. The data analyses for the section on phenomenology and the segregation analysis were carried out by the author under the supervision of Dr David Pauls.

i ACKNOWLEDGEMENTS

I would like to thank Dr Hugh Gurling and Dr Mary Robertson for supervision and guidance for the PhD work. Dr Robertson carried out most of the clinical interviewing on the collection of the Tourette syndrome families. Dr David Curtis very kindly carried out the lod score and statistical calculations. Dr Robin Sherrington and Dr Georg Melmer gave guidance on laboratory techniques. Miss Gursharan Kalsi provided support in the laboratory. Professor Sue Povey performed the fluorescent in situ hybridisation (FISH) analyses on the GRIN 1 clone. Dr Ben Carritt provided the hybrid cell line of the chromosome 3 to 8 translocation and performed the cytogenetic analysis on individuals from family 210. The UK and USA Tourette Syndrome Associations and the UK MRC(Grant number G9023197N) funded the research.

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Re: Prof Mary M Robertson

Dear Ms Winkler:

Mary Robertson is a member of the Tourette Syndrome Association International Consortium for Genetics (TSAICG). As such, she has my permission as Principle Investigator (PI) of the TSAICG to:

(i) include any TSAICG scientific papers on her Curriculum Vitae
(ii) submit any paper she chooses as her own work for consideration for a DSc degree

She was a founding member of the TSAICG and was intimately involved in:

(i) Devising the "Self-Report" assessment schedule used by the Consortium
(ii) She took the lead in the Diagnostic Confidence Index (Robertson et al 1999)
(iii) She was sent as one of two investigators by the TSA to undertake diagnostic quality assurance in Pretoria, South Africa
(iv) She was also sent as one of two investigators by the TSA to undertake diagnostic quality assurance in Japan

As a TSAIGC clinician she has been actively and integrally involved in:

(i) Data collection of both trios and sib-pairs
(ii) Regular annual (at least) meetings of the group (only missed in 2003 when she was ill with cancer)
(iii) Regular monthly conference calls
(iv) Best Estimate Diagnoses
(v) Discussions about and writing of grant applications
(vi) Writing drafts of manuscripts for publication

(vii) Contributed to ideas about the TS phenotype following her early work (Robertson et al 1988) and more recently a factor analysis study on a large cohort of 400 of her patients (Robertson, Althoff, Pauls) which will be used to reanalyse TSAICG data

I hope that this is helpful.

Signed by candidate

David L Pauls, PhD
Principle Investigator, TSAICG

SECTION 2

A SYNOPSIS OF THE WORK SUBMITTED

SYNOPSIS OF RESEARCH – MARY MAY ROBERTSON (1971-2006)

WHAT MAKES US TIC?

INTRODUCTION

I have entitled my thesis "What Makes Us Tic?" as that was the name of my Inaugural Lecture when I was promoted to a personal chair. This is primarily because the majority of my research and international recognition has been for the body of work with the Gilles de a Tourette Syndrome (GTS) over 26 years, with publications spanning 22 years.

In addition to this, I have always considered myself an all-rounder. Evidence for this started early (being awarded the Scholarship for being the best all-rounder in Matriculation at school) and continued into University (I played the guitar and sang in a band for many years). During my adult academic life, with a total commitment to Neuropsychiatry, as part of my University contract I was also a Consultant in charge of various busy general psychiatry wards and the liaison neuropsychiatrist on a neurology ward; this afforded me teaching awards, publications in general psychiatry (especially in depressive illness and epilepsy, as well as some unusual conditions) and co-authorship of a general psychiatry undergraduate textbook, which won a British Medical Association award. That book is now in its third edition and has been translated into 7 foreign languages (Psychiatry at a Glance [Katona and Robertson 2005]). I have published photographs, and latterly 82 poems, the majority being in poetry anthologies of well known British poetry publishing houses.

In this 32 page synopsis, all my submitted peer reviewed work is summarised in order to give a detailed overview of the subjects included. The synopsis is divided into six sections, which are the same as those in the thesis. In the synopsis the peer reviewed papers and correspondence (denoted with the letter c), abstracts (denoted with the letter a), conference proceedings (denoted cp), book chapters (denoted bc) and invited reviews (denoted ir) are numbered, to facilitate easy reference to both the CV and thesis.

At the end of the synopsis, I have chosen a selection of papers which reflect some of my best. The reasons for their having being chosen are also stated. In brief, the publications in this section were chosen as they were the first and largest in the UK and many were the first and remain some of the largest internationally. They were widely cited and are in high impact factor journals. These papers were also included as the majority are from my group and not as a result of international or national collaborative efforts. I included papers, which reflect my all-round approach even within Gilles de la Tourette Syndrome. For each paper chosen, as in the full CV, the number of times it has been cited as well as the journal's impact factor is given.

SYNOPSIS OUTLINE

I am including six sections of publications both in the thesis (Thesis Sections 5 -10) and also in this synopsis:

(1) My early work could be regarded as my "Research Baptism". During this period, I authored three single-author publications, with data in two papers, including hundreds of subjects, and statistically analysed results. These are being included to indicate my development and progress from medical student to resident. Some of these early papers could also be argued to be neuropsychiatric in nature (Section 5 in thesis).

(2) I have then included my work on the psychopathology of PWE, especially depression in PWE, the subject of my MD thesis (section 6 in thesis). An MD is a higher doctoral research degree, similar to a PhD in the USA and Europe, which is available to medical graduates in the United Kingdom and South Africa, as well as other countries influenced by the British medical system and tradition.

(3) I have then included my work on depressive illness, as I maintained that interest after my MD and have published some important papers in the field (Section 7 in thesis)

(4) I have then presented the bulk of my medical work, namely that on GTS, which forms the majority of the thesis: this is also clearly divided into sections in the thesis and which are also outlined in this synopsis (Section 8 in thesis).

(5) I have included a brief section on excerpts of publications from The World Health Organisation (Section 9 in thesis), to which I have been an advisor twice:

(a) On dysthymia in PWE and
(b) On stress and GTS

(6) I have also included, at the end, Section 10, other medical publications (eg concerning academic psychiatry and a review on the Smith Magenis Syndrome) and a few of my non-medical publications, such as photographs and a few poems.

THE SYNOPSIS; A SUMMARY OF MY MAJOR INVESTIGATIONS

Research Baptism (The Early Years)

I began my research interest when I was a medical student. I undertook my first study using a questionnaire, which I designed and gave to 429 senior medical students (4^{th}, 5^{th} 6^{th} years) at the University of Cape Town, with a response rate of 300 (70%). The study documented attitudes to religion amongst the students, won the 1971 Mike Farhquarson Memorial Essay Competition, (as adjudicated by senior UCT academics) and was my first data containing publication (Robertson 1971 [1]), published in Inyanga, the UCT Medical Students Journal.. I then began my career in psychiatry and documented marital discord in 300 patients, including 100 consecutive female psychiatric in-patients, comparing them to 100 gynealogical patients and 100 medical patients, matched for age, sex and, ethnic and socio-economic groups; the psychiatric patients had significantly more marital discord (Robertson 1975 [c1]). I subsequently documented my experience as a locum in the Seychelles Islands showing that much pathology occurred on this so-called "Utopia island" (Robertson 1975 [c2]).

I thereafter collaborated with other residents and we reported a cohort of patients with datura stramonium poisoning (malpitte madness), (Robertson and Morley 1974 [2]), a patient with Crouzon's Disease or craniofacial dysostosis (Robertson and Reynolds 1975 [3]), (both diagnoses could be argued to be neuropsychiatric), and cold injury (peripheral limb injuries sustained while in cold weather, probably caused by altered physiology, which in turn *was* caused by psychiatric illness) in six patients (Dalton and Robertson 1982 [9]). With our psychiatric ward psychologist, I documented a case of anorexia nervosa with a urogenital abnormality (Robertson and Hamburger 1979 [6]). While completing a 3 month locum resident post in orthopaedics (in preparation for sailing around the world), my Consultant and his team including myself, documented interesting case reports of a hepatoma presenting as a bone tumour, and then another of osteitis deformans in South African black individuals, which was an unusual occurrence (Thomas et al 1977 [4]; Robertson and Thomas 1978 [5]).

Depression in the Context of People with Epilepsy

When I was a resident, I conducted a study on the antidepressant action of flupenthixol (see later), which inspired me to undertake more formalised research. I consequently undertook my three year Doctoral Thesis which was awarded in 1983, by the University of Cape Town. My MD thesis was entitled "Depression in people with epilepsy" (PWE).

Publications which resulted from my MD thesis included the documentation of the first, and to the best of my knowledge the only, double-blind trial of pharmacotherapy antidepressant treatment in PWE (Robertson and Trimble 1985 [16]). The study indicated that placebo worked as well as two active agents (amitriptyline [said to increase seizures ie be epileptogenic]) and nomifensine [which was suggested to reduce seizures]) at six weeks. In the second phase doubling of antidepressants resulted in the superiority of one agent. The study suggested that conventional doses of antidepressants in PWE produced an effect indistinguishable from placebo. The pharmacokinetic data were also important suggesting that amitriptyline may be more influenced by the hepatic enzyme induction of the anticonvulsant drugs than nomifensine (which may have accounted for that drug being superior in larger doses). It also showed that there were no significant changes in the serum levels of the anticonvulsants, phenobarbitone and phenytoin, in patients taking the antidepressants amitriptyline or nomifensine, or placebo, which has clinical relevance. A second study investigated the dexamethasone suppression test in PWE (Robertson et al 1986 [17]) and indicated that it was not useful because of hepatic enzyme induction of the anticonvulsant drugs. The third part of the study included the phenomenology and correlates of the depression, and was one of the first substantial challenges to the longstanding Flor-Henry (1969) laterality hypothesis. It was also one of the first documentations that carbamazepine was psychotropic, being associated with an improved mood, and also that phenobarbitone was associated with depressed mood. It also showed that the depression was not intimately linked to epilepsy variables and was highly likely to be multifactorial with a genetic vulnerability to depression (Robertson et al 1987 [20]). I was awarded the Lynda Bateman prize for Epilepsy Research in the United Kingdom in 1987 based on these studies (a separate and thesis-like bound application had to be submitted).

I then undertook two further studies in PWE and affective disorder. The first was a controlled psychopathological study of depression in patients with temporal lobe epilepsy (TLE) in a general hospital setting (Robertson et al 1994 [52]) in which we compared TLE outpatients attending a general hospital with depressed psychiatric patients and healthy control subjects to investigate depressive symptomatology. Both clinician-rated measures and self-report questionnaires were used. Rates of depressive and anxious symptomatology in TLE subjects were higher than those in the control sample, but TLE subjects did not differ significantly from controls on anxiety measures. The depressed psychiatric group scored higher than the TLE and control groups on both depression and anxiety measures. Rates of depressive symptomatology in the TLE group were lower than those reported in previous studies for persons attending specialist epilepsy clinics, but similar to the findings of one community study previously documented. The second study was that of Schmitz et al (1999 [90]) who undertook an investigation examining social and biological risk factors in depression and schizophrenia in PWE. This study indicated that patients with different psychopathologies in PWE (ie schizophreniform psychosis and depression) could clearly be distinguished from controls. However we could not confirm the simple hypothesis that there are biological predictors for schizophreniform psychosis and psychosocial predictors for major depression; neurological and sociological variables appeared to be linked with both psychopathologies, suggesting a multifactorial aetiology. Of note is that treatment with sodium valproate (VPA) was inversely linked with depression, suggesting that VPA may have prophylactic antidepressant properties in PWE.

I also collaborated and published on the lateralising significance of hypergraphia in temporal lobe epilepsy (Roberts et al 1982 [11]) and the description of schizophrenic psychosis associated with aqueduct stenosis (Roberts et al 1983 [13]). I have also co-authored an original paper followed by two single author reviews on clobazam as adjunctive treatment in refractory epilepsy (Allen et al 1983 [14]; Robertson 1986 [cp 4]; Robertson 1995 [cp15]).

The studies included in this section, were some of the first internationally, have been widely cited and gave me an international reputation in the field for many years. Thus, I was first invited to lecture internationally on the topic in 1983 (The 15th Epilepsy International Meeting, Washington DC, USA) and I was consistently invited to speak at international meetings on the topic until 2000. In 1996/7 I was invited to and acted as an Advisor to the World Health Organisation on "Dysthymia in Epilepsy and Neurological Disease" which also resulted in collaborative WHO publications (books; documents) as well as one peer-review paper (Akiskal et al 1996 [WHO 1]). I wrote a paper on the organic contributions to depressive illness in PWE (Robertson 1989 [26] and I have been invited to contribute 10 book chapters including some in substantial American spearheaded Textbooks on Epilepsy (eg Robertson 1988 [bc 9]; Robertson 1997 [bc 26]; Robertson 1998 [bc 28]) and many other reviews on the topic, such as the widely cited Robertson (1980 [26]), Robertson 1992 [cp 11]) and Lambert and Robertson (1999 [cp 18]).

While undertaking my MD I met my first five patients with Gilles de la Tourette Syndrome (GTS), and I decided to focus both clinically and in a research capacity in the area, taking my experience from my MD with standardised assessments and measurements with me into this very new field in the UK, and relatively new field even internationally. However, I also became interested in depressive illness and, as I always was consultant in charge of general adult psychiatric wards (1987-2002), I had ample opportunity to undertake research in depressive illness.

Depressive Illness

My first study in psychiatry began when, as said, I was a resident in 1978 and I conducted a study on the antidepressant action of flupenthixol as well as literature reviews on neuroleptics (major tranquillisers) as antidepressants which resulted in several publications (Robertson and Trimble 1981a [7] 1981b [8]; Robertson & Trimble 1982 [10]; Trimble and Robertson 1983 [12]). This experience as well as my MD thesis work in depression in PWE (above) gave me an interest in depression which I pursued for many years.

Stein et al (1988 [22]) documented toxic interactions between lithium and anti-inflammatory drugs, such as the non-steroidal agents. Studies which ensued in depressive disorder included a neuropsychological study testing working memory in depression (Channon et al 1993 [41]) as well as the effects of structure and clustering on recall and recognition memory in depression (Channon et al 1995 [47]).

Several publications resulted from a three-centre study of which I was Principal Investigator at one site. That collaborative study reported the results of a double-blind comparison of fluoxetine and lofepramine (Robertson et al 1994 [53]), including a large controlled trial of lithium augmentation in depression (Katona et al 1995 [59]). The Katona et al (1995 [59]) study was designed to establish whether (as suggested in a number of open and relatively small controlled trials) lithium augmentation (LA) was more effective than continued antidepressant alone, where response to a standard course of antidepressant treatment has been absent or partial. In the study, lithium or placebo was added on a double-blind basis for six weeks to the drug regime of 62 patients with major depressive illness (in both hospital and primary care settings) who had failed to respond to a controlled trial of fluoxetine or lofepramine. Response was defined as a final Hamilton Depression Rating Scale (HDRS)

score of < 10. Results were as follows: response was seen significantly more frequently in patients taking lithium than in those remaining on antidepressant alone. Rapid response to LA was not consistently observed in this cohort. Mean HDRS scores after six weeks were significantly lower in the lithium group after excluding those who had not achieved significant exposure to lithium (arbitrarily defined as two or more lithium levels > or = 0.4 mmol/l). No differences in the efficacy of LA were apparent between fluoxetine and lofepramine. We concluded that LA is a useful strategy in the treatment of antidepressant-resistant depression. Partial response was, however, frequently observed with continued antidepressant treatment alone, and the superiority of LA appeared to depend on achieving adequate serum lithium levels.

The group also published investigator guesses as to the agents which the patients were taking in the trial (Edwards et al 1994 [51]), platelet 5HT uptake sites labelled with 3H paroxetine before and after active treatment (Lawrence et al 1994 [55]), predictors of response to amine-specific antidepressants (Burns et al 1995 [66]) and, finally, the outcome of refractory depression (Shergill et al 1999 [89]).

In a separate collaboration, the antidepressant treatment of chronic tension-type headache was documented (Walker et al 1998 [86]).

I was also invited to provide a chapter in a predominantly research methods reference book, on the assessment and measurement of mood and its components (Robertson 1988 [bc 11]).

C Katona and I were involved with the World Psychiatric Association Treatment of Depression Module in (1996/7/8), and he and I edited a book on Depression and Physical Illness (Robertson and Katona 1997).

The Gilles de la Tourette Syndrome (GTS)

My main current area of research for 26 years has been GTS. I have undertaken many studies and have personally assessed nearly all of the cohort of over 1200 patients in the clinic. I also supervised numerous junior doctors (see CV) in the assessment and treatment of patients with GTS and instructed and inspired them into undertaking research. In this synopsis I have made headings throughout and have also further subdivided the psychopathology section, to enable easy reading. When there are many investigations in a section, there will be a summary and/or conclusion at the end of the summary of all the individual studies. In all studies standardised assessment schedules were used, including, after its publication, the Yale Global Tic Severity Rating Scale (YGTSS), (1989).

The History of Gilles de la Tourette Syndrome

We (Robertson & Reinstein 1991 [31]) translated and commented on the original French papers by George Gilles de la Tourette (1885), Guinon and Grasset, highlighting the phenomenology and psychopathology of GTS. We then (Rickards et al 1997 [82]) translated for the first time, Seignot's paper, the first to document the successful use of haloperidol in GTS; we showed that in fact, the patient described had also undergone a previous leucotomy, not previously described nor acknowledged.

Clinical Studies: Phenomenology, Psychopathology and the GTS phenotype

Since Dr Georges Gilles de la Tourette originally described the disorder, emphasising the triad of motor tics, coprolalia, echolalia, the phenotypic definitions of GTS have changed. For example, the age at onset has changed with each DSM version (eg 15, 18, 21 years as the upper limit at the age at onset). In addition, distress and impairment were included at one

stage (DSM-IV), but subsequently removed; the current DSM-IV-TR criteria do not include impairment or distress. Coprolalia is not required in any diagnostic categorisation. Nevertheless, there have been few attempts to formally classify GTS patients on the basis of their tic phenomenology. Both the DSM (APA) and WHO (ICD) criteria have always suggested that GTS is a unitary condition.

a) General clinical phenomenology and psychopathology in GTS

The first paper to be published on the topic was in 1984 (Lees, Robertson, Trimble & Murray 1984 [15]) reporting 53 patients, which was by far the largest cohort ever documented in the UK, with only a handful of patients having being documented previously by half a dozen individuals. It was also one of the larger international cohorts at the time, describing, in detail, the clinical features of GTS.

Robertson et al (1988 [21]) then documented a phenomenological analysis of 90 GTS patients, describing the full extent of the associated clinical phenomenology. We thus hinted at possible differing GTS phenotypes, and demonstrated significant associations between various "core" features of GTS. It was the first study of both psychopathology and phenomenology in GTS in the UK and one of the largest internationally, which also employed standardised psychiatric rating scales. A high incidence of depression, hostility and obsessionality was found. Depression was not related to administered medication, while aggression, hostility and obsessionality were significantly associated with copro- and echo- phenomena as well as with a family history of tics or GTS. We also documented and discussed the sleep disorders found in 76/90 patients and the abnormal neurological findings in 26/82 (31%) of patients. Fifty-two (63%) of the 83 electroencephalograms (EEGs) were normal, as were 71/73 CT scans (the 2 abnormalities were cavum septum pellucidum cavities and both were head-bangers). Links between psychopathology and neurological and (EEG) abnormalities were minimal.

Six controlled studies in the psychopathology embracing 244 GTS patients were conducted, comparing the GTS patients with healthy volunteer controls, as well as other specially chosen patient groups (Robertson & Trimble 1988 [23]; Channon et al 1992 [34]; Robertson et al 1993 [39]; 1997 [76]; 2002 [107]; Rickards and Robertson 2003 [113]) including adults in five investigations, and in one study, young people with GTS. Results indicated that patients with GTS have significantly more depressive symptomatology, obsessionality, anxiety, hostility and personality disorders than healthy matched control subjects, and relatively high levels of obsessionality when compared even to people with major depressive illness (Robertson et al 1993 [39]; Robertson et al 1997 [76]).

Robertson et al (1997 [76]) has been the only study to formally investigate personality disorders in patients with GTS. They used both the SCID-11 diagnostic interview and the STPCD self-rated scale to assess GTS patients and healthy controls to assess personality disorders and showed that 25/39 (64%) of GTS patients had personality disorders compared to 2/34 (6%) of the controls. This has significant implications when managing patients with GTS.

b) Obsessional disorder and symptoms in GTS

We have also taken a specific interest in obsessionality and GTS with several papers on the subject. Robertson et al (1988 [21]) first reported that 33/90 (36%) of GTS patients had obsessive compulsive behaviours (OCB) and that their scores on the Leyton Obsessional Inventory (LOI) and Crown Crisp Experiential Index (CCEI) were higher than normative data. The OCB and rating scale scores were significantly associated with being "forced to touch", shoulder shrugging, copro- and echo-phenomena. In the controlled studies, the GTS patients scored significantly higher than controls on either the adult and child Leyton Obsessional

Inventory (LOI) as appropriate (Robertson et al 1993 [39]; 1997 [76]; 2002 [107]; Rickards and Robertson 2003 [113]).

In the controlled study (Robertson et al 1993 [39]) which compared adults with GTS with depressed adults and with normal controls on questionnaires measuring obsessionality, depression, and anxiety, the GTS and depressed groups scored significantly higher than the normal controls on all measures. The GTS subjects had similar scores on measures of obsessionality to those of the depressed subjects, but significantly lower scores on measures of depression and anxiety. This suggests that obsessionality is a prominent feature of GTS.

Three studies specifically examined the phenomenology of obsessions and compulsions in people with GTS, comparing them to individuals with "primary" obsessive-compulsive disorder (OCD). We showed that there were significant differences between the two patient groups, that is, GTS and OCD patients. Although the studies were different in that different instruments were employed, the results were similar in many aspects (Frankel et al 1986 [18]; George et al 1993 [40]; Eapen et al 1997 [81]).

The Frankel et al (1986 [18]) study included 63 GTS patients (from the UK and the USA), 11 OCD patients and 41 healthy controls. A specially designed Inventory was employed. The Inventory scores for the two patient groups were significantly higher than normal controls ($p < 0.001$). The GTS group preferentially endorsed items to do with blurting out of obscenities, imitating the movements of others, counting compulsions and impulses to hurt one-self. The OCD patients endorsed items such as doing things in a specified order, arranging items systematically, counting, routines, rituals, touching one's body and obsessions about people hurting each other.

George et al (1993 [40]) prospectively studied 10 subjects with OCD and 15 subjects with GTS+OCD by using the Yale-Brown Obsessive Compulsive Scale, the LOI, and a new questionnaire specially designed to emphasize the differences in symptoms between these two groups. Results showed that subjects with comorbid GTS+OCD had significantly more violent, sexual, and symmetrical obsessions and more touching, blinking, counting, and self-damaging compulsions. The group with OCD alone had more obsessions concerning dirt or germs and more cleaning compulsions. The subjects who had both disorders reported that their compulsions arose spontaneously, whereas the subjects with OCD alone reported that their compulsions were frequently preceded by cognitions.

The Eapen et al (1997 [81]) study included 16 patients with GTS and 16 matched OCD patients; it suggested that obsessions in GTS patients were more to do with sexual and violent themes, whereas concern about contamination and fear of something going wrong or something bad happening were more common in the OCD group. With regard to compulsions, symmetry/"evening-up" behaviours, saying or doing things "just right" and forced touching were more prevalent in the GTS group, whereas washing and cleaning were more common in the OCD group. Sex of the proband did not account for any of these differences.

The findings from these three studies led us to refer to these behaviours in GTS being known as OCB. We also concluded that there are phenomenologic differences between OCD and GTS+OCD that may reflect differential involvement of neurochemical and neuroanatomic pathways. We also showed that GTS and OCB were genetically related (Eapen et al 1993 [38]). We were one of the first groups to document this and one of the few to have consistently done so over several years, using somewhat different methods, but with broadly the same results.

In another recent study (Cavanna et al 2006 [141]), we analysed the clinical and phenomenological features of tics and behavioural problems in 82 adults with GTS. Two groups were identified and compared: 34 patients with a clinical diagnosis of GTS and OCD (GTS+OCD) and 48 with GTS only (GTS-OCD). GTS+OCD patients scored significantly higher on tic severity, obsessionality (LOI), depression, and anxiety rating scales. Moreover, diagnosis of attention-deficit hyperactivity disorder (ADHD) and depression, echophenomena, and compulsive stereotyped behaviours showed a higher frequency in the GTS+OCD group. It was suggested that comorbid OCD correlates with more severe tics and associated psychopathology.

c) Attention and ADHD in GTS

We also reported that symptoms of poor attention and concentration, or indeed ADHD, were common in people with GTS (Channon et al 1992 [34]; 2003 [110]; Robertson et al 2002 [107]; 2006 [132]). We also demonstrated that GTS and ADHD were not genetically related (Eapen and Robertson 1996 [68]).

d) Self-injurious behaviours (SIB) in GTS

Other studies included a large and first study internationally to specifically examine self-injurious behaviours (SIB) in patients with GTS, demonstrating that those 30/90 (33%) of GTS patients with SIB were significantly more obsessional and hostile, as measured by standardised schedules, and that they also had more severe GTS (an increased number of "tics-ever" [Robertson et al 1989], [24]). Robertson and Gourdie (1990 [27]) documented that SIB also occurred in mildly affected GTS individuals, identified in a pedigree-community setting, with SIB again related to OCB. Robertson (1992 [bc 14]) subsequently summarised the studies reporting SIB in GTS patients, indicating that a substantial percentage of GTS patients in a variety of settings exhibit SIB. It was suggested that SIB is integral to GTS and is associated with obsessionality.

e) Depressive symptomatology and depressive illness in GTS

My interest in affective disorders, particularly depression, has always been maintained, and we specifically examined depressive illness and depressive symptomatology in many studies in GTS patients. We examined depressive symptomatology in community based studies, of which few have been done (Robertson and Gourdie 1990 [27]; Mason et al 1998 [85]; Hornsey et al 2001 [101]), and in which there was no excess of depressive symptomatology in GTS individuals who were identified.

Using controlled studies in the dedicated GTS clinic, we showed that GTS patients had more depressive symptomatology than controls and also that a significant proportion met DSM criteria for major depressive illness. We have also studied both young and adult clinic GTS patients, reporting that the depression was significantly related to echophenomena, coprophenomena, OCB, ADHD, SIB, aggression, increased tic severity (as measured by the YGTSS), conduct disorder in childhood, reduced quality of life and possibly female gender and older age (Robertson et al 1988 [21]; 2006 [132]; Elstner et al 2001 [100]; Eapen et al 2004 [120]; Snijders et al 2006 [134]).

Eapen et al (2004 [120]) also undertook a principal component factor analysis on the associated psychopathology in 91 GTS patients and demonstrated two factors within the psychopathology, namely a depression-anxious factor and an obsessional factor. These factors were not examined to determine if they were associated with specific constellations of tics. Robertson et al (1995 [c 9]) reported two cases of GTS patients who had committed suicide, highlighting the importance of identifying and treating depressive illness. It was suggested that

depression in GTS patients is highly likely to be multifactorial in origin, as is the depression in non-GTS populations (Robertson 2003 [bc 36]]).

f) Interesting hitherto undescribed and/or unusual clinical aspects or psychopathology of GTS patients

We have also described interesting GTS cases, including a patient with savant calendrical calculator ability (Moriarty et al 1993 [44]), comorbid Munchausen's syndrome and GTS (Robertson and Hossain 1997 [77]), comorbid eating disorders and GTS and OCD (Guarda et al 1999 [92]), a cohort of GTS patients with unusual vomiting tics (Rickards & Robertson 1997 [83]), a case of GTS with what we called "palicoprolalia" (Serra-Mestres et al 1998 [c 12]), and we documented one of the first cases of GTS from South America (Eapen and Robertson 1992 [35]) who had typical GTS, emphasising cultural independence. We also described a cohort of adult onset tic disorders (Eapen et al 2002 [103]) who were different from "primary" GTS with a childhood onset, in that they had a later onset, had unusual precipitating factors, and also a relatively poor response to conventional anti-GTS medications.

g) Other Studies on psychopathology and principal component factor analysis studies

A study from two collaborative clinics suggested that Non-Obscene-Socially-Inappropriate behaviours (NOSI) were common in a group of 87 adolescent or adult patients with GTS. Reported NOSI included insulting others (22%), other NOSI comments (5%) and NOSI actions (14%). More often GTS individuals had the urge to carry out these NOSI (30%, 26%, 22%) respectively, which they often attempted to suppress. NOSI was usually directed at a family member or familial person. Approximately a third of patients had resultant social difficulties and NOSI were also associated with ADHD and conduct disorder (CD) suggesting the possibility of an impulse control disorder (Kurlan et al 1996 [67]).

Freeman et al (2000 [97]) established a multisite, international database of 3,500 individuals diagnosed with GTS. The male:female ratio was 4.3:1 for the total sample, with wide variation amongst sites; the male excess occurred at every site. Anger control problems, sleep difficulties, coprolalia, and SIB only reached impressive levels in individuals with comorbidity. Anger control problems are strongly correlated with comorbidity, regardless of site, region, or whether assessed by neurologists or psychiatrists. The mean age at onset of tics was 6.4 years. At all ages, only about 12% of individuals with GTS had no reported comorbidity. The most common reported comorbidity was ADHD. In this study Males were more likely to have comorbid disorders than females. An earlier age of onset predicted a positive family history of tics. A recent study (Cavanna, Robertson & Critchley 2006 [a 23] examined schizotypal traits in 56 patients with GTS, employing Raine's (1999) Schizotypal Personality Questionnaire (SPQ) and standardized schedules, and the predictive intercorrelation between tic-related symptoms and psychiatric comorbidities. GTS patients scored significantly higher for schizotypy than normative samples; total SPQ scores and subscores for Cognitive-Perceptual, Interpersonal and Disorganised schizotypy dimensions correlated significantly with self-report scales measuring depressive, anxious and obsessional symptomatology. The Cognitive-Perceptual and Disorganised factors correlated significantly with severity as measured by the YGTSS.

Another study (Cavanna, Robertson & Critchley 2006 [a 22]) evaluated 41 GTS patients using the Bush-Francis Catatonia Rating Scale (BFCRS) as well as other rating scales. Ninety per-cent scored significantly for catatonia, consistent with sensitivity and lack of specificity of the BFCRS. The BFCRS score did not correlate with the YGTSS but did correlate with attentional problems and the diagnosis of ADHD.

As described earlier, Eapen et al (2004 [120]) undertook a principal component factor analysis on the associated psychopathology in GTS patients and demonstrated two factors within the psychopathology, namely a depression-anxious factor and an obsessional factor.

Cavanna, Robertson and Critchley (2006 submitted for publication [& Robertson 2006 a 24]) investigated the predictive intercorrelations between tic-related symptoms and psychiatric comorbidities in 70 patients with GTS using correlational, hierarchical cluster and a non-hierarchical principal-component factor analysis. Results showed that GTS patients scored higher on measures of schizotypy than normative samples, using the SPQ. Moreover, total SPQ scores and sub-scores for schizotypy dimensions correlated significanty and clustered with obsessional, depressive and anxiety symptoms. The relationship between schizotypy and tic severity scores was much weaker. Of note is that five clusters and five factors were obtained. The clusters were as follows: (1) CD/ODD/anger dyscontrol (2) forced touching, ADHD, SIB, stammering (3) OCD, schizotypy, depression, anxiety (4) coprolalia, copropraxia, echolalia, echopraxia, palilalia, palipraxia, (5) alcohol abuse. The factors were as follows: (1) depression, anxiety, schizotypy, OCD (2) anger dyscontrol, CD/ODD, (3) echolalia echopraxia, palilalia, palipraxia, alcohol abuse, coprolalia, copropraxia (4) forced touching, ADHD (5) stuttering, SIB. It was therefore concluded, inter alia, that the GTS phenotype is heterogeneous and not unitary as suggested by both DSM and WHO criteria.

Robertson, Althoff and Pauls 2006 (in preparation [& Robertson 2006; a 24]) described 419 consecutive patients with GTS who were systematically assessed using a standardized semi-structured interview that collected information on a wide range of tic symptoms. These tics were grouped using agglomerative hierarchical clustering with no *a priori* assumptions concerning their relatedness. Scores for the symptom clusters were then used as variables in a principal components factor analysis. The findings showed that five factors were obtained. The first factor included coprolalia, copropraxia, echolalia, echopraxia, palilalia, palipraxia, abnormal intonation when talking, random words and aggressive behaviours. Factor 2 included complex motor tics and grunting. Factor 3 included compulsive behaviours (e.g., repetitive looking, adjusting clothing, SIB, finger tapping, touching others and tensing body parts). Factor 4 included simple motor and phonic tics. Factor 5 included shoulder shrugging and touching self. It was therefore, once again, concluded that the GTS phenotype is heterogeneous and not unitary as suggested by both DSM and WHO criteria.

Robertson and Cavanna (2006 submitted [& Robertson 2006; a 24]) have also undertaken hierarchical clustering analysis and principal component factor analysis in a multiply affected GTS pedigree (Robertson and Gourdie 1990) and demonstrated three factors: one factor was of "tics only".

h) Psychopathology conclusions

In appears, from these studies, that GTS may well not be the unitary condition as set out by the diagnostic criteria guidelines of the two major internationally accepted groups such as the American Psychiatric Association and The World Health Organisation. We suggest that it is far more complex with both genetic (*vide infra*) and clinical heterogeneity. The precise phenotype as far as inheritance is concerned, has however, still to be determined.

The Assessment of individuals with Gilles de la Tourette Syndrome

Two schedules for assessing patients with GTS have been developed and tested in the clinic.

In the Lees et al (1984 [15]) study, we used a self-report questionnaire for the GTS assessment as well as examinations. I had realised, however, that for both motor and vocal (phonic) tics and associated phenomena (eg copro- echo- pali-, and symptoms of ADHD and OCD), as well as family history, a self-report schedule was not sufficient. Therefore in the early 1980s I devised the fore-runner to the National Hospital Interview Schedule (NHIS; Robertson and

Eapen 1996 [70]) which has been used to assess all the cohort of over 1200 GTS patients in the clinic ever since. This also included the patient's tic history, tics present at interview and tics present in the last week, as well as "tics ever" and direct tic examination of first-degree relatives.

In the early 1990s the Tourette Syndrome Association International Genetic Consortium (TSAIGC) devised a rating scale for assessing the likelihood of having GTS, and I took the lead in the development of it, assessing 280 consecutive GTS patients using the instrument, and the Tourette Diagnostic Confidence Index (DCI), (Robertson et al 1999 [96]) was published. The DCI was feasible, acceptable, and its correlation with other instruments (eg the YGTSS) and association with psychopathology provided support for its allowing as assessment of lifetime by the giving each of the core symptoms of GTS a numerical score, and thus obtaining a figure which gives the likelihood of having GTS (range 0% -100%). All GTS patients at the clinic (and thus publications since have also been assessed using that instrument since the early 1990s.

The Prevalence of Gilles de la Tourette Syndrome

GTS was once considered to be very uncommon with few cases documented in the UK and worldwide. This belief was held by many until the late 1990s. However, from my standpoint, seeing the families of patients in the clinic where 42/90 patients had a family history of tics or GTS (Robertson et al 1988 [21]) and having noted in a large pedigree that 50/85 family members had undiagnosed tics or GTS (Robertson and Gourdie 1990 [27]), it was decided to undertake prevalence studies.

We have conducted several epidemiological studies, including the first undertaken in New Zealand (Robertson et al 1994 [48]) indicating that GTS was unusual in that population. We investigated the point prevalence and reported the clinical characteristics of GTS in New Zealand. Forty probable cases were identified and the clinical symptoms were similar to those described in cohorts from other parts of the world.

This was followed by a pilot study in 169 13-14 year old schoolchildren in the UK, indicating that GTS was common (Mason et al 1998 [85]), and a definitive study including 918 13-14 year olds in schools in West Essex in the UK, which suggested a prevalence of between 0.46% and 1.76% (Hornsey et al., 2001 [101]). This figure was even higher in people with various learning disabilities (Eapen et al 1997 [78]) with 65% of youngsters with emotional and behavioural difficulties (EBD) having tics and 24% of students with learning difficulties having tics.

Finally, we studied the prevalence of GTS in people with autistic spectrum disorder (ASD). An earlier smaller-scale pilot study (Baron-Cohen et al 1999 [93]) of youngsters with autism revealed that 8.1% of such patients were co-morbid for GTS. We then (Baron Cohen et al 1999 [94]) undertook a large scale study to attempt to replicate the first. Four hundred and forty-seven pupils from nine schools for children and adolescents with autism were screened for the presence of motor and vocal tics. Results confirmed the co-morbid diagnosis of definite GTS in 19 children, giving a prevalence rate of 4.3%. A further 10 children were diagnosed with probable GTS (2.2%). We concluded that the rate of GTS in autism exceeds that expected by chance, and the combined rate (6.5%) is similar to the rates found in the smaller-scale study.

As these studies indicated that GTS was much more common than was once thought, and as we had shown that comorbidity was high (previous section), we studied the prevalence of GTS in 200 consecutive adult in-patients in a cross-sectional design on general adult psychiatry wards using the NHIS (Eapen et al 2001 [102]) and found no cases of GTS. However 2 were observed to have motor tics, 10 had a history of tics present for less than a year and 7 reported a family history of tics. We calculated that 19 (9.5%) qualified for inclusion in a broadly defined

GTS diathesis, but that these rates were significantly lower than those in a similar epidemiological study.

In conclusion, we have demonstrated that GTS is much more common than was previously thought, in both mainstream populations as well as in people with learning disabilities and autism. However, it appears that GTS patients are not over-represented on general psychiatry in-patient wards.

The effect of GTS on the patient and the family: Quality of Life (QOL) and Care-Giver Burden encountered in Gilles de la Tourette Syndrome

We undertook the first study formally investigating the Quality of Life (QOL) in 103 people with GTS using the SF-36 and the Quality of Life Assessment Schedule (QOLAS). We demonstrated that patients with GTS showed significantly worse QOL than a general population sample. The GTS patients had better QOL than patients with intractable epilepsy as measured by the QOLAS. Factors influencing QOL domains in GTS patients were employment status, tic severity, OCB, anxiety and depression (Elstner et al 2001 [100]).

We also were the first to evaluate Care-Giver Burden and GTS, examining parents for psychopathology (Cooper et al 2003 [117]). To investigate the mental health and caregiver burden in parents of children with GTS, we conducted a cross-sectional cohort survey at our GTS clinic and a paediatric asthma hospital outpatient clinic over a 6-month period. The main outcome measures were parent mental health (General Health Questionnaire [GHQ]-28) and caregiver burden (Child and Adolescent Impact Assessment) scores. Results showed that the response rate achieved was 89.7%. Of the parents of children with GTS, 76.9% achieved caseness on the GHQ-28 compared with 34.6% of the parents of children with asthma; this effect remained significant after controlling for demographic variables. Parents of children with GTS also experienced greater caregiver burden, and this burden was significantly correlated with GHQ caseness. We concluded that parents of children with GTS are at risk of psychiatric morbidity; we suggested that an intervention targeting caregiver burden might be helpful in reducing this.

These studies indicate that these aspects of the disorder (ie the consequences of GTS on the patient and the family) are important and relatively under-researched. Both types of studies are continuing and two more papers are currently under editorial review.

The Aetiology of Gilles de la Tourette Syndrome

i. Genetics and Family Studies of GTS.

Between the mid 1980s and 2006, I have been involved with genetic studies of both consecutive families and opportunistic extended families of probands who have GTS, and latterly, also studies including both sib-pairs and trios with GTS.

Robertson & Trimble (1991 [30]) described a multigenerational pedigree from the Middle East, which, at face value, looked as if the pattern of inheritance was compatible with autosomal dominant transmission.

Robertson & Gourdie (1990 [27]) then described the first large UK study, in which I interviewed 85 individuals in a multigenerational pedigree: 50 were diagnosed as "cases": 29 had GTS, 17 had chronic multiple tic (CMT) disorder without GTS, while 4 had OCB-only as a diagnosis. The Robertson & Gourdie (1990 [27]) kindred was then submitted to complex segregation analysis which showed that GTS was inherited as a single major gene with autosomal dominant inheritance (Curtis et al 1992 [32]). We then undertook a complex

segregation analysis on the nuclear families of 42 consecutive GTS probands and showed that not only was GTS transmitted by a single major autosomal dominant gene, but that OCB was a phenotype of the gene (Eapen et al 1993 [38]).

Following these findings, in studies including samples from predominantly the large pedigree many candidate areas of the genome, as well as some of special interest, were excluded. These included areas of chromosomes 3 and 8 (Brett et al 1996 [71]), the 5HT1A receptor and tryptophan oxygenase genes (Brett et al 1995 [63]), the neuro-receptor sub-unit genes (Brett et al 1997 [64]) and gene encoding of the NMDA receptor channel (Brett et al 1994 [58]) were all excluded. Brett et al (1995 [62]) also demonstrated that linkage analysis excluded a role for the genes coding for Dopamine D1, D2, D3, D4, D5 receptors, Dopamine Hydroxylase, Tyrosinase and Tyrosine Hydroxylase in the pedigree. More recently, a full genome scan on the large kindred was then undertaken, which demonstrated areas of interest on chromosomes 5, 10 and 13 (Curtis et al 2004 [119]). This either meant that there was heterogeneity within the family or that an affected individual married into the family of whom we were initially unaware.

We therefore conducted a study to explore these findings further. As said earlier, Robertson and Cavanna (2006 submitted [Robertson 2006 [a 24]) have also undertaken hierarchical clustering analysis and principal component factor analysis in a multiply affected GTS pedigree (Robertson and Gourdie 1990) and demonstrated three factors: one factor was of "tics only". This suggests that there is both clinical and genetic heterogeneity in GTS. It also means that individuals who had been previously diagnosed as "non-cases" (but who had very mild obsessional symptoms (assessed by the Leyton Obsessional Inventory, but who had not qualified for the diagnosis of OCB), had married into the pedigree.

In addition it was shown that in GTS patients there is bilineal inheritance (ie inheritance from both paternal and maternal sides) in 39 high-density families in which five or more relatives were reported to have GTS and 39 families of consecutively ascertained probands referred for evaluation (Kurlan et al 1994 [54]). We also demonstrated possible genomic imprinting in GTS, in that there was evidence for earlier age at onset in maternally transmitted cases (Eapen et al 1997 [75]) and also showed that GTS and ADHD were not genetically related (Eapen and Robertson 1996 [68]).

Robertson and Trimble (1993 [42]) documented that the majority of chromosomes in GTS were normal, with only familial polymorphisms in two cases and one XYY individual. However, as clues to the genetic underpinnings of GTS were still warranted, we documented a patient and her mother with GTS and the chromosome 22q11 deletion syndrome (previously known as the Catch 22 syndrome), (Robertson et al 2006 [138]), suggesting that the COMT gene (occurring in the area) abnormalities may well be an endophenotype for GTS. Our studies have thus suggested that GTS is highly likely to be genetically heterogeneous.

The Tourette Syndrome Association International Consortium (1999 [95]) (TSAIC) for genetics, of which I have been a member since about 1987]) using sib-pair analysis, undertook the first systematic genome scan in GTS using 76 affected sib-pair families with a total of 110 sib-pairs. While no results reached acceptable statistical significance, the multipoint maximum-likelihood scores (MLS) for two regions (4q and 8p) were suggestive (MLS >2.0) and four additional areas genome regions also gave multipoint MLS between 1.0 and 2.0. The TSAIC has published several other studies in GTS, including a genome wide scan of hoarding (Zhang et al 2002 [104]) which suggested that significant allele sharing occurred at the 4q and 5q sites and that the joint effects were important. Based on the fact that OCD is an aetiologically heterogeneous disorder (as recent factor analyses have consistently identified several symptom dimensions, two of which are associated with

increased familial risk for OCD) and that both of these symptom dimensions are also frequently seen in association with GTS. Leckman et al (2003 [105]) studied obsessive-compulsive (OC) symptom dimensions within families (between sibs and between parent-child pairs). Using data collected by the TSAIC for Genetics Affected Sibling Pair Study, the authors selected all available GTS sib pairs and their parents for which these OC symptom dimensions (factor scores) could be generated. This group included 128 full sibs and their mothers (54) and fathers (54). Four OC symptom dimension scores were computed for each family member using an algorithm derived from item endorsements from the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) symptom checklist. In addition to a series of univariate analyses, complex segregation analyses were also completed using these quantitative OC symptom dimension scores. Factor 1 and Factor 2 scores were significantly correlated in sib pairs concordant for GTS. The mother-child correlations, but not father-child correlations, were also significant for these two factors. Segregation analyses were consistent with dominant major gene effects for both Factor 1 and Factor 2. We concluded that familial factors contribute significantly to OC symptom dimension phenotypes in GTS families. This familial contribution could be genetic or environmental. Other documentations from the TSAIC for Genetics have taken place, evaluating the genes for the adrenergic receptors alpha 2A and alpha 1C concluding that they were not major genetic factors contributing to the susceptibility to GTS (Xu et al 2003 [106]). Verkerk et al (2003 [116]) demonstrated that CNTNAP2 was disrupted in a family with GTS and OCD, hypothesising that disruption or decreased expression of CNTNAP2 could lead to a disturbed distribution of K+ channels in the nervous system, thereby influencing conduction and/or repolarisation of action potentials causing unwarranted movements in GTS.

Despite two of our early studies (and indeed several internationally) indicating an autosomal dominant mode of transmission, the results overall, give clues to the fact that GTS is very highly likely to be genetically heterogeneous. This progression of our studies concurs with others in the world. Ours is one of the few groups to have published consistently in the field of GTS genetics for 16 years, having commenced the studies early in the 1980s.

ii Neuroimmunology and the possible role of streptococcal infections in Gilles de la Tourette Syndrome

Three neuroimmunological studies have examined links to the PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus) syndrome, identifying a sub-group of these patients with raised ASO titres, and also a subpopulation that express anti-basal ganglia antibodies (ABGAs).

Our first study in the field, Church et al (2003 [112]) investigated 100 consecutive GTS patients in a cross-sectional study. We compared them to children with neurological disease (n=50) and recent uncomplicated streptococcal infection (n=40), adults with neurological disease (n=50) and healthy adults (n=50) all of whom formed the control group. We showed that ASOT was significantly raised in both GTS children, compared with paediatric neurological controls (64% vs 15%) and GTS adults compared with neurological adult patients and healthy controls (68% vs 12% vs 8% respectively). Western immunoblotting showed positive binding in 20% and 27% of GTS children and adults, compared with 2-4% of the controls, which was also significant. The most common basal ganglia binding was to a 60kDa antigen, similar to the proposed antigen in Sydenham's chorea. Serological evidence of recent group A streptococcal infection, assessed by a raised ASOT, was detected in 91% of GTS patients with positive ABGAs, compared to 57% with negative ABGAs, which was significant.

Martino et al (2005 [128]) then investigated the immune-mediated response in GTS, and its relationship with streptococcal infection, measuring serum levels of soluble intercellular

adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin in patients with GTS, compared to healthy and diseased controls. Soluble VCAM-1 and sE-selectin were significantly elevated in children and adults with GTS, and sVCAM-1 was higher among ABGA-positive adults with GTS. No correlation of adhesion molecule levels to clinical severity or anti-streptococcal antibodies was observed. Children with Sydenham's chorea and PANDAS showed an increased level of sICAM-1, but not sVCAM-1 and sE-selectin. These results provided some initial evidence for a role of adhesion molecules and systemic inflammation in GTS, and supported the hypothesis of an ongoing immune-mediated process in some patients with GTS.

Rizzo et al (2006 [136]) subsequently took blood on 69 patients with GTS and 72 age and sex matched tic-free controls. Laboratory staff were blinded to the diagnostic status of the subjects. Evidence of recent streptococcal infection was defined using antistreptolysin titres. ABGA were determined using human basal ganglia sections. We reported raised antistreptolysin titres 41/69 (59%) of GTS patients and 14/72 (19%) controls which was highly statistically significant. Positive ABGAs were found in 22/69 (32%) of subjects with GTS compared to 7/72 (10%) controls, which was also significant (p-value:0,002). Raised antistreptolysin titres were detected in 18/22 (82%) patients with GTS with positive ABGAs and 22/47 (47%) with negative ABGAs (p-value:0,01).

In conclusion, all three of our studies in the area support the reported association between streptococcal infection and ABGAs and a neuroimmunological hypothesis in a subset of patients with GTS.

iii Pre- and peri- natal events in the aetiopathology of GTS

One of the first studies to note pre- and peri-natal difficulties in GTS patients was that of Lees et al (1984 [14]) who reported that 13/53 GTS patients (24.6 %) had such problems. These included induced labour (3), the umbilical cord round the neck (3), neonatal jaundice (2), delivery by caesarian section 2, forceps delivery (2), a prolonged labour (1), prematurity (1) and a twin sibling dying at birth (1). These results are in accord with subsequent studies (Leckman et al J Am Acad Child Adolesc Psychiatry 1990; 29 (2): 220-226) which suggested labour and peri-natal difficulties are important in the GTS and others which demonstrated that lower birth weight may even lead to more severe tic disorder and more EEG abnormalities (Hyde et al Neurology 1992; 42 (3): 652-658 and Hyde et al Br J Psychiatry 1994; 164 (6): 811-817). Thus, pre- and peri- natal difficulties may well affect the phenotyic expression of GTS. To the best of my knowledge no controlled study has been published to date, examining such difficulties in patients with GTS and comparing them to a matched number of births a comparitive sample of population. I envisage such a study and with all my pre- and peri natal data on hundreds GTS patients it would be feasible.

Conclusions aetiology

Our genetic studies demonstrate that GTS is very highly likely to be genetically heterogeneous and our neuroimmunological studies support the reported association between streptococcal infection and ABGAs and a neuroimmunological hypothesis in a subset of patients with GTS. Finally our data show that 24.5% of GTS patients have birth difficulties which may well affect the phenotyic expression of GTS. Thus, the aetiology of GTS is complex and has yet to be fully determined. The correct definition of the phenotype is crucial for this.

Special Investigations and the Neurophysiology of GTS

Acknowledging the quest for biological markers in GTS, we have undertaken a series of special investigations and neurophysiological studies, which may shed light on the neurological and biological underpinnings of GTS.

Robertson et al (1987 [19]) described copper abnormalities in 10/80 GTS patients who had an abnormally low serum copper. In 2 of the patients radioisotope studies were carried out. Both exhibited abnormalities of copper handling, in that an abnormally fast disappearance of copper from the plasma was noted, as well as an abnormally slow uptake by the liver. The rates of intestinal absorption and urinary excretion were normal. An abnormal site of sequestration of copper in the body was not identified.

Robertson et al (1988 [21]) reported that 52 (63%) of 83 EEGs were normal in GTS patients. In other words the EEG in patients with GTS is not really informative unless a diagnosis of epilepsy is being considered.

Robertson et al (1988 [21]) also demonstrated that medications affected both psychopathology and IQ (WAIS). With regards to the psychopathology, patients receiving butyrophenones (haloperidol and pimozide) were significantly less obsessional. The effects on IQ will be discussed under neuropsychology.

Gaynor et al (1997 [a 21]) studied kynenurenine (KYN) in GTS patients, as it had been shown to increase tic-like behaviour in an animal model of GTS, and was also reported to be elevated in GTS patients. The KYN pathway is the principal route for the metabolism of tryptophan (TRY) and plasma KYN levels give a gross index of the pathways activity. In the liver the first enzyme is cortisol inducible Tryptophan Dehydrogenase (TDO), while in extrahepatic tissues, including brain, this is replaced by cytokine-inducible indolamine dioxygenase (IDO). Plasma samples were taken from 72 GTS patients and 46 matched healthy controls, after an overnight fast. There was no increase in TRY in GTS patients, cortisol was unchanged, but the KYN and neoptrin levels were significantly elevated in GTS patients. These increases were not related to medication. Neoptrin but not cortisol was significantly correlated with KYN levels in both GTS and control subjects. These results suggest that KYN in GTS patients is more likely to be due to induction of IDO rather than TDO.

Whitefield et al (1995 [c 10]) studied visual field defects in 24 GTS patients (24 eyes) and compared them with 12 (24 eyes) of age and sex- matched controls. No ocular disease was detected in any of the subjects and none had previously undergone visual field testing. Visual field tests were performed using a Humphrey Field Analyst running a central 24-2 full threshold test. Data collected included mean deviation (MD) scores, an indication of the overall field abnormality and corrected pattern standard deviation (CPSD) scores and localised field defects. Results showed that 21/24 visual field tests in each group were reliable (according to the reliability indices built into the software). Results also showed that there were no statistically significant differences in either MD or CPSD scores between GTS and control eyes. The difference in MD approached significance, and a large sample might be expected to yield a significant result. However, the MD score for a particular patient would not in our opinion, serve as a biological marker for GTS, since there was a large overlap between MD scores in the GTS patient group and controls. We thus concluded that visual fields do not serve as a useful biological marker for GTS.

Gobel et al (1992 [a 3]) led the way in our neurophysiological studies. We investigated 13 GTS patients (aged 15-42 years) and 10 healthy control subjects with the same age range and performed auditory and visual 3-stimulus oddball tasks, and an auditory selective

attention task which consisted of a high (1.5 kHz) or low (1.2 kHz) pitch tone delivered to the right or left ear in random order at a rate of 1.second. All pitch-ear combinations were equiprobable and one was designated as target on separate runs with responses for all 4 possible targets being recorded. Division of attention was evaluated by examining different wave forms for responses to the same physical stimulus presented to attended and unattended ears. Results from the oddball tasks suggested that GTS patients had attentional difficulties, and responses in the selective attention task indicated a clear difference from controls; this suggests that GTS individuals have impaired ability to attend to one ear at a time.

Nowak et al (2005 [125]) analyzed predictive and reactive grip force behaviour in 15 patients with GTS and 15 sex- and age-matched healthy control subjects. Nine patients were without medication; six patients were on medication. In a first experiment, participants lifted and held instrumented objects of different weight. In a second experiment, participants performed vertical point-to-point and continuous arm movements at different frequencies with a hand-held object. In a third experiment, preparatory and reactive grip force responses to sudden load perturbations were analyzed when a weight was dropped into a hand-held cup either by the subject or unexpectedly by the experimenter. Compared to the healthy subjects, GTS patients had increased grip forces relative to the load force in all tasks. Despite this finding, they adjusted the grip force to changes in load force (due to either a change in the mass lifted or accelerating the mass during continuous movements) in the same way as healthy subjects. The temporal coupling between grip and load force profiles was also similar in patients and healthy controls, and they displayed normal anticipation of impact forces when they dropped a weight into a hand-held cup. We found no significant effect of medication on the performance of GTS patients, regardless of the task performed. These results are consistent with deficient sensory-motor processing in GTS.

Orth et al (2005 [126]) used transcranial magnetic stimulation (TMS) to examine the excitability of two different inhibitory systems in the human motor cortex: short interval intracortical inhibition (SICI) and short interval afferent inhibition (SAI) in 10 healthy non-smoking controls and eight untreated non-smoking patients with GTS. Compared with the healthy control group, both SICI (measured at a range of conditioning intensities) and SAI were reduced in patients. This is consistent with the suggestion that reduced excitability of cortical inhibition is one factor that contributes to the difficulty that patients have in suppressing involuntary tics. In addition, the reduced SAI indicates that impaired intracortical inhibition may not be limited to the motor cortex but also involves circuits linking sensory input and motor output. A single dose of nicotine reduced tic severity as assessed by blind video scoring in the majority of GTS patients. In addition, it abolished the difference between patients and controls in SICI and SAI. There was no effect of nicotine, and no difference between controls and patients in measures of motor or SICI threshold. This indicates that cholinergic input can modulate the efficiency of SICI and SAI differently in GTS and healthy controls.

In conclusion, with regards special investigations in GTS, although some GTS patients had abnormal copper and abnormal copper handling, an abnormal site of sequestration of copper in the body was not identified. We also showed that the EEG in patients with GTS is not really informative unless a diagnosis of epilepsy is being considered. We demonstrated that the IQ can be adversely affected by neuroleptics. Our neurophysiological results suggest attentional difficulties in GTS, and responses in selective attention tasks suggests that GTS individuals have impaired ability to attend to one ear at a time. We concluded that visual fields do not serve as a useful biological marker for GTS. Finally, our results were also consistent with deficient sensory-motor processing in GTS, and also indicated that cholinergic input can modulate the efficiency of SICI and SAI differently in GTS and healthy controls.

The Neuropsychology of GTS

We have examined and published on many and various aspects of psychological functioning and projects include Executive Functioning, IQ, theory of mind, the Intention Editor, attentional problems, social problems, and aspects of childhood developmental functioning; treatment studies are envisaged. We have identified deficits of attention on complex tasks, which are magnified in those GTS patients with comorbid ADHD. .

Motor skills have been included in the section on neuropsychological aspects of GTS. It is perhaps quite unusual that some of the motor phenomena of GTS have specific *content.* Echopraxia is a clear example of this, where a GTS patient involuntarily repeats ("echoes") the actions of another person after observing them. Our group has described echopraxia in 21 % of 53 patients (Lees et al 1984 [15]) to 23% of 90 GTS patients (Robertson et al 1988 [21]).

Robertson et al (1988 [21]) demonstrated that medications affected both psychopathology and IQ (WAIS). Patients who were not receiving butyrophenones had a higher FIQ, whereas patients receiving no medication at the time of the study and those never having had any major tranquillisers at all, had higher FIQ, PIQ and VIQ. These data are important when considering prescribing medication to patients, particularly youngsters, who have to succeed in education and then as adults in employment.

I have collaborated with three separate groups of neuropsychologists investigating different areas of cognitive functioning. Channon et al (1992 [34]) compared adult GTS patients to healthy volunteers and demonstrated that GTS subjects were significantly impaired relative to normal controls on several "complex" experimental tasks of attention, including serial addition, block sequence span (forwards) and cancelling target letters, particularly when alteration between two sets of targets was required in the latter two tasks. Since the groups were matched for IQ, which was in the normal range, these findings represent selective deficits rather than global impairments in global functioning for the GTS group.

Channon et al (2003 [115]) examined social problem solving in real-life-type situations in GTS individuals. Previous studies of cognitive functioning in GTS had usually focused on non-social, abstract tasks, with mixed findings as to whether there is evidence of impairment in executive functions in those without comorbid disorders. This study therefore focused primarily on social functioning, using a problem-solving task known to be sensitive to frontal lobe lesions. GTS participants without comorbid diagnoses were compared with matched healthy control participants on a problem-solving task, using a range of interpersonal problem scenarios presented on video. A set of more abstract executive tests was also included. Results indicated that participants with GTS were found to perform below a matched control group on the problem-solving task both in generating a range of potential problem solutions, and in selecting appropriate final solutions. They also performed more poorly on aspects of executive function. This study provided evidence of difficulties in both social and non-social aspects of functioning in GTS.

In another study, young people with GTS-alone, GTS+ADHD, or GTS+OCD were compared with a healthy control group, on a set of measures of executive functioning, memory, and learning (Channon et al 2003 [110]). The GTS-alone group was impaired on one executive measure involving inhibition and strategy generation but did not differ significantly from the healthy control group on other measures. The GTS+ADHD group showed impairment on several executive measures. There was no evidence of impairment in implicit aspects of memory and learning for any of the GTS groups.

Although associations between social cognition involving theory of mind and non-social executive skills have frequently been reported, dissociations in performance have also been found. Channon et al (2004 [121]) therefore examined social and non-social cognition in uncomplicated GTS. Adult GTS participants without comorbid diagnoses were compared to matched healthy control participants on social cognition measures involving theory of mind and empathy, and on non-social executive tasks. Participants with GTS were found to make more errors than a matched control group on an inhibitory task, but did not differ on other executive measures or on the social cognition measures.

Crawford et al (2005 [129]) compared adolescents with "pure" GTS (ie GTS without ADHD, OCD, depression, anxiety) to healthy controls on a set of executive measures. On the Sentence Completion task the GTS patients were slower to make both sensible and nonsensical completions and they had higher error scores on the nonsensical completions. On the Flanker task the GTS patients were less accurate than the controls. The GTS group and controls did not differ on tasks of working memory or reward learning. These results indicate that uncomplicated GTS patients do not have widespread executive impairments.

Channon et al (2006 [133]) finally evaluated carefully screened adult participants with GTS examining cognitive impairment associated with frontostriatal dysfunction. The findings showed the GTS group to perform more poorly on one test involving behavioural inhibition (sentence completion), but did not provide strong support for an interpretation based solely on inhibitory deficits, and there was no evidence of impairment on another behavioural inhibition task (Flanker test). There were also no differences between the groups on tasks involving working memory (n-back), task switching, or object alternation learning. The findings provide further evidence that uncomplicated GTS is associated with only mild, circumscribed impairment.

As we were interested in the possible relationships between GTS and people with autistic spectrum disorder (ASD) we have conducted studies in the area. We have also investigated the frontal systems and the "Intention Editor". Previous studies had found a subgroup of people with autism or Asperger Syndrome who pass second-order tests of theory of mind. However, such tests have a ceiling in developmental terms corresponding to a mental age of about 6 years. It is therefore impossible to say if such individuals are intact or impaired in their theory of mind skills. We (Baron-Cohen et al (1997 [79]) therefore reported the performance of very high functioning adults with ASD (including individuals with both autism and Asperger Syndrome) with normal or above average IQ, on an adult test of theory of mind ability. The task involved inferring the mental state of a person just from the information in photographs of a person's eyes. Relative to age-matched healthy controls and a clinical control group (adults with GTS), the group with ASD were significantly impaired on this task. The ASD sample was also impaired on Happe's strange stories tasks. In contrast, they were unimpaired on two control tasks: recognising gender from the eye region of the face, and recognising basic emotions from the whole face. This provides evidence for subtle mindreading deficits in very high functioning individuals on the autistic continuum. The GTS group were also unimpaired on the task. We also showed that within the normal population, females were significantly better on the test of theory of mind than males.

Baron-Cohen et al (1994 [50]) demonstrated that children with GTS had deficits in "intention editing", that is, in the ability to inhibit one of two simultaneously competing intentions. In the paper we describe a cognitive mechanism, the Intention Editor (IE), which is triggered whenever there are several intentions competing in parallel with each other. This mechanism is hypothesised to be a subcomponent of a larger mechanism, the Supervisory Attentional System (SAS: Shallice 1988) which serves inhibition in general. The IE interrupts one of several simultaneously activated intentions, preventing it from executing its action, utterance,

or thought. This mechanism appears to develop during the first five to six years of life. We proposed that an impairment in the development of this mechanism may account for the triad of symptoms in children with GTS (involuntary movements, involuntary utterances and obsessive thoughts). This mechanism was tested with normal children aged 3-6 years old and also with children with GTS in 2 experiments. In Experiment 1, subjects were required to make one hand movement while inhibiting making a (different) hand movement that the other hand was simultaneously making. In experiment 2, they were asked to say one thing, while inhibiting saying something else. On both tasks, normal 6 year olds were significantly better than normal 4 year olds, but children with GTS performed worse than normal 6 year olds despite having a mean age of 12 years. These results constitute preliminary evidence that the IE is dysfunctional in GTS.

Baron-Cohen and Robertson (1995 [65]) then reported the results of three patients: a case of "pure" autism, a case with GTS and an individual comorbid with both GTS and autism. Based on previous studies, we predicted that there would be a "theory of mind" deficit in the first, an intention-editing" deficit in the second, and a co-occurrence of the deficits in the third. Finally, we predicted that an "executive function" deficit would not distinguish the patients. These predictions were supported.

Watkins et al (2005 [127]) studied executive function in 20 GTS patients, 20 OCD patients and a group of age- and IQ matched healthy controls who completed psychiatric rating scales and who also completed psychometric and computerised cognitive tests, the latter chosen for their sensitivity to other fronto-striatal disorders, and included pattern and spatial recognition memory, attentional set-shifting and a Go/No-go set-shifting task, planning, and decision making. Compared to controls, OCD patients showed a variety of selective deficits and abnormalities. GTS patients were impaired in spatial recognition memory, extra-dimensional set-shifting, and decision making. Neither patient group was impaired in planning. When comparing GTS and OCD patients, the GTS group showed difficulties in the quality of decision making.

In conclusion, we have demonstrated that GTS individuals have selective deficits rather than global impairments in cognitive functioning. We also showed that there is evidence of difficulties in both social and non-social aspects of functioning in GTS, but no evidence of impairment in implicit aspects of memory and learning for GTS. We also showed that GTS individuals make more errors than controls on inhibitory tasks, but do not differ on social cognition measures. We have shown that "pure" GTS patients, that is those with uncomplicated GTS, do not have widespread executive impairments. In addition, children with GTS have deficits in the ability to inhibit one of two simultaneously competing intentions (the Intention Editor), and also that GTS patients are unimpaired on theory of mind tasks. We have demonstrated that GTS individuals are not impaired in planning. When comparing GTS and OCD patients, the GTS group showed difficulties in the quality of decision making. We are one of the few groups to have examined GTS-only patients in neuropsychological functioning.

Neuroimaging Studies in Gilles de la Tourette Syndrome

We have investigated patients with GTS with both structural and functional techniques looking for brain abnormalities, beginning our investigations in the early 1980s. We began with CT (computerised tomography) studies, and progressed on to MRI (magnetic resonance imaging) and functional neuroimaging (SPECT [single photon emission tomography] and PET [positron emission tomography]) studies.

Robertson et al (1988 [21]) undertook CT scans on the largest cohort of GTS patients investigated using such methods: the majority were normal (71/73). The 2 abnormalities were

cavum septum pellucidum cavities and both were headbangers (which had also been described in the literature on boxing injuries). These studies showed that, in general, CT scans in GTS individuals were normal, but led the way to subsequent MRI studies and other functional neuroimaging techniques.

The first study published (Hall et al 1990 [cp 8]) was the first internationally to study perfusion in GTS. We studied 25 patients (aged 7-48 years) HMPAO/SPECT. We compared the GTS patients with 10 healthy control subjects. We demonstrated, for the first time, a wide range of perfusion deficits in the frontal, parietal and temporal cortex (Hall et al 1990 [cp 8]).

To further test the hypothesis of possible orbito-frontal/basal ganglia dysfunction in GTS, we studied 20 unmedicated GTS subjects, 10 of whom also had comorbid OCD (George et al 1992 [36]). The subjects were examined with high-resolution HMPAO/SPECT and the labelled regional cerebral blood flow (rCBF) ligand technetium-99m-d,l-hexamethy-propylene amine oxime (99TcM-HMPAO). As a group GTS subjects showed significantly elevated right frontal/visual cortex activity compared with control subjects. A sub-analysis comparing simple GTS versus GTS+OCD failed to reveal significant differences in regional flow.

Moriarty et al (1995 [64]) examined 50 GTS patients and 20 controls using HMPAO/SPECT. Patients were rated for tic severity and mood. Scans were analysed quantitatively using internal ratios to the occipital cortex. Results indicated that patients differed from controls on measures of relative blood flow to the left caudate, anterior cingulate cortex and the left dorsolateral prefrontal cortex. Severity of tics was related to hypoperfusion of the left caudate and cingulate and a left medial temporal region. Hypoperfusion in the left dorsolateral prefrontal region was related to mood. We concluded that the areas found to be hypoperfused in this study are consistent with known functions of fronto-striatal circuits. A wide range of perfusion patterns was seen; however, no characteristic patterns for behavioural subgroups were documented with this technique.

In a study of family members with either GTS, OCD or tics, we did not detect any differences in cerebral perfusion between the disorders, emphasising the biological links between them (Moriarty et al 1997 [74]). Thus, we studied 20 subjects from 5 families affected by GTS, including individuals with OCB but no tics, were examined using HMPAO/SPECT. Results indicated that there were abnormalities of regional cerebral perfusion in individuals with GTS, OCB and tics; hypoperfusion occurred in striatal, frontal and temporal areas. We concluded that regional cerebral blood flow patterns in individuals with OCB in families affected by GTS are comparable to their relatives with GTS and differ from individuals with primary OCD in the absence of a family history of tic disorders (Moriarty et al 1997 [74]).

George et al (1994 [57]) found no differences in dopamine receptor availability in unmedicated GTS patients when compared to controls. GTS patients taking D2 blocking medications had significantly decreased 123 I-IBZM binding compared with control subjects in both the right and left basal ganglia. The study concluded that the D2/D3 receptor availability as measured by 123 I – IBZM- SPECT is not abnormal in GTS.

Serra-Mestres et al (2004 [118]) then demonstrated that GTS patients when compared to controls had significantly higher dopamine transporter binding in the caudate and putamen nuclei. No associations, however, were found between striatal binding ratios and measures of affect or GTS-related behaviours.

In a PET study, it was demonstrated that simple motor tics were associated with the sensorimotor cortex, while more complex tics (such as coprolalia and clear vocal tics) were shown to be associated with activity in prerolandic and postrolandic language regions, insula, caudate, thalamus and cerebellum in a functional neuroanatomy study employing

PET techniques combined with time-synchronized audio and videotaping of tics (Stern et al 2000 [98]). Thus, these data suggest that different types of tics may indeed have different underlying biological mechanisms.

In an MRI study, we demonstrated that normal basal ganglia asymmetry of the caudate nucleus with left-sided predominance was not present in patients with GTS. There was an increased cross-sectional area of corpus callosum (CC) and a loss of normal correlation between cross-sectional area of CC and whole-brain index in the GTS patients was also found (Moriarty et al 1997 [80]).

In conclusion, our neuroimaging studies have used functional neuroimaging and, for the first time and then subsequently, we demonstrated using HMPAO/SPECT, a wide range of perfusion deficits in the frontal, striatal, parietal and temporal areas. We also showed that D2/D3 receptor availability as measured by 123 I – IBZM-SPECT is not abnormal in GTS, but that GTS patients when compared to controls had significantly higher dopamine transporter binding in the caudate and putamen nuclei. We have also suggested using PET, that different types of tics may indeed have different underlying biological mechanisms. We also performed structural neuroimaging, suggesting initially that in general, CT scans in GTS individuals were normal and thus of no use in routine investigations. We also showed with MRI that there was an increased cross-sectional area of CC and a loss of normal correlation between cross-sectional area of CC and whole-brain index in the GTS patients.

Because of my longstanding interest in neuroimaging, I have been invited to review and make comments on neuroimaging studies in GTS several times, all single author papers. I was invited to write the first Editorial in the European Journal of Nuclear Medicine on GTS (Robertson 1990 [ir 3]) and a commentary in Nature Medicine (Robertson 1996 [ir 8]) commenting on a publication in Science (Wolfe et al 1996)

The Treatment of patients with Gilles de la Tourette Syndrome

A number of treatment studies have been carried out including early studies on the long-term usefulness of sulpiride, a substituted benzamide, in 63 patients with GTS of whom 59% had worthwhile beneficial effects (Robertson et al 1990 [29]). Risperidone was found not to be helpful for tics (Robertson et al 1996 [73]); this was a counter-intuitive finding and may well have been due to the fact that it was a retrospective case note study, rather than a prospective controlled design. Thereafter, we conducted a placebo-controlled trial using sulpiride and fluvoxamine in patients who has both GTS and OCD (George et al 1993). In this study we conducted a 14 week placebo controlled double-blind trial of sulpiride and fluvoxamine, followed by a 4 week single blind study. Sulpiride monotherapy significantly reduced tics and non-significantly reduced OCD symptoms. Fluvoxamine alone or with sulpiride non-significantly reduced tics and OCD symptoms. Eapen et al (1996) showed that fluoxetine was useful for the OCB/OCD aspects in our GTS patients. Most recently we have documented the largest cohort of 11 patients treated successfully with a relatively new agent, aripiprazole (Davies et al 2006): this is the largest study (11 patients) to date in the medical literature using aripiprazole successfully in GTS patients. Ten out of 11 patients improved; the only patient who failed to respond received 5 mg; all the rest were taking 10-20mg daily, with only a few transient side effects. We were also one of the pioneers of the successful use of laryngeal botulinum toxin (Botox) injections for troublesome coprolalia (Trimble et al 1998 [88]) and in one patient we described a limbic leucotomy for severe GTS which was associated with severe SIB (Robertson et al 1990 [28]).

We have also investigated the use of repetitive transcranial magnetic stimulation (rTMS) in GTS. In a single-blinded, placebo-controlled, crossover rTMS trial (Muenchau et al 2002 [108]), in which 16 patients with GTS received in random sequence 1 Hz motor, premotor,

and sham rTMS, which each consisted of two 20-minute rTMS sessions applied on 2 consecutive days. In the 12 patients who completed the trial, there was no significant improvement of symptoms after any of the rTMS conditions as assessed with the MOVES scale. As that study showed no effect of 1Hz rTMS on tics in GTS, we (Orth et al 2005 [124]) modified the rTMS protocol in order to investigate some of the possible methodological reasons for the negative outcome in that study. In a single blinded placebo-controlled cross-over study in five GTS patients without obsessive compulsive disorder we probed whether longer trains (1800 stimuli) of 1 Hz pre-motor cortex rTMS at 80% of active motor threshold and application to both hemispheres can improve tics in GTS. This was measured with the YGTSS, the MOVES self-rating scale and video analysis. We found no significant effect of either left pre-motor cortex stimulation alone, or left pre-motor followed by right pre-motor cortex stimulation. Our results suggest that the rTMS protocol used in this study is not useful for the treatment of tics in GTS and that rTMS protocols therefore need to be modified substantially in order to explore their potential for the treatment of tics in GTS.

I am currently collaborating with an Italian group and we (Servello et al 2006) have recently submitted a paper documenting the neurosurgical effects of deep brain stimulation (DBS) in 18 GTS patients (17-46 years; 15 male) who were resistant to at least six months of treatment with both standard and innovative medications, as well as psycho-behavioural techniques. The site of DBS was placed bilaterally in the centro-median parafascicular (CM-Pfc) and ventralis oralis complex of the thalamus. Patients were evaluated after surgery according to a protocol which included immediate assessment as well as formal assessments at least every three months, including "on-off" and "sham-off" in the first 9 patients. All patients responded well to DBS, although to differing degrees. The duration of the follow-up assessments ranged from 3 – 18 months. Motor tics responded to DBS somewhat better than phonic tics. There were no serious permanent adverse effects. We thus concluded that DBS is a useful and safe treatment for severe GTS. Only a total of 11 patients with GTS treated with DBS in 9 separate communications have been published previously internationally. We are preparing a further paper on the effect of DBS on the neuropsychiatric aspects of GTS, and as well as a single case report of one patient in whom the DBS was targeted in the Globus Pallidus Internum (Porta et al; Robertson et al).

In summary, in the treatment of patients with GTS, we and our immediate collaborators have always been in the forefront of the field and, in many instances, early pioneers investigating with new medications, double-blind trials and innovative techniques such as Botox injections, rTMS, psychosurgery and finally, and most recently, DBS.

GILLES DE LA TOURETTE SYNDROME CONCLUSIONS

Our studies have provided a body of work which has resulted in profound changes in the knowledge of GTS in the UK and internationally. GTS was once thought to be a rare and bizarre curiosity. The work over the years has shown that GTS is quite common (affecting 1% of youngsters), that the clinical presentation varies enormously, and that it is highly likely to be clinically heterogeneous, with "pure motor and vocal tics" as only one phenotype. People with GTS have been shown to have more psychopathology than healthy people, particularly depression and obsessionality. The obsessionality differs from that in primary OCD. People with GTS also have significant SIB, which is in turn, significantly associated with OCB. However, individuals identified in the community (in both family/genetic and epidemiological studies) as "cases", having GTS were mildly affected as far as tics were concerned, had no significant depression, but did have significant obsessionality and also SIB. We have demonstrated that GTS adversely affects both the individual's quality of life and also that of the patients' carers/parents. We have demonstrated that GTS has a genetic basis which is complex, and that some (OCB), but not other disorders (ADHD), may be genetically linked to GTS. We have also suggested that some infections may be of some relevance in its genesis or

development in a subset of GTS patients. Using neuroimaging scans, we have shown differences between patients with GTS and healthy control volunteers in both structural and functional neuroimaging. Our neuropsychological studies have indicated subtle deficits in particular areas, differences between GTS and controls. We have undertaken special investigations indicating that some GTS patients have abnormal copper and abnormal copper handling, that routine EEGs are not warranted, that the IQ can be adversely affected by neuroleptics, and that kynenurenine metabolism is disturbed in GTS. We have shown that visual field defects are not a useful biological marker in GTS. Our neurophysiological results suggest that GTS patients have attentional difficulties, and that their selective attention task performance is clearly different from controls; this suggests that GTS individuals have impaired ability to attend to one ear at a time. Further neurophysiological studies are consistent with deficient sensory-motor processing in GTS, and also indicate that cholinergic input can modulate the efficiency of short interval intracortical inhibition and short interval afferent inhibition differently in GTS and healthy controls. We have shown that there is effective treatment for GTS, but that this is far from simple, and ranges from a variety of medications, to injections in the vocal cords, to even psychosurgery and DBS in a few patients who are severely affected; in our studies, only rTMS and risperidone were shown not to be useful . In pratice our early work with sulpiride resulted in my using it as first line medication in adults and some children, if tics were the predominant symptoms and it was felt that a neuroleptic was indicated. With our recent success with aripiprazole, we hope to study the drug further, and are using it increasingly as it is relatively free of side effects, particularly prolactinaemia (which did occur with sulpiride) and weight gain (which occurs with almost all the new "atypicals").

REVIEWS OF GILLES DE LA TOURETTE SYNDROME

In addition to the original research, I have been invited to write numerous review articles and book chapters on GTS. The majority of these are as a single author; occasionally I invited co-authors to join me. For the sake of clarity and to cross-reference with my CV, I have numbered these publications. These include those in high impact factor journals such as Nature (Robertson 1996 [ir 8]), Brain (Robertson 2000 [99]), the Journal of Child Psychology and Psychiatry (Robertson 1994 [49]) and the British Journal of Psychiatry (Robertson 1989 [25]). Relatively recently I have had reviews on the epidemiology of GTS (Robertson 2003 [114]), the behavioural treatments available for GTS (Robertson 2004 122]), affective disorders, with particular reference to depression, and GTS (Robertson 2006 [139]) and GTS and comorbid ADHD and its treatment (Robertson 2006 [135]) published. Many other reviews have been published (see CV).

I have also been invited to contribute on GTS to major American spearheaded textbooks devoted to neuropsychiatry, neurology, epilepsy and movement disorders. These include Robertson and Yakeley (1997 [bc 21]); second edition (Eapen, Yakeley, Robertson 2003 [bc 35]), Robertson (2003 [bc 36]), Schrag and Robertson (2006 [bc 39]). I have also been invited to contribute to American books devoted solely to GTS such as: Robertson 1992 [bc 13]), Robertson and Yakeley 1993 [bc 15]) and its second edition (Eapen, Yakeley, Robertson [37]), as well as Robertson 1992 [14]) and Robertson and Orth 2006 [bc 38]).

WORLD HEALTH ORGANISATION PUBLICATIONS

I have been included as a co-author on a paper on dysthymia in neurological disorders (Akiskal et al 1996 [WHO 1]) and have published on dysthymia in epilepsy (Robertson 1997 [WHO 3]) and stress in GTS (Robertson 1998 [WHO 4) and was included in a WHO document (WHO/MNH/MND/98.14 [WHO 2]).

I was invited to be an advisor for a third time on comorbidity, but had to decline because of prolonged treatment for cancer.

ACADEMIC, MISCELLANEOUS & NON-MEDICAL PUBLICATIONS

As a committed academic I have been interested in the careers of others. Thus, in a series of papers investigating issues in academic psychiatry, we showed first, that when studying the CVs and appointment process, even at Senior House Officer, Registrar and Senior Registrar (all resident) levels, CV predictors of success in psychiatry included having a publication of any kind. We further demonstrated that the achievement of one or more data containing publications was a more discriminating factor. We also showed that having a first degree (eg BSc) before studying medicine, was positively associated with appointment to a career post in psychiatry (Katona and Robertson 1993 [37]).

We then undertook a study to consider whether the "end-of-firm" examination (EOFE) in psychiatry fulfilled goals by examining the internal consistency of the EOFE and the final medical examination at university level and the correlations between these examinations scores and subscores (MBBS in London; MBChB in Cape Town; MD in the USA & Europe), (Livingston et al 1998 [87]). Students who failed their EOFE were followed to monitor progress and final medical university examinations (MBBS). 180 students took the EOFE and MBBS. All components of the EOFE and MBBS correlated significantly with the total mark. The psychiatric essay was less well correlated with the final mark but correlated well with total essay marks. Students who failed EOFEs at their first attempt received extra tuition and only 2 failed finals. The implications are that essay writing ability may not carry over into high performance in other areas tested and may be a test of other skills. Extra tuition benefited failing students whose results fell outside the pattern of prediction. Thus EOFEs may be a useful tool if acted upon to prevent student failure.

A subsequent study demonstrated that, in the United Kingdom, males were more likely to have academic posts, as compared to NHS (National Health Service) posts. Men occupied 81% of academic posts and 63% of NHS posts (all grades). Furthermore, data showed that there were more male professors 135 (89%), than females, with only 17 (11%) of professors of psychiatry being women. With regards to NHS consultants (attendants in the USA), 2203 (67%) were men and 1099 (33%) were women (Killaspy et al 2003 [111]).

These papers reflect my long term commitment to teaching (including being awarded many Departmental and indeed University prizes twice – see CV) and the nurturing of medicine as a profession as well as academic life is important to me. They demonstrate that as senior academics we can spot medical students who have trouble with certain examinations and help them to pass final medical examinations, and thus help them become doctors. When considering a career, one can then give advice on whether an academic or clinical career is preferable, as far as obtaining another degree and undertaking research resulting in publications.

We (Killaspy et al 2004 [123]) showed, for the first time, that a specialist ward exclusively dedicated to psychiatric patients who were homeless (also with a dedicated community mental health team (CMHT)), improved their mental health in that they engaged with services more after discharge and had increased compliance with medication. We undertook the study, using a prospective controlled design, 50 patients admitted to a hospital during a 12 month period. One year after discharge housing stability and engagement with services were compared for patients admitted to the designated ward (n= 29 = cases) and those admitted elsewhere (n= 21 = controls) Cases were significantly more likely to be street homeless at admission and had moved housing significantly more than the controls in the preceding 12 months. Both groups were equally likely to be discharged to stable accommodation, and 12 months later, there was

no difference in housing stability. However, there was a highly significantly greater improvement for engagement for cases compared to controls. In addition, factors influencing medication non-compliance improved highly significantly only in cases. We thus concluded that a designated ward, if feasible and affordable, is preferable for psychiatric patients who are most vulnerable.

I have included a review on Munchausen's syndrome (Robertson and Cervilla 1997 [ir 10]) as I lectured to medical students on unusual disorders, gave a lecture at the Royal College of Psychiatrists and also appeared as an expert on a BBC documentary on Munchausen's syndrome. I have also included an unusual case of folie a deux between mother and adult son (Christopherson and Robertson 1999 [91]) which is the first report of the condition between a mother and her adult son of normal intelligence (the only previous report of a mother and adult son, was one in which the son had Down's syndrome).

I have included a thorough review of the Smith Magenis Syndrome (SMS), (Shelley and Robertson 2005 [131]) as it gives a good overview of a relatively unusual neuropsychiatric topic. We have also recently submitted a paper on a case with GTS with comorbid for SMS (Shelley et al 2006). The SMS is a complex paediatric neurobehavioural genetic syndrome ascribed to interstitial microdeletion of chromosome 17 band 11.2 and which has distinctive behavioural, neurocognitive and neuropsychiatric features. We have recently submitted a paper (Shelley et al 2006) which we believe is the first published case description of a co-occurrence of GTS with SMS. We suggested that the genetic loci in the deletion interval of chromosome 17p11.2 may be a promising region for containing a gene or genes of aetiological importance in the development of the GTS phenotype.

I have included four photographs of the ship in which I sailed almost around the world and which were published in a South African Photography and Travel magazine. I have also included a few poems, initially of my illness, but then showing that I have "moved on" and have included two poems about South Africa and two about London.

A SELECTION OF SOME OF MY MOST IMPORTANT PEER REVIEWED PUBLISHED PAPERS TO DATE AND MY FAVOURITE NON-MEDICAL PUBLICATIONS

All publications in this section were chosen as they were the first and largest in the UK, and many were the first and remain some of the largest internationally. All the publications in this section have been widely cited and are in respectable international journals with, for my subject, high impact factors. Only the Journal of Child Psychology and Psychiatry is not listed in the Citation Index. The papers are included as the majority are from my group and not as a result of international or national collaborative efforts. I have also tried to include papers which reflect my all-round approach in GTS and other subjects, including psychopathology, neuropsychology, neuroimaging, neurophysiology, prevalence, genetics and treatment studies, the development of an assessment schedule and four review articles.

RESEARCH BAPTISM

ROBERTSON MM (1971). Attitudes to religion: a survey amongst medical students at the University of Cape Town. Inyanga:40:32-42.

This was my first data containing publication which won a medical school prize.

DEPRESSIVE ILLNESS

ROBERTSON MM & TRIMBLE MR (1982). Major tranquillisers used as antidepressants: a review. Journal of Affective Disorders:4:173-193. Cited 71 times in SCI **IF: 3.078**

I conducted this review and documented, for the first time in a large review article, that major tranquilisers (neuroleptics) could be used successfully as antidepressants. It was my first publication as a resident that was widely cited.

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CHANNON S, BAKER JE, **ROBERTSON MM** (1993) Working memory in clinical depression: an experimental study. Psychological Medicine 23, 87-91 Cited 52 times in SCI **IF: 3.476**

Continuing my interest in depressive illness, this paper is an important neuropsychological study of working memory in depressive illness.

=

KATONA CLE, ABOU-SALEH MT, HARRISON DA, NAIRAC BA, EDWARDS DRL, LOCK T, BURNS RA, **ROBERTSON MM** (1995) Placebo controlled trial of lithium augmentation of fluoxetine and lofepramine. British Journal of Psychiatry, 166, 80-86 Cited 95 times in SCI **IF: 4.956**

Continuing my interest in depressive illness further, this paper was the first large double-blind placebo controlled study to demonstrate that lithium could be used successfully as an augmenting agent of traditional antidepressants in depressive illness. We concluded that lithium augmentation is a useful strategy in the treatment of antidepressant-resistant depression. Partial response was, however, frequently observed with continued antidepressant treatment alone, and the superiority of lithium augmentation appeared to depend on achieving adequate serum lithium levels.

DEPRESSION IN PEOPLE WITH EPILEPSY

ROBERTSON MM & TRIMBLE MR (1985). The treatment of depression in patients with epilepsy: a double blind trial. Journal of Affective Disorders:9:127-136. Cited 40 times in SCI **IF: 3.078**

This study remains the only placebo-controlled double-blind antidepressant treatment trial to be conducted in people with epilepsy (PWE) in the medical literature. Results indicated that placebo worked as well as two active agents at six weeks. This was important, as it suggested that conventional doses of antidepressants in PWE produced an effect indistinguishable from placebo. The pharmacokinetic data were also important suggesting that amitriptyline may be more influenced by the hepatic enzyme induction of the anticonvulsant drugs than nomifensine.

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ROBERTSON MM, TRIMBLE MR & TOWNSEND HRA (1987). The phenomenology of depression in people with epilepsy. Epilepsia:28:(4):364-372. Cited 141 times in SCI **IF 3:227**

This study included the phenomenology and correlates of the depression, and was one of the first substantial challenges to the longstanding Flor-Henry (1969) laterality hypothesis; it was also one of the first documentations that carbamazepine (CBZ) was psychotropic, which paved the way for being CBZ and other anticonvulsants being used as mood stabilisers, which is common practice today. It also showed that the depression was not intimately linked to epilepsy variables and that the depression was highly likely to be multifactorial. It is one of the most widely cited papers.

ROBERTSON MM, CHANNON S, BAKER J (1994) Depressive symptomatology in a general hospital sample of outpatients with temporal lobe epilepsy: a controlled study. Epilepsia, 35 (4) 771-777 Cited 26 times in SCI **IF: 3.227**

This study was one of the first studies of psychopathology indicating that PWE, particularly temporal lobe epilepsy, were more depressed than healthy control individuals.

WORLD HEALTH ORGANISATION PUBLICATIONS

AKISKAL HS, BOLIS CL, CAZZULO C, COSTA E SILVA, GENTIL V, LECRUBIER Y, LICINIO J, LINDEN M, LOPEZ-IBOR JJ, NDIAYE IP, PANI L, PRILIPKO L, **ROBERTSON MM**, ROBINSON RG, STARKSTEIN SE, THOMAS P, WANG Y, WONG M-L (1996) World Health Organisation Meeting -Conference de L'Organisation Mondiale de la Sante - Dysthymia in neurological disorders. Molecular Psychiatry, 1, 478-491 **Cited 6 times in GS IF 9.335**

This paper was my only collaborative WHO publication in a peer review journal and the Impact Factor is very high.

GILLES DE LA TOURETTE SYNDROME

ROBERTSON MM, TRIMBLE MR & LEES AJ (1988). The psychopathology of the Gilles de la Tourette syndrome: a phenomenological analysis. British Journal of Psychiatry: 152, 383-390. Cited 140 times in SCI **IF: 4.956**

This was one of the first and remains one of the largest and widely cited documentations describing both the clinical phenomenology and psychopathology of GTS. It was one of the first to demonstrate associations between core features of GTS and psychopathology.

ROBERTSON MM, TRIMBLE MR & LEES AJ (1989). Self injurious behaviour and The Gilles de la Tourette Syndrome. A clinical study and review of the literature. Psychological Medicine:19:611-625. Cited 77 times in SCI **IF: 3.476**

This paper was the first and remains the largest documentations describing self-injurious behaviours (SIB) in GTS. Consequent on that paper I was invited to speak at the 2nd International USA Tourette Association scientific meeting on GTS and my topic was SIB (with a resultant publication in Advances in Neurology). I was also invited to write an article in Neuroscience Year 1993.

ROBERTSON MM & GOURDIE A (1990) Familial Tourette's Syndrome in a large British Pedigree: Associated Psychopathology, Severity of Tourette's and Potential for linkage analysis. British Journal of Psychiatry 156, 515-521 Cited 64 times in SCI **IF: 4.956**

BRETT PM, CURTIS D, **ROBERTSON MM**, GURLING HMD (1995) Exclusion of 5HT1A serotonin neuroreceptor and tryptophan oxygenase genes in a large British kindred multiply affected with Tourette's Syndrome, chronic multiple tics and obsessive compulsive behaviour American Journal of Psychiatry, 152 (3), 437-441 Cited 28 times in SCI **IF: 8.286**

The first paper was the second large pedigree (50/85 cases identified in members interviewed by myself) of a GTS proband described internationally (the first was Kurlan et al 1986). It paved the way for many publications (Brett et al, Curtis et al, Eapen et al 1997 [75]) and the factor analysis paper (Robertson and Cavanna 2006). The second paper is in a very high impact factor journal.

ROBERTSON MM, SCHNEIDEN V & LEES AJ (1990) Management of Gilles de la Tourette syndrome using sulpiride. Clinical Neuropharmacology, 13, 229-235 Cited 39 times in SCI **IF: 1.890**

This publication documented the successful use of sulpiride for the motor and vocal tics in GTS. It remains the largest number of patients treated successfully with sulpiride. Due to this publication, the USA attempted to get the FDA to approve sulpiride. Several colleagues on the North American continent import sulpiride on a named-patient-basis as a result of this paper.

This paper also resulted in a double-blind placebo controlled study which showed that sulpiride was significantly superior to placebo for both tics and OCB in GTS patients.

FRANKEL M, CUMMINGS JL, **ROBERTSON MM**, TRIMBLE MR, HILL MA & BENSON DF (1986). Obsessions and compulsions in the Gilles de la Tourette syndrome. Neurology:36:(3):378-382. Cited 167 times in SCI **IF: 4.947**

GEORGE MS, TRIMBLE MR, RING HA, SALLEE FR, **ROBERTSON MM** (1993) Obsessions in Obsessive-Compulsive Disorder (OCD) with and without Gilles de la Tourette Syndrome (GTS). American Journal of Psychiatry 150, 93-97 Cited 102 times in SCI **IF: 8.286**

EAPEN V, **ROBERTSON MM**, ALSOBROOK JP II, PAULS DL (1997) Obsessive compulsive symptoms in Gilles de la Tourette's syndrome and obsessive compulsive disorder: differences by diagnosis and family history. American Journal of Medical Genetics (Neuropsychiatric Genetics) 74 (4), 432-438 Cited 40 times in SCI **IF 10.649**

EAPEN V, PAULS DL, **ROBERTSON MM** (1993) Evidence for autosomal dominant transmission in Gilles de la Tourette Syndrome - United Kingdom cohort study. British Journal of Psychiatry, 162, 593-596 Cited 104 times in SCI **IF: 4.956**

The first three publications are some of the important works describing significant differences between the OCB in GTS and the symptoms in "primary" OCD. Frankel et al was the first internationally. The fourth not only provided evidence for autosomal dominant transmission in GTS, but also showed that GTS and OCB were genetically related.

ROBERTSON MM, CHANNON S, BAKER JE, FLYNN D (1993) The psychopathology of Gilles de la Tourette Syndrome: a controlled study. British Journal of Psychiatry, 162, 114-117 Cited 39 times in SCI **IF: 4.956**

This was one of the first if not the first controlled study of psychopathology indicating that patients with GTS are more disadvantaged than healthy individuals, with particular relevance to depression, anxiety and obsessionality.

76. **ROBERTSON MM**, BANERJEE S, FOX HILEY PJ, TANNOCK C (1997) Personality disorder and psychopathology in Tourette's syndrome: a controlled study. British Journal of Psychiatry, 171, 283-286 **Cited 14 times in SCI IF: 4.956**

This is the only formal investigation into PDs in people with GTS internationally

GEORGE MS, TRIMBLE MR, COSTA DC, **ROBERTSON MM**, ELL PJ (1992) Elevated frontal cerebral blood flow in Gilles de la Tourette Syndrome (GTS): a Tc99HM-PAO SPECT study. Psychiatry Research -Neuroimaging, 45 (3), 143-151 Cited 43 times in SCI IF 1.957

MORIARTY J, CAMPOS COSTA D, SCHMITZ B, TRIMBLE MR, ELL PJ, **ROBERTSON MM** (1995) Brain perfusion abnormalities in Gilles de la Tourette's Syndrome. British Journal of Psychiatry 167, 249-254 Cited 53 times in SCI **IF: 4.956**

MORIARTY J, VARMA AR, STEVENS J, FISH M, TRIMBLE MR, **ROBERTSON MM** (1997) A volumetric MRI study of Gilles de la Tourette Syndrome, Neurology 49 (2), 410-415 Cited 41 times in SCI **IF: 4.947**

Our neuroimaging studies have been some of the pioneering international studies in neuroimaging of GTS. Hall et al (1990: although in a conference proceeding) was actually the first to document worldwide to demonstrate, using SPECT, a wide range of perfusion

deficits in the frontal, striatal, parietal and temporal areas, from which the first study here followed. The second study, of family members with either GTS, OCD or tics in individual members, did not detect any differences in cerebral perfusion between the disorders, emphasising the biological links between them, one of the few of its kind involving family members and searching for a possible endophenotype for GTS. The third, an MRI study, demonstrated that normal basal ganglia asymmetry with left-sided predominance was not present in patients with GTS and that there was an increased cross-sectional area of corpus callosum, again one of the first.

THE TOURETTE SYNDROME ASSOCIATION INTERNATIONAL CONSORTIUM FOR GENETICS (including **M.M. Robertson)** (1999) A complete genome scan in sib-pairs affected with Gilles de La Tourette Syndrome. American Journal of Human Genetics, 65 (5), 1428-1436 Cited 71 times in SCI IF: **12.649**

This collaborative study reported the first systematic complete genome scan in GTS and indicated that GTS was not transmitted by a single major autosomal dominant gene, identifying more than one area of interest, thus paving the way for the notion of genetic heterogeneity in GTS.

ROBERTSON MM, BANERJEE S, KURLAN R, COHEN D, LECKMAN JF, McMAHON W, PAULS DL, SANDOR P, van de WETERING BJM (1999) The Tourette Diagnostic Confidence Index: development and clinical associations. Neurology, 53 (9), 2108-2112 Cited 23 times in SCI IF: 4.947

I took the lead in this paper for the USA Tourette Syndrome International Genetic Consortium, which devised a physician rated scale for lifetime certainty of GTS and which was developed to assist in genetic studies in order to be able to quantify the degree of "caseness" (or not) of individuals so that this could be included in the analyses; the advantage of this was that if an individual was incorrectly assigned, this quantifiable number could be calculated into the equation, and was not as damning as would be a mistake of "caseness" (or not).

BARON-COHEN S, SCAHILL V, IZAGIURRE J, HORNSEY H, **ROBERTSON MM** (1999) The prevalence of Gilles de la Tourette Syndrome in children and adolescents with autism: A large scale study. Psychological Medicine, 29 (5), 1151-1159 Cited 28 times in SCI IF: 3.476

This was the first large scale investigation to formally study the prevalence of GTS in people with autism, showing that it was 6%. This has been important as many professionals have been alerted to the coexistence of the two disorders which has major management and indeed educational implications.

BARON-COHEN S, JOLLIFFE T, MORTIMORE C, **ROBERTSON M** (1997) Another advanced test of theory of mind: evidence from very high functioning adults with autism or Asperger Syndrome. Journal of Child Psychology and Psychiatry 38 (7), 813-822 **Cited 173 times in GS IF 3.927**

This is our second most widely cited paper giving insights into the cognitive functioning of individuals with autistic spectrum disorder, and also discussing theory of mind which has relatively recently, become an "in vogue" concept.

HORNSEY H, BANERJEE S, ZEITLIN H, **ROBERTSON MM** (2001) The prevalence of Tourette syndrome in young people in mainstream schools. Journal of Child Psychology and Psychiatry, 42 (8), 1035-1039 **Cited 20 times in GS IF 3.927**

This was the third international large scale of the prevalence of Tourette syndrome in young people in mainstream schools, indicating that GTS is no longer rare, but may well be as high as 1% of youngsters (in this study aged 13-14 years). There are now 7 published studies internationally in the new millenium giving similar results which indicate that GTS is not a rare disorder.

ORTH M, AMANN B, **ROBERTSON MM**, ROTHWELL JC (2005). Excitability of motor cortex inhibitory circuits in Tourette Syndrome before and after single dose nicotine Brain, 128 (6) 1292-1300 **Cited 1 time in SCI IF: 7.535**

This recently published neurophysiological paper is in a highly respected high impact factor journal and has given some new insights into the neurophysiology of GTS.

ROBERTSON MM and EAPEN V (1992) The pharmacologic controversy of CNS stimulants in Gilles de la Tourette syndrome. Clinical Neuropharmacology 15, (5), 408-425 Cited 41 times in SCI **IF: 1.890**

This invited review article was for many years one of the widely cited on a difficult management topic. I have subsequently updated this, taking many new studies and new drugs into account (Robertson 2006 [135]).

ROBERTSON MM (1989). The Gilles de la Tourette syndrome: the current status. British Journal of Psychiatry:154:147-169. Cited 177 times in SCI **IF: 4.956**

ROBERTSON MM (1994) Annotation: Gilles de la Tourette Syndrome - an update. Journal of Child Psychology and Psychiatry 35 (4), 597-611 **Cited 36 times in GS IF 3.927**

ROBERTSON MM (2000) INVITED REVIEW. Tourette syndrome, associated conditions and the complexity of treatment. Brain, 123, 425-462 Cited 81 times in SCI: **IF: 7.535**

These three invited reviews were then subject to peer review, and remain some of the most widely cited reviews on GTS in the UK, and indeed, internationally. In the UK certainly they disseminated knowledge about GTS to many professionals of all disciplines. The first paper is the most widely cited of all papers that have been published by our group. The British Journal of Psychiatry is taken by every Member and Fellow of the Royal College of Psychiatrists both in the UK and abroad, as well by many institutions. It was therefore probably the first comprehensive review that many psychiatrists in the UK (and Royal College members/fellows abroad) had read. The second was my first publication in a journal dedicated to child psychiatry. The third is in a highly respected high impact factor journal and is included on a USA Tourette Syndrome Association CD (also included in the submission with the thesis); that CD has been to date distributed to between 3,000 and 6,000 medical professionals, and over 2,000 psychologists in the USA (2 of my papers were included on the CD) and is thus widely read through the UK and USA by a wide variety of professionals interested in GTS.

ROBERTSON MM (1996) D2 be or not to be? Nature Medicine, 2 (10) 1076-1077
IF 28.878

This, although not subject to peer review, is an invited single author publication which is in one of the highest Impact Factor journals internationally (IF 28.878).

ACADEMIC, MISCELLANEOUS & NON-MEDICAL PUBLICATIONS

KATONA CLE and **ROBERTSON MM** (1993) Who makes it in psychiatry: CV predictors of success in training grades. Psychiatric Bulletin 17, 27-29

This is the first of a series of papers which reflects my commitment to both medical and psychiatric education, and academic life.

SHELLEY BP, **ROBERTSON MM** (2005) The neuropsychiatry and multisystem features of the Smith-Magenis syndrome: a review. Journal of Neuropsychiatry and Clinical Neurosciences 17, 91-97 **Cited 2 times in GS IF: 2.304**

I have chosen this as it is a thorough review, but also should be seen in tandem with our paper submitted (Shelley et al 2006) which we believe is the first published case description of a co-occurrence of GTS with SMS. It is important as we suggested that the genetic loci in the deletion interval of chromosome 17p11.2 may be a promising region for containing a gene or genes of aetiological importance in the development of the GTS phenotype, which is as indicated previously, highly complex.

My chosen poems are The Hug (indicating that serious, cancer changes ones life) and the poems in the Postgraduate Medical Journal (detailing my journey through cancer, including having had serious septicaemia as a result of chemotherapy), I have chosen Magical Medical Moments (which is great fun), Sunrise: Durban Beach South Africa 24/2/2006 (showing my love for South Africa) and London (using Cockney rhyming slang about a city in which I have lived since 1978). They also illustrate that both in my life and poetry, I have "moved on" after a cancer journey with 10 months of active treatment. All four photographs submitted are my favourites, and record my almost a year in 1976 sailing on a square rig ship, almost around the world Westwards from Tahiti to Cape Town on a Brigantine, as ship's doctor.

Signed by candidate

Mary May Robertson 8th August 2006

SECTION 3

CURRICULUM VITAE

SECTION 4

LETTERS OF SUPPORT
&
COLLATERAL EVIDENCE

tourette syndrome association, inc.

■ 42-40 bell boulevard suite 205 bayside, new york 11361-2820 tel: 718 224 2999 fax: 718 279 9596 e-mail: ts@tsa-usa.org
1301 k street nw suite 600 east tower washington, dc 20005 tel: 202 408 6443 fax: 202 408 3260 e-mail: tsdc@tsa-usa.org

May 12, 2006

Ms. Adri Winkler
Manager Postgraduate Administration
Room N2. 19. 1
Wernher & Beit Building North
Anzio Road
OBSERVATORY 7925
South Africa

Dear Ms. Winkler:

It is with the greatest pleasure that I write this letter to you in support of Mary M. Robertson, MBChB, MD, DPM, MRCPCH, FRCP, FRCPsych, Emeritus Professor of Neuropsychiatry at UCL, in support of her application for the degree of Dsc (Med). Dr. Robertson is, without question, a true international leader in the fields of Tourette Syndrome research and clinical treatment, as attested to by her many decades of service to the field and the incredible Curriculum Vitae she has compiled, a copy of which I know you have received. Still actively traveling the world today on behalf of, and deeply involved in, Tourette Syndrome science and medicine, her prominence in the field as well as her CV will continue to grow.

Here in the United States, the Tourette Syndrome Association, Inc., founded in 1972, is the only national non-profit organization providing for the education, awareness, and service needs of both medical and allied professionals, as well as patients and the lay public. Additionally, we oversee and fund and international research program concerning the cause of, treatment for, and, hopefully someday, a cure for Tourette Syndrome. I can tell you that Dr. Robertson remains steadfastly involved all aspects of our operation mentioned above. Whenever called upon, she is there to help. She is also a charter Lifetime Member of our Association.

By 1980, with an expanding wealth of knowledge about the disorder and a rising interest among the world's leading scientists and clinicians in it, it became obvious that a gathering of research and clinical experts was needed. The result was the 1st International Scientific Symposium on Tourette Syndrome in 1981 in New York City, and Dr. Robertson was a part of it. This was following by the 2nd, 3rd and 4th symposia, in 1991 in Boston, 1999 in New York and 2004 in Cleveland. Whether as an organizing committee member, international board member, speaker or facilitator, Dr. Robertson played a significant role in each event. I must also add that each of

these symposia became a published stand alone volume of the very prestigious series, "Advances in Neurology," volumes 35, 58, 85 and 99. Additionally, Dr. Robertson was selected as the Keynote Address at our organization's major national conference in 1996 in Burbank, CA.

A premier research body of our organization, commencing in 1985, is The International Consortium for Tourette Syndrome Genetics, a world renowned group composed of thirty elite researchers from around the globe. Dr. Robertson was a founding member of this consortium and remains today a distinguished associate, serving as a Center Principal Investigator as well as an integral part of its Authorship/ Publications Committee. Her contributions are invaluable. Attesting to the quality of this consortia's research and investigative abilities, it was honored by a multi-year, multi-million dollar grant from the National Institutes of Health, the very first time such a consortium as part of a organization such as the Tourette Syndrome Association was so rewarded.

For more than two decades now, the Scientific Advisory Board of our association has recommended promising research projects for annual funding to our Board of Directors. A stringent peer review process by all members of the Science Advisory Board assess each project relative to the needs of our research program and the quality of science it contains. Only a small percentage are accepted for funding and Dr. Robertson's name has been prominent among the recipients. Her variety of investigations has also been outstanding with projects such as "Genetics of Gilles de la Tourette Syndrome," "Kynurenine Metabolism in Gilles de la Tourette Syndrome," "Epidemiology of Tourette Syndrome and Obsessive Compulsive Disorder," "Repetitive Transcranial Magnetic Stimulation in Tourette Syndrome" and "A Longitudinal investigation into PANDAS."

Dr. Robertson is probably the most gifted clinician dealing with Tourette Syndrome in the United Kingdom and we never hesitate recommending her to citizens of that nation who make inquiry's for help to our organization. Her advice relative to treatment in dealing with children and adults with the disorder is sought after by other professionals and regularly finds its way beyond her nation's borders, even here to the US. Her genuine and compassionate manner has a way of relieving the incredible stress and torment experienced on a daily basis by her patients, and her overall diagnosis and care eases their pain and suffering.

Whether its her writings about Tourette Syndrome in books and papers, her addressing audiences of fellow professionals, patients or lay public about the disorder, her clinical treatment of patients, her humanism, her research into the disorder's deepest mysteries or just sitting around and talking Tourette with fellow doctors, scientists and concerned public, Dr. Mary Robertson always is at the top of her game.

Dr. Mary Robertson has devoted a major part of her professional and personal life to helping people touched by Tourette Syndrome while seeking its cause and cure. She has become an international authority on the disorder and a world respected leader in its clinical and scientific fields. When viewed in context as but a part of the absolutely incredible body of work described in her Curriculum Vitae, and demonstrated in daily practice, it's obvious we are witnessing the career of a woman of greatness and one who, I believe, deserves the level of achievement recognized by and honor and accolades associated with the degree of Dsc (Med).

Respectfully submitted,

Signed by candidate

President

tourette syndrome association, inc.

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Ms Adri Winkler,
Postgraduate Administration,
Room N2.19.1, Wernher & Beit Building North,
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Anzio Road,
Observatory,
Cape 7925,
South Africa.

25 July 2006

Dear Ms. Winkler,

I understand Professor Mary May Robertson is applying for a DSc (Med) from the University of Cape Town. I know the degree is granted only rarely to individuals of exceptional merit, with an international reputation, who have published seminal papers in their field over at least two decades. I don't think there is any doubt that she fulfils these criteria.

I have known Mary Robertson for eighteen years, originally as a medical student when she gave me an enduring interest in Tourette syndrome which is how I came to chair this charity, of which she was formerly vice-chair. Her teaching was highly prized by students, then as now as well demonstrated by her prizes including best teacher in the medical school, won not once but twice. In the last two years and now as a neurologist I have been privileged to see patients with her in a jointly run clinic for people with this condition.

Her academic excellence is allied to not only personally providing services to a neglected group of patients but also to inspiring others to follow her lead through enthusiasm, energy and passion. In the face of substantial general psychiatric commitments in the past she developed a very large Tourette syndrome clinic and published widely with international recognition.

In establishing this major body of research on Tourette syndrome in the United Kingdom she has undoubtedly had a significant impact on the current level of knowledge, professional awareness and delivery of care for these patients in this country, and elsewhere. Hers is one of a few names that are internationally known as leaders in research into this area.

She has received an honorary Fellowship of the Royal College of Physicians and honorary Fellowship of the Royal College of Paediatrics and Child Health. I am not sure if the assessors will be familiar with the UK system of postgraduate medical diplomas. As a UK physician, rather than the chair of this charity, I can tell you that both of these are high honours for someone initially from a different specialty, i.e. psychiatry. Membership of each Royal College is usually by examination during specialisation and Fellowship later follows for those doctors active primarily in the appropriate specialty. Professor Robertson was awarded honorary membership of both of these colleges- each one would be honour enough but the combination is highly distinctive, reflecting the breadth of her academic and clinical reputation. Each College subsequently raised her to the Fellowship. This is in addition to her

Fellowship of the Royal College of Psychiatrists which she acquired through the usual route. In simple terms the resulting "letters after her name" including this triple Fellowship are almost certainly unique.

In the year 2000 the Tourette Syndrome (UK) Association made a special award to her in recognition of her contributions, and indeed also for her own clinical care of countless patients. There can be few clinicians held in such high regard by so many patients.

I wish her well in her application for a DSc (Med) degree both personally and on behalf of this charity and its members who are people affected by Tourette Syndrome in the UK. I believe she strongly deserves this scientific distinction.

Yours sincerely,

Signed by candidate

Dr. Jeremy Stern
Chairman

TOURETTE SYNDROME (UK) ASSOCIATION

This

Certificate of Appreciation

is presented by the Board of Trustees to

Professor Mary M Robertson

(a Founder Member and former Vice-Chairman of the Association)

in grateful recognition of her many exceptional contributions
to the clinical care of people with Tourette's syndrome,
internationally recognised research on the condition,
and to the
TOURETTE SYNDROME (UK) ASSOCIATION

Chairman Signed by candidate

General Secretary Signed by candidate

TOURETTE SYNDROME (UK) ASSOCIATION LIMITED

In this, the 20th Anniversary Year

30th October 2000

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Please ask for ext. 396

15 October, 2002

PRIVATE AND CONFIDENTIAL
Professor Mary Robertson,
Professor of Neuropsychiatry,
National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG

Dear Professor Robertson,

I have pleasure in informing you that the Professional and Regional Affairs Board propose to recommend to the College that you should be admitted to its Membership without examination under Bye-Law 117. This is the means by which the College can admit to its Membership a select number of individuals in recognition of their exceptionally distinguished contributions in the field of medicine.

If you are willing to accept this nomination there are certain formalities. Enclosed are a record sheet and the Form of Faith, and I should be grateful if you would complete these and return them to Clive Constable, Head of Professional Affairs here at the College. As a Member of the College you would be eligible for election to the Fellowship and you may attend all College Lectures and have the use of the Library. However, we hope that you will also become a Collegiate Member so that you may have a close association with the College and receive a regular circular about our activities. Details on this are enclosed, together with a Direct Debit Mandate form to be completed. The current subscription is £125 per annum.

If you accept nomination, we hope you will be able to attend the ceremony for formal admission of new Members, to be held on **Wednesday 15 January 2003,** at 4.45 pm (you would need to arrive here for about 4.15 pm). This is followed by a lecture, and dinner at which you would be seated on the President's table as our guest (along with a guest of your own).

I very much hope you will accept this election as well as accepting the invitation to the admission ceremony and dinner. Perhaps you could let me know whether or not that would be possible? If you have any queries whatsoever, please feel free to contact Clive Constable on the above extension or email address.

Yours sincerely

Signed by candidate

Professor Ian Gilmore
Registrar

Royal College of Physicians
Setting higher medical standards

11 St. Andrews Place
Regent's Park, London NW1 4LE

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Textphone +44(0) 20 7486 5687
Facsimile +44(0) 20 7487 5218

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Professional Affairs

Telephone extension 396
Direct facsimile 020 7224 2032
clive.constable@rcplondon.ac.uk

17 July 2006

Ref. CC/CMP/Letters 170706 Winkler

Ms Adri Winkler
Manager Postgraduate Administration
Faculty of Health Sciences
University of Cape Town
Room N2.19.1, Wernher & Beit Building North
Anzio Road
OBSERVATORY
Cape 7925
South Africa

Dear Ms Winkler

Re: Professor Mary May Robertson

Please accept this letter as confirmation that Professor Mary Robertson is a Fellow of this College.

Professor Robertson was initially made a Member of the College, in 2002, having been elected under our Bye-law 117. This enables the College to confer Membership on doctors who are not Physicians, but who have contributed to Medicine and the work of Physicians in a way which the College wishes to honour. Membership awarded in this way should not be confused with Membership obtained through examination under the MRCP(UK), and so is not a statement of clinical ability. However, Membership under Bye-law 117 is not commonly awarded, and it is rare for a Psychiatrist to be honoured in this way.

Since being made a Member of the College, Professor Robertson has subsequently been elected as a Fellow, in 2004. Although a College of Physicians we cover the interests of 30 specialties and subspecialties in the UK. Psychiatry is not one of these and it is comparatively rare for a Psychiatrist to be elected to Fellowship.

I hope that this information is of help to you, but if you require any clarification please do let me know.

Best wishes

Signed by candidate

Clive Constable
Director of Professional Affairs

Citation read at the awards ceremony for membership of the Royal College of Physicians March 2003

Mary Robertson is Professor in Neuropsychiatry at University College London and consultant neuropsychiatrist at Queen Square.

She graduated from the University of Cape Town but has spent most of her professional life in Great Britain.

She has played a major role in developing the understanding of Gilles de la Tourette syndrome in all its psychobiological aspects: brain function, genetics, cognition, phenomenology and treatment. It used to be regarded as an exotic rarity but largely through Professor Robertson's work we know that it occurs, to some degree, in some 1-2% of all children and to an even greater extent in children attending special schools. Her work for children has been recognized by our sister College of Paediatrics and Child Health who have also elected her a member.

As a syndrome Tourettes has links to many other important conditions, such as obsessive compulsive disorder, and these conditions are all now, better understood because of her researches. It is a particularly exciting area, throwing light on the dark no man's land between brain and mind. Professor Robertson is a leading international expert in all aspects of the condition and those who wish for further knowledge may read Brain of the year 2000, to which she has contributed as single author a review of 37 pages, much of it derived from the over a hundred original peer review research papers for which she has been responsible.

She is co-chairman of the European Society for the study of Tourettes and is medical adviser to national organisations devoted to Tourettes in the United Kingdom, Ireland, Canada, Germany and Italy. The World Health Organisation has made use of her expert knowledge and she is also on a United Nations Panel of experts.

She has also carried out important work in the recognition and treatment of depression, particularly in the setting of epilepsy which was the subject of her MD thesis and many subsequent publications.

It would seem that she could spare little time from the laboratory and the word processor but she somehow manages to do much else. She is in very great demand as an organiser and lecturer and she

Signed by candidate

finds it difficult to say no to what for her is an evangelical mission. She has given many invited lectures in over 20 different countries.

She remains an active clinician running a ward for acutely ill psychiatric patients as well as a huge outpatient clinic for patients with Tourette Syndrome. When it comes to getting resources appropriate to the complex needs of some of her patients she is a tigress, as many a mauled manager has discovered

She is a great teacher and for a number of years students at UCL medical school have voted her best teacher in Psychiatry and one year in any subject in the whole school. She has co-authored and edited five books including a popular psychiatric textbook already translated into five languages. She is also adept at getting students involved in research projects and has been midwife to a number of student research publications. The Deanery turns to her by preference when a student needs help for psychiatric problems.

She is of course very active in the Royal College of Psychiatrists. She is on the Council, is Sub-Dean and takes a special interest in education. She chairs the group that advances the interests of both women patients and professionals in psychiatry and is active in promoting flexible training issues.

In her spare time she is an avid and knowledgeable fan of opera and a fair weather sailor- in contrast to the time that she raced across the Atlantic from the Cape to Rio in a 37 foot yacht and then completed the circum-navigation of the world in a square-rigged Brigantine from Tahiti back to the Cape - but that is another story.

She is a most exceptional person and should be a very contributory member of the College. Although busy, it is well known that if you want a job done, ask a busy person.

It gives me great pleasure to present Professor Mary Robertson to our College.

Signed by candidate

Dr Oscar Hill FRCP, FRCPsych

PATRON
HRH The Princess Royal

Royal College of Paediatrics and Child Health

50 Hallam Street, London W1W 6DE

Telephone: (020) 7 307 5600 Fax: (020) 7 307 5601 E-mail: enquiries@rcpch.ac.uk

2nd August 2006

Ms Adri Winckler
Manager Postgraduate Administration
Faculty of Health Sciences
University of Cape Town
Room N2.19.1
Wernher & Beit Building North
Anzio Road
OBSERVATORY
Cape 7925
South Africa

Dear Ms Winckler

Re: Application for the award of the DSc (Med) degree – Professor Mary May Robertson

I understand that Professor Robertson is applying for a DSc (Med). She was elected a Member and then Fellow (2006) of The Royal College of Paediatrics and Child Health.

This is extremely rare, and has only in fact, happened with 10 individuals of 9 ½ thousand College Members/Fellows.

I wish her well in her application for the DSc (Med).

Yours sincerely

Signed by candidate

Sask' ttignon
Membership Supervisor

Royal College of Paediatrics and Child Health

We the undersigned by virtue of the power invested in our offices by the authority of Her Majesty and Her Privy Council certify that

Dr Mary May Robertson

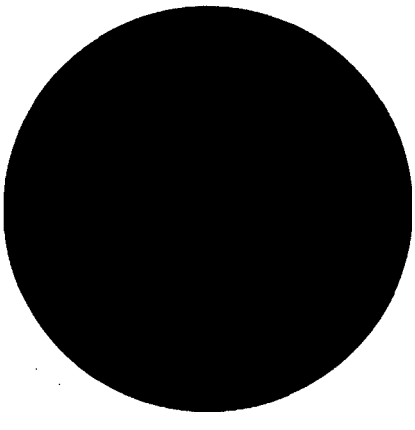
has been elected to Membership of the Royal College of Paediatrics and Child Health according to Bye Law 5 (i)(b) in recognition of their medical work with children and promotion of child health.

Dated this day of 1st November 2001

President Signed by candidate

Vice President Signed by candidate

Honorary Secretary Signed by candidate



YEARBOOK OF INTERNATIONAL ORGANIZATIONS
RUE WASHINGTON 40 - 1050 BRUXELLES - BELGIUM
T. (32 2) 640 18 08. FAX 643 61 99.
E-mail: yearbook@uia.be Website: http://www.uia.org

IMPORTANT

eadline/Date limite: 18 July/juillet 2005 **Ref: #D-D9278**

European Society for Tourette Syndrome,
Prof Mary Robertson,
UCL Dept Psychiatry Behavioural Sciences,
Gower Street,
London WC1E 6BT,
UK.

ROOF TO CORRECT FOR THE 43rd EDITION (2006/2007)
PRINT VERSION, CD-ROM AND ONLINE

/e should like to improve and update the information we distribute on your organization. We do try to ıeck websites if resources allow but, to avoid error, please review the following text:
correct this proof of your organization's description and add any new information; AND/OR send us elevant **brochures, statutes or other documents** (in English, if possible) from which we may extract etails to improve the description;
mark, on the **membership checklist** (on the back of the information page), those countries in which our organization has members, or which may themselves be members, AND/OR send us your own **list of nembers**.
your organization has its own **logo**, we should welcome the opportunity to include it with your rofile in the online version of the Yearbook. You can send it attached to an e-mail to logos@uia.be, or n a diskette / CD.

LEASE QUOTE THE ABOVE REFERENCE IN YOUR REPLY

---

uropean Society for Tourette Syndrome (ESTS)

ontact Prof Mary Robertson, UCL Dept of Psychiatry and Behavioural Sciences, Gower Street, London /C1E 6BT, UK.

ounded Nov 2000, Copenhagen. Also referred to as *European Society for the Study of Tourette yndrome*.

lembers Membership countries not specified.

lo recent information received

LEASE SEND US ANY OTHER RELEVANT INFORMATION:

Do you have electronic services (Fax, E-mail or Website)?
What are the **aims** of your organization?
How is your organization **structured**?
What are the official and/or working **languages**?
How many **staff** members are there (please specify full or part-time, paid or voluntary)?
How is your organization **financed**? What is the annual budget?
If your organization has been granted **consultative status** by an intergovernmental body, we shall nsert a mention when we receive the official list.
Please indicate any **intergovernmental bodies** with which your organization has formal contacts.
With which **international non-governmental bodies** has your organization formal contacts?
Please give details of major **activities** - projects, programmes, plans, etc. Note: we do not include ctivities of a transient nature.
Does your organization hold international **events** (conferences, seminars, etc)? Please give details or both past and future events.

U.S. Department of Justice

Matthew H. Mead
United States Attorney
District of Wyoming

REPLY TO: CHEYENNE

Post Office Box 668
Cheyenne, WY 82003-0668
307-772-2124
FAX/307-772-2123

Post Office Box 1056
Casper, WY 82601
307-261-5434
FAX/307-261-5471

933 West Main
Lander, WY 82520
307-332-8195
FAX/307-332-7104

October 1, 2002

Letter e-mailed to: m.robertson@ucl.ac.uk

Professor Mary M. Robertson
UCL Dept. of Psychiatry & Behavioural Sciences
Wolfson Building
48 Riding House Street
London, ENGLAND W1N 8AA

Re: *United States of America v.*
USAtty-WY-2002R00080; USDC-WY-02CR080J

Dear Professor Robertson:

My name is Lee Pico and I am a federal prosecutor with the United States Department of Justice in Wyoming . I am currently prosecuting an individual who threatened to kill the President, who to this point is claiming Tourette's syndrome as a defense. Attorney Michael H. Reese of Cheyenne, Wyoming is defending Mr. Mr. Reese and I are attempting to find an expert who would be acceptable to both sides.

In our efforts to find an expert in that field, I was given your name by Kenneth Rickler, M.D., at the Behavioral Neurology, Butler Hospital. As I understand it, you have been an expert witness in the past for other proceedings and may consider using your expertise in future proceedings. I have outlined the facts of the case below to help you in your consideration of this matter. I appreciate your time in reviewing the case.

The Defendant is He is an adult male, approximately 25 years old, who was formerly in the armed services. At the time of the incident, was traveling through Casper, Wyoming, on his way to Kansas where his parents live. Mr. stopped at a pawn shop/Western Union to make arrangements for his mother to wire him money to complete his trip home. According to one witness, while on the phone said, "Mother don't worry, I won't use anthrax. I'll use a pipe bomb or something . . . what can they do, arrest me?" A little later when President Bush was on the television, Mr. , who had been sitting, abruptly stood up and pointed at the television saying, "I'd like to blow his head off." later stated, "somebody should blow his brains out." A second witness indicated that , prior to calling his mother, spoke with an unidentified person on the phone and became upset when the person to whom he was

talking supposedly hung up on him. After being hung up on, stated directly to the second witness, "Have you ever wanted to hurt a friend? I mean really bad." The witness also noted that later, while pointing at President Bush on the television, stated, "I would aim for the back of his head, low and left of center."

Attached is a report from Dr. , a pediatric neurologist from , who diagnosed Mr. with Tourette's when he was 11 years old.

Please contact me at your earliest convenience to discuss the matter. You can reach me at 1-800-836-5801. If that is busy, feel free to call me collect at (307) 772-2124. I look forward to hearing from you.

Sincerely,

MATTHEW H. MEAD
United States Attorney

Signed by candidate

Assistant United States Attorney

FLP:cme
c: Michael H. Reese
Wiederspahn & Reese, P.C.
211 West 19th Street, Suite 300
Cheyenne, WY 82001

N:\CEichelberg\ obertson letter.wpd

04-05 Feedback, Module: Tics and Tourette's								
Date	Lecturer	No of forms	Objectives achieved	Amount learned	Teaching Aids	Overall Assessment	Overall mean	Some Comments
17/11/2005	Prof. M Robertson	21	5	5	5	5	5	V. interesting, precise and inspiring, pitched at right level for medical students, interesting addition to core lectures
06/04/2005	Prof. M Robertson	8	5	5	5	5	5	Really good fun
06/07/2005	Prof. M Robertson	10	5	5	5	5	5	Fascinating
Overall mean							**5**	

Robertson M Home, 12:05 16/06/2006, Student Feedback

To: Robertson M Home
From: Deana D'Souza <rejuuts@ucl.ac.uk>
Subject: Student Feedback
Cc: rejuuts
Bcc:
Attached: N:\MyWork\WordDocuments\04-05\Feedback CTP 04 05\04 05 CTP feedback\BC\Tics.doc;

Dear Prof Robertson,

At the Departmental UG Teaching committee meeting which took place on 14 September 2005, student feedback for 04-05 was reviewed. The feedback was remarkably good and the Chair Dr Gill Livingston congratulated all teachers involved in core teaching.

The **minimum** overall mean score **is 1** and the **maximum is 5** out of 5.

Attached is the feedback for the module that you taught.

Best wishes
Deana

Deana D'Souza
Undergraduate Administrator
Department of Mental Health Sciences
Royal Free & University College Medical School
UCL, Wolfson Building, 48 Riding House Street
London W1W 7EY
Tel: 020 7679 9460
Fax: 020 7679 9426
d.dsouza@ucl.ac.uk

CLINICAL NEUROSCIENCES

FEEDBACK FORM

Please ring the numbers which best represent your view.

Date: 6/7/05 Title of Teaching Session TICS + TOURETTE

Teacher: PROF MARY ROBERTSON

Venue: _____

1. Objectives: The objectives were all achieved

Strongly disagree 1 2 3 4 (5) Strongly agree

2. Amount Learned: I learned a lot from this teaching session.

Strongly disagree 1 2 3 4 (5) Strongly agree

3. Teaching Aids: The visual material, handouts and/or videos used were useful and of high quality

Strongly disagree 1 2 3 4 (5) Strongly agree

4. Overall Assessment: I would rate this teaching session very highly.

Strongly disagree 1 2 3 4 (5) Strongly agree

Please write any specific comments below

EXCELLENT! $\times 1000 \times 10^6 \times 10^9$.

Thank you for completing this form

CLINICAL NEUROSCIENCES

FEEDBACK FORM

Please ring the numbers which best represent your view.

Date: 28/06/06 Title of Teaching Session TICs & Tourettes

Teacher: Prof Mary Robertson

Venue: Rm 315

1. **Objectives:** The objectives were all achieved

Strongly disagree 1 2 3 4 (5) Strongly agree

2. **Amount Learned:** I learned a lot from this teaching session.

Strongly disagree 1 2 3 4 (5) Strongly agree

3. **Teaching Aids:** The visual material, handouts and/or videos used were useful and of high quality

Strongly disagree 1 2 3 4 (5) Strongly agree

4. **Overall Assessment:** I would rate this teaching session very highly.

Strongly disagree 1 2 3 4 (5) Strongly agree

Please write any specific comments below

Excellent talk + videos!

Thank you for completing this form

CLINICAL NEUROSCIENCES

FEEDBACK FORM

Please ring the numbers which best represent your view.

Date: 28/6/06 Title of Teaching Session Tourettes

Teacher: Mary Robertson

Venue: Bloomsbury

1. Objectives: The objectives were all achieved

Strongly disagree 1 2 3 4 (5) Strongly agree

2. Amount Learned: I learned a lot from this teaching session.

Strongly disagree 1 2 3 4 (5) Strongly agree

3. Teaching Aids: The visual material, handouts and/or videos used were useful and of high quality

Strongly disagree 1 2 3 4 (5) Strongly agree

4. Overall Assessment: I would rate this teaching session very highly.

Strongly disagree 1 2 3 4 (5) Strongly agree

Please write any specific comments below

Fantastic - thank you very much!

Thank you for completing this form

CLINICAL NEUROSCIENCES

FEEDBACK FORM

Please ring the numbers which best represent your view.

Date: 28/06/06 Title of Teaching Session Tics & Tourette

Teacher: Prof Roberlson

Venue: Rm 315 Wolfson Bldg

1. Objectives: The objectives were all achieved

Strongly disagree 1 2 3 4 (5) Strongly agree

2. Amount Learned: I learned a lot from this teaching session.

Strongly disagree 1 2 3 4 (5) Strongly agree

3. Teaching Aids: The visual material, handouts and/or videos used were useful and of high quality

Strongly disagree 1 2 3 4 (5) Strongly agree

4. Overall Assessment: I would rate this teaching session very highly.

Strongly disagree 1 2 3 4 (5) Strongly agree

Please write any specific comments below

excellent. engaging, entertaining. an inspiration esp like the videos.

Thank you for completing this form

CLINICAL NEUROSCIENCES

FEEDBACK FORM

Please ring the numbers which best represent your view.

Date: 28/6/06 Title of Teaching Session Histhaviothy

Teacher: PROF MARY ROBERTSON

Venue: Wolfson building

1. Objectives: The objectives were all achieved

Strongly disagree 1 2 3 4 (5) Strongly agree

2. Amount Learned: I learned a lot from this teaching session.

Strongly disagree 1 2 3 4 (5) Strongly agree

3. Teaching Aids: The visual material, handouts and/or videos used were useful and of high quality

Strongly disagree 1 2 3 4 (5) Strongly agree

4. Overall Assessment: I would rate this teaching session very highly.

Strongly disagree 1 2 3 4 (5) Strongly agree

Please write any specific comments below

Best lecture I've had this year, thoroughly engaging.

Thank you for completing this form

CLINICAL NEUROSCIENCES

FEEDBACK FORM

Please ring the numbers which best represent your view.

Date: 28/6/06 Title of Teaching Session Tics & Tourettes

Teacher: Prof Robertson

Venue: Room 315, Wolfson Building

1. Objectives: The objectives were all achieved

Strongly disagree 1 2 3 4 (5) Strongly agree

2. Amount Learned: I learned a lot from this teaching session.

Strongly disagree 1 2 3 4 (5) Strongly agree

3. Teaching Aids: The visual material, handouts and/or videos used were useful and of high quality

Strongly disagree 1 2 3 4 (5) Strongly agree

4. Overall Assessment: I would rate this teaching session very highly.

Strongly disagree 1 2 3 4 (5) Strongly agree

Please write any specific comments below

Really fantastic. Arranged to go to clinic on 3/7/06 as a result.

Thank you for completing this form

SECTION 5

RESEARCH BAPTISM – THE EARLY YEARS

Reprinted from Inyanga: 1971: 40:32-42.

Attitudes to Religion

A Survey amongst Senior Medical Students at the University of Cape Town

by Mary Robertson (VI)

Winner of the 1971 Mike Farquharson Memorial Essay Competition as adjudicated by Prof. E. B. Dowdle and Dr. D. Bosman

Today we live in a world society bound together by economic interdependence, rapid communication and travel. It is therefore less and less possible for us to isolate ourselves from the encounter with other nations, cultures and so, religions. There is an increased meeting with persons of other faiths not only through international business, governmental and cultural affairs, but also in daily life.

This meeting of persons of different faiths results in deep affinities and deep divergences being discovered. It can raise radical questions concerning one's own faith, whatever this may be, and deeper understanding may result in significant changes in a person's interpretation of his faith. For instance, the impact of Western culture has led to profound modifications of Buddhism and Hinduism: and it has been argued that the impact of Western culture upon Eastern societies will soon be followed by an equally profound influence of Eastern cultures upon the West.[15]

For these reasons it is important that one should subject one's attitude to religion to constant reappraisal and at the same time try to understand the attitudes of those whose beliefs are different.

The purpose of this essay is to report on a survey of attitudes to religion conducted amongst senior medical students at the University of Cape Town; to compare these results with other surveys done; to draw conclusions from these data; and, using these conclusions, to discuss briefly some attitudes to religion.

Material and Methods

Questionnaires were handed out to 4th, 5th and 6th year medical students before various lectures during April 1971, and were collected on either the same or the following day. Of the 305 questionnaires which were returned, five were discarded because of gross inconsistency and/or inadequacy. This left a total of 300, out of a possible 429. This was a 70 per cent overall response.

The individual class responses were:—

Table 1

6th year	79 per cent
5th year	71 per cent
4th year	62 per cent
Mean	70 per cent

Possible explanations for the number (30 per cent) of students who failed to return questionnaires are:—

(a) Absence from the lectures at which the questionnaires were handed out.
(b) Lack of motivation.
(c) Reluctance to co-operate.

The students were required to fill in their year of study and sex, but no other personal details such as name or age.

The questionnaire consisted of four sections. Each student was asked to answer all questions in Section 1, and then the questions in one of the other three sections depending on whether he answered "Yes", "No" or "Uncertain" when asked in Section

1 whether he believed in a God/Creator/ Supreme Being.

Male students formed 84 per cent of the sample, and female students 16 per cent.

To some questions, the answers were simply "yes" or "no". In others, the students replying did not write their opinions, but under each topic checked one or more of several alternative opinions with which they felt themselves to be most closely in agreement. Obviously this method does not provide a true scale of measurement, since the alternative items are not given a value in proportion to the intensity with which they are felt. The results obtained, however, can be turned readily into a study of the percentages of students who favour each of the opinions contained in the questionnaire — a recognised method of study.[6]

Reliability and Significance

This is not a random sample, but as 70 per cent of the population under consideration are included it may be considered to be representative (although the 30 per cent who did not hand in questionnaires may have affected the results as they represent to a certain extent a selected group).

The results were computerised in order to assess their statistical signficance, if any.

Results and Discussion

For the purposes of the discussion the three groups will be designated Believers, Non-Believers and Uncertains.

Let us begin the discussion with replies to the pivotal question of the study: "Do you believe in a God?"

Table 2

Total No.	%	*Answer*
180	60	Yes
51	17	No
69	23	Uncertain
300	100	Total

It is interesting to compare these results with those of a survey[8] done on non-medical male students at William's College in the Eastern United States, in 1967. The question put to these students was: "Do you feel that you require some form of religious orientation or belief in order to achieve a fully mature philosophy of life?" and the results were: Yes 65 per cent, No 22 per cent and Doubtful 13 per cent.

About three-fifths in both cases either believe in a God as in the present survey, or feel the need for religious orientation or belief, as in the William's College survey. A similar survey was done at William's College in 1948, the results to the same question being: Yes, 85 per cent, No 5 per cent and Doubtful 10 per cent.[7] The interesting fact that emerges is that those feeling need for religious orientation or belief, however they define it, were in a far more significant majority nineteen years earlier.

There are two points which need consideration. Firstly, why do the majority of these students either believe in a God or need religious orientation in their lives, and as the converse, why do others not believe? Secondly, why has the number needing religious orientation decreased at William's College by 20 per cent in the past nineteen years?

Column "a" of Table 3 shows the reasons advanced by Believers for their belief in a God. The vast majority reported that they believed either as a philosophy of life or to provide meaning for life, or both. Only a very small number believed because of the promise of Heaven, while a negligible number believed because of the threat of hell or no life after death.

Columns "b" and "c" show the reasons advanced by Non-Believers and Uncertains for Believers belief in a God.

It is immediately obvious that there is a great difference between the reasons advanced by Believers for their belief in a God

Table 3

Reasons for belief in a God	*a*	*b*	*c*
Threat of hell	0 (0)	24 (10·5)	9 (6)
Threat of no life after death	1 (·5)	45 (20)	13 (9)
As a philosophy of life	42 (40)	41 (18)	35 (23)
Provides a meaning for life	57 (54)	53 (23)	49 (32)
Promise of heaven	5 (5)	24 (10·5)	17 (11)
Habit, never considered otherwise	1 (·5)	41 (18)	28 (19)
	106 (100)	228 (100)	151 (100)

and the reasons for belief attributed to them by Non-Believers and Uncertains. Whereas Believers believed primarily to give meaning to life or as a philosophy of life, Non-Believers and Uncertains thought that Believers had very different reasons.

Firstly, more than one reason was attributed by Non-Believers (2.3 reasons) and by Uncertains (1.5 reasons) to Believers, whereas the Believers themselves only chose one alternative. The percentages choosing each of these alternatives were scaled down by these factors to allow for this discrepancy (figures in parentheses). Secondly, a considerable proportion of Non-Believers thought that Believers believed either because of the promise of heaven (10.5 per cent), and the more negative alternatives, viz. the threat of hell (10.5 per cent), the threat of no life after death (20 per cent) and habit (18 per cent), none of which were favoured by the Believers themselves. Thirdly, the same applies to the Uncertains to a large extent, with the exception that a smaller percentage attributed the threat of hell or fear of no life after death to the Believers.

There is a significant difference between the reasons given for their belief in a God by Believers and the reasons attributed to them by Non-Believers and Uncertains.

The argument that habit is an important reason for continued belief in God, as is claimed by 41 per cent of Non-Believers and 28 per cent of Uncertains, is refuted to a large extent in Table 4, which shows the extent to which Believers have questioned their faiths.

Table 4

Believers who have	%
Never doubted their faiths	6
Questioned their faith occasionally	35
Questioned their faith frequently ...	51
No answer	8
	100

The vast majority of such students (86 per cent) have questioned their faiths either occasionally or frequently, and so habit is probably not a major factor in continued belief.

A large proportion of Non-Believers and Uncertains considered also that life after death was important amongst Believers' reasons for their faiths. In fact, however, as many as 48 per cent of all Believers (and fully 77 per cent of believing Jews) are uncertain about or do not believe in the existence of a life after death. (The fact that only 23 per cent of believing Jews believe in a life after death may be partially explained by the fact that the question of immortality, which figures prominently in other religions, is not dealt with in the Torah — the entire code of Jewish law found in the first five books of Moses.[13])

An interesting point is that 14 per cent of students who were uncertain of the existence of God nevertheless believed in a life after death.

Why is it that Non-Believers do not believe? They were not asked this question directly, but some idea of their reasons can be obtained from their replies to other questions. Firstly, 27 per cent felt that it was intellectually unacceptable to believe. Further evidence about their reasons for not believing can be obtained from the answers they gave when asked what factors would make them more inclined to believe in God. (Table 5.)

Table 5

Factors which would make Non-Believers (Column a) and Uncertains (Column b) more inclined to believe in a God.

	"a"	"b"
One universal faith/religion	12%	29%
Belief without committing oneself to a religion ...	8	33
If God was not anthropomorphised	12	26
If God was a general, not a personal God	14	20
If religion was less formal	8	29
None of the above	61	16
No answer	8	16

We must accept that other alternatives could have been given, in which case the percentage of students who answered "none of the above" might have been less. For example, 6 per cent of Non-Believers wrote in that they would be more inclined to believe if the existence of God could be proved. Nevertheless it is significant that the majority of Non-Believers chose none of the alternatives given. Thirdly, we can get some idea of Non-Believers' attitudes from their replies to the question "Why do you think Believers believe in God?" (Table 3). A large proportion felt that Believers believed out of habit (41 per cent), because of the threat of hell (24 per cent) or for fear of no life after death (45 per cent); that these reasons were perhaps rather cynical may be indicated by the fact that they did not correlate with the reasons given by Believers.

The Freudian criticism of the idea of God is interesting. He holds that inasmuch as God is the father, the believer is the child. The believer claims, like a child, that there must be a father who rescues him, who watches and punishes him, who is pleased by obedience, flattered by praise and angry because of disobedience. Fromm,[7] a Neo-Freudian, holds that the majority of people have not overcome the infantile stage in their personal development and hence adhere to this concept of God. This may help to explain why some feel it is intellectually not acceptable to believe. However, Fromm also points out that there are people who have overcome this concept of religion. The truly religious person, he holds, if he follows the essence of the monotheistic idea, does not pray for anything, does not expect anything from God; he does not love God as a child loves his father; he has acquired the humility of sensing his limitations to the degree of knowing that he knows nothing about God. God becomes to him a symbol of the totality of that for which man is striving, the realm of the spiritual world, of love, truth and justice.

Some Non-Believers said that they would be more inclined to believe in God if there was proof of his existence. Various "proofs" have been advanced: it is for the individual to decide on their validity. These include the ontological proof, derived from man's idea of God; the cosmological proof which holds that for a universe as orderly as ours there must be a creator; the teleological proof holding that this creator must have intelligence and purpose; the pragmatic proof which holds that belief in God brings good results; and

the mystical proof. Degrees of religious faith, as with all faith, range from high to low. Perhaps the highest is the unshakable certainty of the mystic that his immediate experience, which is for him the equivalent of sensory knowledge, confirms the existence of God.[1]

Some students (12 per cent and 26 per cent) answered that they would be more inclined to believe if God was not anthropomorphised. Others (14 per cent and 20 per cent) would be more inclined to believe if God was a general and not a personal God.

Buddhism dispenses with both these issues in that Nirvana, the highest destiny of the human spirit according to Buddhism, "is not defined as personal creator", but sufficiently close to the concept of God as Godhead to warrant the name in this sense. Nirvana is permanent, stable, ageless, power, happiness, "the real Truth and the supreme Reality". It is the Good, the place of unassailable safety, the supreme goal, "the eternal, hidden and incomprehensible Peace".[14]

Why has the number of religiously orientated people at William's College fallen by 20 per cent in the past nineteen years? This tendency pertains not only to William's College, as it corresponds with the change among better educated and more affluent people in the American national population. The main explanations for it are thus probably broad and general rather than specific and local. It seems reasonable to assume that at least some of the changes and thus explanations can be applied to a group concerned in a survey such as the present one, as it also includes people of a higher education at university.

One explanation may be that, with the advancement of knowledge, psychology and science, the "need" for religion is recognised as being more of a need than before: those who rely on scientific explanations for phenomena would not only no longer need God as the explanation for many things, but would require scientific proof thereof, and, being unable to obtain it, would deny the concept altogether. Other explanations which have been forwarded[9] are that there probably exists a relationship between the lessening of religious commitment and the increased protest activity among students. This hypothesis is supported by a curve showing American student activism which was exactly the inverse of the traditional religious commitments curve. Greater individuality and autonomy of students, as shown by the greater number reacting to religious beliefs taught them, is another likely explanation, since research shows an association between individual autonomy and liberal religious orientation.

In general Uncertains were found to be intermediate in three attitudes between Believers and Non-Believers, as one would expect. For example, their replies to the question "What factors would make you more inclined to believe in a God?" (Table 5) showed that as a group they are far readier to believe than Non-Believers.

No significant differences were demonstrated between the sexes, as shown in Table 6.

Table 6

	Men	*Women*
Yes	59	64
No	18	14
Uncertain	23	22
	100	100

The women students showed only a slightly higher degree of religious orientation than did the men students, agreeing with one study done in America.[5] In most studies, however, it has been the rule to find women more interested in religion, however defined. They are more often the church-goers, more

often devout in their personal lives, and more often the family mentors in matters of religion. One must guard against exaggerating this finding though, as the measured differences between the sexes seldom exceed 20 per cent.[1]

Table 7 shows the periods of life during which Non-Believers and Uncertains adopted their present attitudes.

Table 7

Period of Life	*Non-Believers*	*Uncertain*
Always been so	20%	13%
At high school	43	48
During A.C.F. training	4	1
At university	31	34
No reply	2	4
	100	100

It is interesting to note that a seemingly higher percentage of students adopted their present attitudes at high school. Allport[1] holds that on the average, the early and middle twenties are the least religious period of life, as it is then that the alienation from the parental codes has become complete and then, too, that youth feels most secure in pursuing his life ambition. He continues that in the thirties, however, people often decide to follow the parental code. This explanation would agree with most research on religion and the life cycle which shows that orthodox beliefs and practices tend to decrease starting at about the age of 16, agreeing with the present survey, and continuing until about 30, whereafter they increase again.[9]

An interesting point is to consider and compare attendance of religious services. Table 8 shows the frequency of attendance of religious services by Believers and by Non-Believers at the stage when they were still attending services.

Table 8

	Believers	*Non-Believers*
Every week	22%	29%
Most weeks	19	25
Occasionally	42	14
On important religious occasions only ...	10	12
Never	7	10
No reply	—	10
	100	100

Slightly higher percentages of Non-Believers attended services every or most weeks, while many more Believers attend services occasionally only.

The reasons for attendance at religious services are shown in Table 9.

Table 9

Reason for attendance at religious services	*Believers*	*Non-Believers*
Wanting to	66%	29%
Sense of obligation ...	22	28
Duty in the religion ...	8	24
Habit	2	18
Social occasion	3	10

There is a significant difference between the reasons given for attendance at religious services by the two groups. The majority of Believers attend because they want to,

Table 10

	Believers	*Non-Believers*	*Uncertain*
Did receive parental encouragement	70%	47%	52%
Did not receive parental encouragement ...	30%	53%	48%

Table 11

	Number	*Total (a) % of Sample*	*Believers (b) % of Total*	*Non-Believers (c) % of Total*	*Uncertain (d) % of Total*
Christian	173	58	61	16	23
Anglican	— 81	— 27	— 51	— 22	— 27
Methodist	— 28	— 10	— 61	— 14	— 25
D.R.C.	— 14	— 5	— 86	— 14	— 0
Presbyterian	— 25	— 8	— 72	— 8	— 20
Roman Catholic ...	— 25	— 8	— 72	— 8	— 20
Jewish	75	25	47	25	28
Islamic	9	3	89	0	11
Hindu	4	1	50	0	50
Non-Sectarian	15	5	100	0	0
Other	16	5	88	0	12
Never belonged ...	8	3	0	50	50
	300	100			

whereas the majority of Non-Believers used to attend for largely negative reasons, i.e. out of a sense of obligation, duty or because of habit.

Whether or not the individual continues to adhere to the religion in which he was brought up seems to depend to a large extent on the extent of parental encouragement of religious interest. This is shown by Table 10.

Table 11 shows the percentage of students who at one time or another have belonged to the various different religions (Column a), as well as a breakdown of each group into those who still believe (Column b), and those who are now Non-Believers (Column c) or Uncertains (Column d).

The most significant facts from the table are that 86 per cent of D.R.C., 89 per cent of Islam, 88 per cent of other and 100 per cent Non-Sectarians still adhere to their religion. (Other includes, Baptist, Lutheran, Moravian, Church of Christ and New Apostolic faiths.)

The results correlate well with whether or not the individual was taught and encouraged by his parents with regard to a particular religion. (Table 12.)

Table 12

Religion	%
Islam	100
Other	88
D.R.C.	86
Roman Catholic	80
Presbyterian	72
Methodist	68
Jews	68
Non-Sectarian	60
Hindu	50
Anglicans	41

The religions in which parental influence was most frequent, i.e. Islam, "Others" which as we have seen include conservative Protestant denominations, and D.R.C., had the greatest percentage of continued adherence.

Conversely a religion in which parental influence appears to have been least frequent, notably Anglicanism, had a lower percentage of continued adherence.

It is also interesting to note that 87 per cent of Believers in the survey intend to instruct their children in religion. Another point of note is that 100 per cent of Islamic students received parental encouragement in their religion, and 100 per cent of those who still adhere to the faith intend to instruct their children in religion. Both of these reasons may serve to explain the astounding fact that in some areas where Islam and Christianity are competing for converts, Islam is gaining at a rate of 10 : 1,[14 15] as among the Christians in the survey, only 79 per cent were encouraged in and only 89 per cent tend to instruct religion.

Not only is parental encouragement important, but so is authoritarianism and rigidity in the various religions. Consider, for instance, the top four religions in Table 12.

One of the distinctive things about Islam is not its ideal but the detailed proposals it sets forth for achieving it. When its innumerable laws are supplemented with only slightly less authoritative Hadith or tradition based on what Mohammed did or said informally, we are not surprised to find Islam the most socially vocal of man's enduring religions. The Muslim faith calls the individual to establish a very explicit kind of social order. Faith, politics, religion and society are inseparable in Islam.[14] The Roman Catholic Church, too, exercises to some extent an authoritarian power over its members.[10] The Baptists have always regarded the problem of authority and power as of fundamental concern. Some modern Baptists insist that the minister has no special authority even in his own congregation, but according to one sociologist, "the Baptists have a genius for obscuring the problem of authority by means of a labyrinth of theological doctrines".[11] The D.R.C. also has a strict way of teaching, as at the National Conference in 1939, of the Federasie van Afrikaanse Kultuurvereniginge, the Institute of Christian-National Education (I.C.N.E.) was organised "to ensure the continual propagation and furtherance of the historically-developed ideal of Christian and National education and for ensuring that the general lines of policy laid down . . . (by the Institute) . . . should find acceptance in a systematic way".[12]

Although many observers have noted recently that college students are turning away from traditional religion, this does not mean that interest in religion is waning, as at the same time enrolment in religious courses has risen on many campuses in recent years.[9] What amount of interest in religion is shown in the present survey? Seventy-two per cent of the students have religious discussions occasionally, 18 per cent often, 9 per cent never and 1 per cent did not reply. Table 13 shows the amount of reading about religions done by students.

Table 13

	% of Students
Reading about the individual's own religion	34
Fair coverage of religious literature	34
Extensive reading generally	5
One particular religion besides that of the individual	4
No religious reading at all	24

The results also showed that 23 per cent of the Believers belonged to a religious society at university, while 77 per cent did not. Of those who belonged, about a third appeared to be active members, the rest only attending functions occasionally or when they were particularly interesting ones.

The question of prayer was interesting. Table 14 shows the replies to the question "Do you believe in the power of prayer?" given by Believers and Uncertains.

Table 14

	Believers	*Uncertains*
Belief in the power of prayer	76%	38%
No belief in this power	16	43
No reply	8	19
	100	100

Table 15 demonstrates the benefits derived from and attributes given to prayer by Believers and Uncertains.

Table 15

	Believers	*Uncertains*
Achieves direct communication with God ...	57%	4%
Enriches spiritual being	51	31
Release of tensions and guilt feelings	43	92
Clarification of ideas for oneself	42	54
None of the above ...	4	8

The two striking features are firstly that 57 per cent of Believers believe that prayer achieves direct communication with God, whereas only 4 per cent of Uncertains hold this view; secondly, by far the majority of Uncertains who believe in the power of prayer hold that it releases tensions and guilt feelings.

It is interesting to compare results with another survey,[4] in which the youths who prayed fairly regularly commented on their reasons for doing so: 33 per cent replied that "God" listens and answers, 27 per cent that prayer helps in time of trouble, 18 per cent that one feels better afterward, 11 per cent answered that it remained one of one's obligations to man and society, while 4 per cent admitted that habit was an important reason. It would seem therefore that prayer has a twofold action: a natural function concerning the person alone (the main choices of Uncertains but also chosen by Believers) and a supernatural function involving God too (chosen almost exclusively by Believers).

When questioned about a life after death, Believers and Uncertains replied as is shown in Table 16.

Table 16

Belief in a life after death	% *Believers*	% *Uncertains*
Yes	52	14
No	14	64
Uncertain	34	22
	100	100

It is interesting to bear in mind, once again, that various aspects of life after death were attributed to Believers by Non-Believers and Uncertains as to their reasons for believing in a God. Yet, 14 per cent and 22 per cent of Uncertains do believe in or are uncertain of the existence of a life after death, while only 52 per cent of Believers believe in its existence. Of Believers, 75 per cent of those who do believe in a life after death think that atheists can participate, while the remainder do not. More than 95 per cent of the same group believe that people of other religions can participate/go to heaven.

The assessment of tolerance was made using the replies to questions concerning monopoly on God, pity of other people and whether or not Believers held that people of other faiths and atheists could go to heaven: 91 per cent of Believers did not feel that their religion had a monopoly on God, while 6 per cent did; 3 per cent failed to answer the question. A fair percentage of each group pitied the fanatically religious, the figures being: Believers 35 per cent, Non-Believers 45 per cent and Uncertains 40 per cent. 16 per cent of Believers pitied atheists,

9 per cent pitied agnostics, while 4 per cent pitied people of other faiths. 4 per cent of Non-Believers pitied those who simply believe, while the remaining students in all three groups pitied no one. In general we can see that the students are fairly intolerant of the fanatically religious. Believers, on the whole, are tolerant of other faiths. Although about 5 per cent do not seem so. They are less tolerant of atheists, however, and the most tolerant of all seem to be Uncertains, as they pity neither Believers nor Atheists, only the fanatically religious. A question regarding Ecumenism was included on all answer sheets, but as it is primarily a Christian concept, only the results of Christian students will be shown. (Table 17.)

Table 17

In favour of Ecumenism	53%
Not in favour of Ecumenism ...	19
No reply	28

It must be noted that on many of the answer sheets of those who did not reply, remarks indicated that the question was not understood. An argument against the Christian Ecumenical movement is that it is beginning to seem "increasingly parochial", and this may account for some of the negative replies. The author[15] also states, however, that a true ecumenical movement in the sense of comprising the whole inhabited world (oikoumene) with its plurality of cultures and religions, may well start in the last third of this century.

Finally, students were asked whether they would object to marrying someone whose religious attitudes differed from their own. Believers were asked if their marriage partners would have to belong to the same religion as themselves and whether they would object or not if their partners were atheistic. The results were as shown in Table 18.

In general just under half of the Believers stipulated that their partner must be of the same religion and that they would object if their partner was atheistic. It is interesting to compare these figures with the answers given by Non-Believers when asked if they would object if their partners believed (No 84 per cent, Yes 16 per cent). These results seemed to indicate that Non-Believers had a higher degree of tolerance in this matter. Similarly, 84 per cent of Uncertains would not object if their partners were religious and 80 per cent would not object if their partners were atheistic: again this shows a higher degree of tolerance.

Table 18

	Yes	*No*	*No reply*
Partner must be of same religion ...	41%	56%	3%
Objection if partner was atheistic ...	44%	53%	3%

These differences in tolerance probably reflect the fact that for Believers religion is an important element in their lives, whereas for Non-Believers and Uncertains, by definition, religion is of minor importance. An interesting point is that it has been shown that the change towards a common religious affiliation is most frequently towards the affiliation of the spouse having the greater amount of education.[2]

Conclusion

This survey does not pretend to be a sophisticated statistical analysis of current religious attitudes amongst senior medical students. Its object has been to assess attitudes on a broad scale and to further interest and enquiry. In the words of Kahlil Gibran: ". . . your ears thirst for the sound of your heart's knowledge. You would know in words that which you have always known in thought".[8]

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Malpitte Madness

A REPORT OF TEN CASES

M. M. ROBERTSON, J. E. MORLEY

SUMMARY

We report 10 cases of malpitte (*Datura*) psychosis in teenagers ranging from 14 to 15 years of age. Patients showed derangement of liver function tests and/or cholinesterase activity. Management is discussed with special reference to phenothiazines being contra-indicated. The psychosocial problems associated with the recent epidemic of malpitte abuse are discussed and the disturbed family backgrounds of our patients are given.

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The use of malpitte or 'mad seeds' (*Datura stramonium*) by schoolchildren has reached noticeable proportions in South Africa. The abuse of malpitte leads to the problem of an acute psychiatric emergency presenting to the medical practitioner or casualty department.

The distribution of the *Datura* species is worldwide. These plants have been recognised as poisons and hallucinogens since antiquity, having been used in religious and magic rites. Among the Chibchas of South America, the plant was given to wives and slaves to stupefy them prior to their being buried alive during the funerals of their masters.[1] Lewin[2] believes that *Datura stramonium* was the plant accidentally eaten by Mark Anthony's troops on their retreat from Partha in AD 38, producing in them stupor, insanity, and in some cases, death. The Algonquin Indians of California use the plant to help solve the problem of the adolescent search for identity, while the Jivaro tribes give *Datura* seeds to unmanageable children in the hope that the spirits of their ancestors may come to admonish them.[3]

The earliest specific mention of *Datura stramonium* was by the Arab physician Avicenna in the 11th century; he was aware of its intoxicating as well as medicinal potentials.[4]

In more recent times, there occurred a case of mass poisoning of British troops by *Datura stramonium* during the American Revolution.[3] The soldiers gathered some 'James-Town weed' for a salad, which turned them into 'natural fools' for several days. It was reported that some sat 'stark naked in a corner, like monkeys grinning and making mows (faces) at them', while others 'would have wallow'd in their own excrements, if they had not been prevented'.

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The Xhosa of South Africa sometimes bind the leaf around the head for the relief of headache, and this practice has been found on occasion to result in sweating, in addition to marked and persistent dilatation of one pupil. The Xhosa and Fingo both use the leaf to blister the skin over inflammations where there is no open sore.[5]

In South Africa there have been reports of scattered episodes of accidental poisoning, including the death of a 16-year-old schoolboy in King William's Town.[6] Poisonings in military units, orphanages, schools, hostels, mine compounds for Black workers, and in circumstances where contaminated flour has been used in making home-made bread, have been reported.[5]

Datura stramonium contains, as the psychoactive compounds, hyoscyamine as the chief alkaloid, with scopolamine and atropine occurring in lesser concentrations. In South Africa, poisoning is more common by eating the seed, and less common by eating the leaf.

We report 7 cases of *Datura stramonium* poisoning treated at the Johannesburg General Hospital, in addition to 3 cases which presented to the Crisis Clinic, Johannesburg, over the past few months. We will discuss the psychosocial problems associated with the recent epidemic of malpitte abuse.

CASE REPORTS

All 7 patients treated at the Johannesburg General Hospital for malpitte intoxication were teenagers, their ages being 14 or 15 years. Their clinical presentations were similar in that they were all agitated, aggressive and disorientated. They presented with fatuous affect, and laughed inappropriately, as well as talking to themselves in a confused, illogical manner. Other clinical observations are shown in Table I. The clinical features lasted for as long as 36 hours in some patients.

Case 1

A 14-year-old girl, at the time of taking malpitte, was being cared for in a place of safety. She and a group of friends, all of whom were admitted to hospital, had taken the malpitte. She came from a family of 9 children, who had parents who gave them regular hidings, even up to the age of 14 years. The patient had a history of impulsive behaviour, of having run away from home several times, and had failed the previous year at school. Her general picture was one of an emotionally deprived child in an excessively large family. In her diagnosis, the possibility of psychopathic traits was mentioned.

TABLE I. CLINICAL SIGNS OF MALPITTE POISONING

Case	Pulse rate beats/min	Fixed dilated pupils	Reflexes	Temp. °C	Hallucinations	Others
1	136	+	Normal	36,0	V + A	Dry mouth
2	108	+	—	36,5	A	—
3	110	+	Very brisk mild clonus	35,6	V + A	Dry mouth
4	104	+	Brisk			Incontinent
5	120	+	Brisk	37,3	A	Dry mouth
6	104	+	—	37,2	A	—
7	124	+	Brisk	36,7	A	Incontinent,
				37,1	V + A	Dry mouth

V = visual; A = auditory; + = present.

Case 2

A 15-year-old boy was also being cared for at a place of safety, and took the malpitte with three friends. He and his sister had been orphaned as babies, and had spent their lives in the care of foster-parents. His school career was problematical, and after his stay at the place of safety, he was to be sent to an industrial school.

Case 3

This patient was a 14-year-old girl of good intelligence. She, however, experienced a very unhappy childhood because her parents fought incessantly. Her parents eventually separated when she was 11 years old, and she remained in the care of her father and his girlfriend. Her mother moved to Europe and there was very little postal communication between them, although the patient would have liked more. She had neurotic traits as a child, and abused various drugs, including dagga and LSD. She appeared to be a very disturbed girl, having twice taken overdoses and having required psychiatric treatment. She was diagnosed as having a hysterical personality and longer-term psychiatric treatment was refused by the patient and her father, both of whom had very poor insight.

Case 4

This patient was a 15-year-old boy, who had taken malpitte on his own and was being cared for in a place of safety. The patient, the second of 8 children, had been in an orphanage for 7 years because of domestic problems. He returned home to a poor environment for a short period, but as a result of an inspection visit by welfare officers, who found the family in need of care, 6 children were removed to a place of safety. Long-term psychiatric treatment was suggested.

Case 5

This patient was a 14-year-old intelligent boy, from a good school and well-to-do home, who, with a friend, took malpitte 'for kicks'. It was the first time he had abused a drug and there appeared to be no important domestic or environmental problems.

Case 6

This patient was a 14-year-old boy, cared for at a place of safety. The parents had separated when he was young, and his mother was at that time living in Europe. The boy and siblings absconded from home on various occasions, and there was also a history of petty theft. Because of this and the domestic environment, the boys were placed under care.

Case 7

A 15-year-girl had been in an orphanage for many years because her parents did not support her. She played truant from the orphanage and was therefore placed in the care of Child Welfare who admitted her to a place of safety. She never adapted to the life there however, and her behaviour was so aggressive that she was sent to an industrial school for more vigilant safekeeping.

Cases 8, 9 and 10

These patients presented at the Crisis Clinic in Johannesburg. They were males whose ages ranged from 16 to 18 years. Their clinical pictures were similar, with visual, auditory and tactile hallucinations. They were confused and avoided tactile contact. They exhibited ataxia, fatuous affect, tachycardia, dry mouth, fixed dilated pupils and sensitivity to light.

Two patients were 16 years old and were friends. The effect of the malpitte wore off after a few hours and they became more lucid. At follow-up the next evening they were found to be from middle-class immigrant families who lived in isolated communities. They often played truant from school but had not abused drugs before. The mother of one boy was an alcoholic, but otherwise there appeared to be no serious pathology in either family. The two boys took the malpitte in the veld

TABLE II. LIVER FUNCTIONS IN CASES OF MALPITTE POISONING

Case	Alkaline phosphatase	LDH	SGOT	γ-globulins	Albumin	Cholinesterase: Admission	Cholinesterase: Day 1	Cholinesterase: Day 2	Cholinesterase: Day 3
1	N	↑	↑	↑	↓	57	81	95	
2	↑	↑	↑	↑	↓	—	81	97	100
3	N	N	N	↑	↓	66	81		
4	—	—	—	—	—	81	81		
5	↑	↑	↑	↓	N	—	100		
6	↑	↑	↑	—	—	—	97	100	100
7	N	N	N	↑	↓	97	100		

because they wanted 'a kick' and the malpitte were easily available.

The third case was an 18-year-old male who remained so psychotic during the period at Crisis Clinic that he was referred to hospital accompanied by a volunteer worker.

MANAGEMENT

Since fatalities have been reported from malpitte poisoning, and because of the possibility of liver damage (see Table II), we recommend that cases should be admitted to hospital for at least 18 hours' observation.

Treatment of malpitte poisoning is mainly symptomatic with sedation playing a key role. The patient may be sedated with clothiapine (Etomine), diazepam (Valium) or barbiturates. Phenothiazines, which are used for many hallucinatory states, should theoretically be avoided owing to their action and atropine-like side-effects,[4] which may potentiate the action of *Datura*.

Miotic eyedrops, such as pilocarpine, may be used if photophobia from pupillary dilatation is a prominent complaint. Gastric lavage may be performed even if a period longer than the normal gastric emptying time has elapsed since ingestion. Some authors use physostigmine in addition to sedation, but we did not find this necessary.

A complication not seen in our series, which may produce a problem, is hyperpyrexia due to inhibition of sweating and urinary retention. Such hyperpyrexia can be treated by maintaining a low environmental temperature by using cold baths, sponges or fans, while urinary retention is treated by catheterisation. Massive doses of malpitte can produce convulsions and respiratory depression which may require artificial ventilation.

After-care is important, and we found that some of our cases necessitated either long-term outpatient or inpatient treatment, depending on their underlying problems.

DISCUSSION

In South Africa today, the problem of drug abuse among teenagers is common. The background psychological factors include curiosity, boredom, rebellion against taboos and authority, escapism and peer group acceptance. In addition, malpitte are readily available at no cost, are fast-acting and pleasurable in effect, except for the frequent frightening 'come-down' which follows the acute phase. This may account for the fact that Phoenix House, the registered drug rehabilitation centre in Johannesburg, reports no simple cases of malpitte abuse, most subjects having abused LSD, dagga, sedatives or tranquillisers as well.

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Crouzon's Disease (Craniofacial Dysostosis)

A NEUROPSYCHIATRIC PRESENTATION

M. M. ROBERTSON, H. T. REYNOLDS

SUMMARY

A sporadic case of Crouzon's disease which did not exhibit mental retardation, is presented. The aetiology, diagnosis and treatment of the syndrome are summarised.

S. Afr. Med. J., **49**, 7 (1975).

Crouzon's syndrome, first described by Crouzon in 1912, is one of the craniofacial dysostoses, characterised by premature closing of one or more cranial sutures.

Dodge *et al.*[9] reviewed and illustrated the diagnostic criteria for the syndrome originally listed by Crouzon as being: (*i*) synostosis of one or more of the cranial sutures resulting in skull deformity; (*ii*) prognathism; (*iii*) parrot-beaked nose; (*iv*) exophthalmos plus external strabismus; and (*v*) hereditary occurrence.

The facial appearance of the patient is characteristic, and Bertelsen[2] states that perhaps the one feature which best characterises the disease is maxillary hypoplasia, while Fleischer[11] holds that this is the most constant morphological aberration in the syndrome. Many authors[2,14,18,21] agree that it is this hypoplastic maxilla which results in the relative mandibular prognathism.

The exophthalmos is due to shallow orbits.[14,18,30] Other features commonly associated with the syndrome are a drooping of the lower lip,[14,18] hypertelorism[14,21,31] and psittacorhina,[18] as well as acrocephaly — an abnormally high or pointed head.[30] The skull's ultimate shape is determined by which cranial suture closes first, and by how many sutures close and at what age.[21]

Visual difficulties result from the optic manifestations which, in addition to the exophthalmos, are: optic nerve damage or atrophy (seen in 80%),[2,14,18,21] spontaneous subluxation of an eye,[14] nystagmus,[14,18,21] high myopia, exposure keratitis[2] and narrow optic foramina.[30]

The radiological features of the skull are characteristic, showing hypoplastic maxillae,[2,18,31] brachycephaly, frontal bossing[14] or prominent frontal bones,[18] ridging of the sagittal suture,[14,18] increased digital markings, which are almost always present,[2,14] scaphocephaly[2,26] and shallow orbits.[14,18,21,30]

Auricular manifestations have been reported in association with the syndrome,[21] for example, auditory canal atresia, anomalies of the middle ear, low-slung and abnormally formed ears.

The oral manifestations of Crouzon's disease are: hypoplastic maxilla,[2,14,18,21] V-shaped palatal arch instead of the normal U-shaped arch, dental malocclusion, partial clefting of the palate,[14] high-arched palate, partial adontia and unerupted teeth.[21] The tongue has been described as being enlarged in some cases.[9]

Hydrocephalus may be associated with the disorder.[2,14,21,30] Fishman *et al.*[10] reported 14 patients in whom hydrocephalus was associated with craniosynostosis. The hydrocephalus, which appeared to be an associated anomaly rather than a direct consequence of the craniosynostosis, is most often communicating, but stenosis and atresia of the aqueduct may be present. A recent survey of craniosynostosis in the Amish by Cross and Spitz[9] revealed one case of communicating hydrocephalus in a patient with Crouzon's disease.

Mental retardation is often associated with the syndrome.[14,30]

CASE REPORT

A 28-year-old female was referred to the psychiatric ward of the Johannesburg General Hospital by social workers on 27 May 1974. She presented with a right-sided headache, but her main complaints, which had increased over the previous 2 months, were of anxiety attacks with closing up of the throat and chest, difficulty in breathing, numbness of the limbs, palpitations and shaking, followed by fatigue and headaches. The attacks lasted for about one and a half hours. She had never experienced a loss of consciousness, incontinence or injury with any of these attacks. She also complained of being depressed, and attributed this to her father's recent death, and the fact that she did not like her work or her home environment. She lives in a hostel for the blind.

History

She was born on 15 January 1946, the last of 6 children, an instrument delivery to a 46-year-old woman and a 61-year-old father. She was noted to be disfigured at birth. Her milestones were normal and, in fact, she walked at the age of 9 months. The gradual onset of blindness occurred at the age of 2 years, and the patient underwent cranial surgery at 5 years of age, presumably to relieve pressure. She was medically supervised for the next 4 years. She therefore started her schooling late, at the age of 9 years, attending a school for the blind. She coped adequately and never failed. However, at the age of 20 years, in 1966, when she was in Form II, she had a nervous breakdown which necessitated her leaving school. While at school she had taken a 3-year course in weaving, which she completed in 21 months. At this time, 1968, she once again had a nervous breakdown, spent 15 months at home with her parents and consulted a psychiatrist. Each time her symptoms were those of palpitations, tightness in the chest and lack of self-confidence.

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Date received: 9 August 1974.

She took a course as a telephone operator, but found the strain too much. In 1968 she began cane work at the institute for the blind, where she has been ever since. At her place of work she met a semi-blind man with whom she became friendly, and afterwards they became engaged. They are planning to get married.

Her family history was non-contributory.

Previous personality. The patient had spent a reasonably happy childhood, but had never made friends easily, and did not enjoy or join in group activities. As a child she had nightmares, but no other neurotic traits. There was evidence of obsessionality and antisocialism throughout her life. Since her first nervous breakdown in 1966 she has suffered from headaches, developed a poor appetite and experienced difficulty both in falling asleep and in early morning wakening. Apart from her Crouzon's syndrome she had had no serious illnesses.

Physical Examination

The patient presented as a neat woman of average build. She has a high, narrow, pointed head with flattening of the forehead and a scar from previous surgery, a prominent parrot-beaked nose and marked hypoplasia of the maxilla. Classical oral manifestations included a short upper lip, a high V-shaped, arched, partially-cleft palate, gross dental malocclusion and relative mandibular prognathism (Figs 1 and 2).

The ocular signs deserve special mention. Exophthalmos was present and the exophthalmometric measurements were 27 mm for both eyes, which is clearly above normal (normal 15 - 18 mm). The pupils were eccentric. The eyes showed a divergent squint, both horizontal and rotatory nystagmus and limitation of movement. Both eyes were myopic, the left being more severe (R : 1,50/ $-$ 2,00 $\times$ 90°; L : $-$6,00/ $-$1,50 $\times$ 90°). There was markedly decreased visual acuity in both eyes, and the fixation was poor. The interpupillary distance was increased, being 65 mm. There were flecks of opacification on the lens which was flatter than normal. Fundoscopy revealed bilateral marked optic atrophy and a deposition of pigment in the region of the maculae.

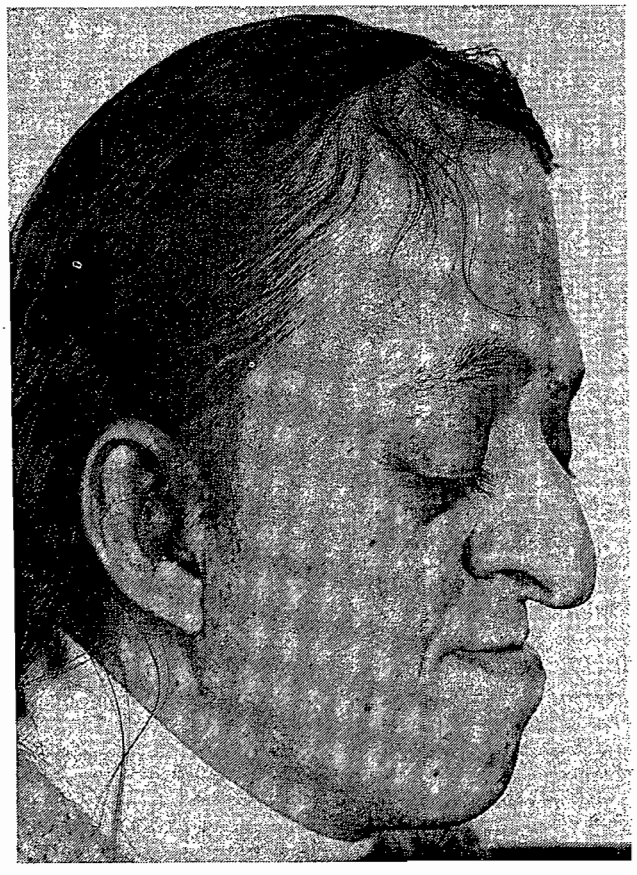

Fig. 1. Lateral view. Note flattening of the forehead, parrot-beaked nose, hypoplastic maxilla and relative mandibular prognathism as well as the shortened upper lip.

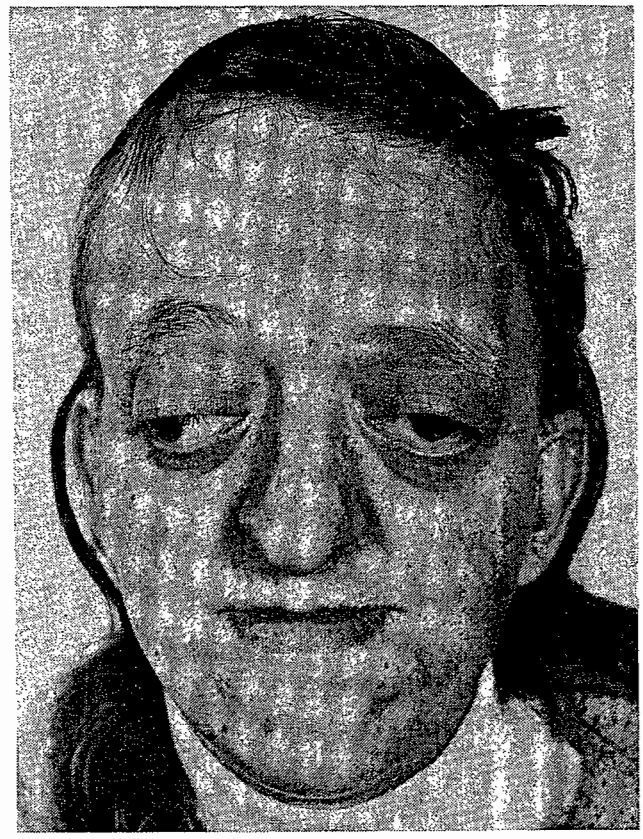

Fig. 2. Anterior view. Note high pointed head, exophthalmus and divergent squint.

The dorsal spine showed fairly marked scoliosis, convex to the right. The blood pressure, pulse rate and the rest of the physical examination were normal. There was no syndactyly, and her ears were normal.

Mental Examination

The patient was fully conscious and orientated but extremely anxious, agitated and aggressive. Her affect was labile and depressed, but not suicidal. Conversation and thought were logical, relevant and coherent. Intelligence was assessed as being low average.

She admitted to various phobias of height, water and enclosed spaces. A history of impulsive behaviour and temper tantrums was elicited. No other evidence of temporal lobe epilepsy or other ictal phenomena was elicited or observed, nor indications of hallucinations, delusions or thought disorder. Paranoid features emerged, in that she felt people stared at her, ostracised her and treated her as abnormal, but these feelings are probably realistic.

Wechsler Adult Intelligence Scale:[39] Owing to the patient's blindness, only a verbal estimate of intellectual functioning could be obtained. The verbal IQ was 90, which places her within the 'dull normal' range. The distribution of scores is uneven. Least points were scored on the general information subtest, which possibly suggests an impoverished relationship with the environment. This is consistent with her blindness. She attempted to compensate by intellectualisation, as found in the high level of abstraction in the similarities subtest, and with elaborate descriptive definitions in the vocabulary subtest.

Qualitative assessment: The patient was anxious and tended to over-elaborate. The responses suggested a suspicious, rigid, moralistic and often aggressive attitude to her environment.

Special Investigations

Full blood count and ESR, urea and electrolytes, rapid plasma reagin, thyroid functions, glucose, liver function tests, and cholesterol were all normal, as was her ECG. There was a pressure of 135 mm water in the cerebrospinal fluid, but the biochemical and morphological studies were normal.

An X-ray examination was made of her skull on the anteroposterior view. Marked asymmetry was noted, the right hemicranium being larger. There were large bone defects on the right frontal, parietal and temporal bones (from previous surgery). Both brachycephaly and acrocephaly were seen. Increased digital markings were noted on the left parietofrontal area. The optic foramina appeared small on both sides, with rather dense walls (Fig. 3). The lateral plates showed, in addition, towering of the frontal region of the skull, shallow orbits, and a clearly hypoplastic maxilla with relative mandibular prognathism (Fig. 4).

The electro-encephalogram was abnormal owing to the presence of paroxysmal sharp wave and spike discharges arising in leads from the right temporal region, where phase reversals indicative of focal electrical disturbance were also present. Background activity was dysrhythmic, of low voltage and β activity was present in all leads. These features suggested focal cortical dysfunction arising in the right temporal region.

Chromosomal studies showed the patient to be 46,XX, with no abnormalities.

Diagnosis and Treatment

A diagnosis was made of Crouzon's syndrome and reactive depression with temporal lobe dysfunction.

The patient was treated with propranolol (Inderal) 20 mg *t.d.s.*, maprotiline HCl (Ludiomil) 25 mg *t.d.s.* and supportive psychotherapy. She responded well enough to be discharged to outpatients after 2 weeks on this therapy, which was supplemented with carbamazepine (Tegretol).

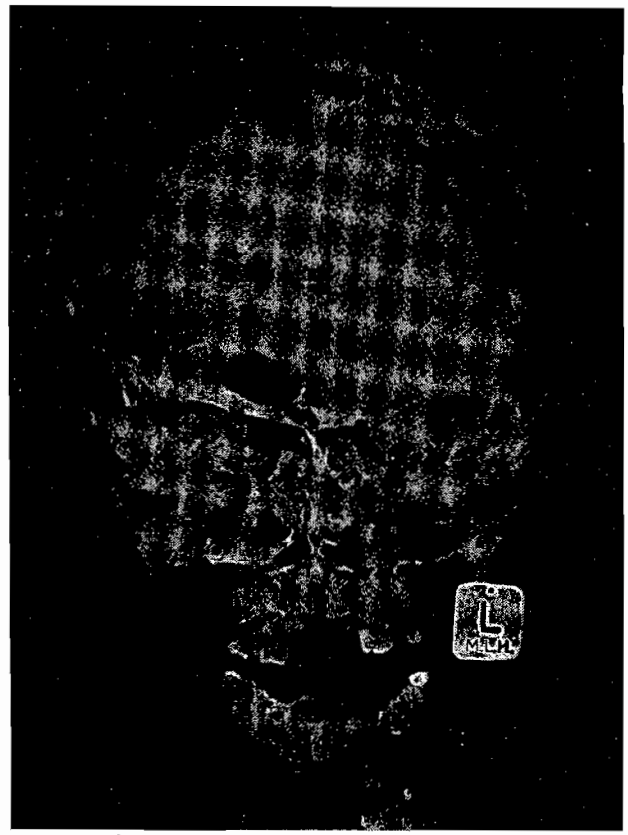

Fig. 3. Anteroposterior view. Note the larger right hemicranium showing defects of previous surgery, increased digital markings and the small optical foramina with dense walls.

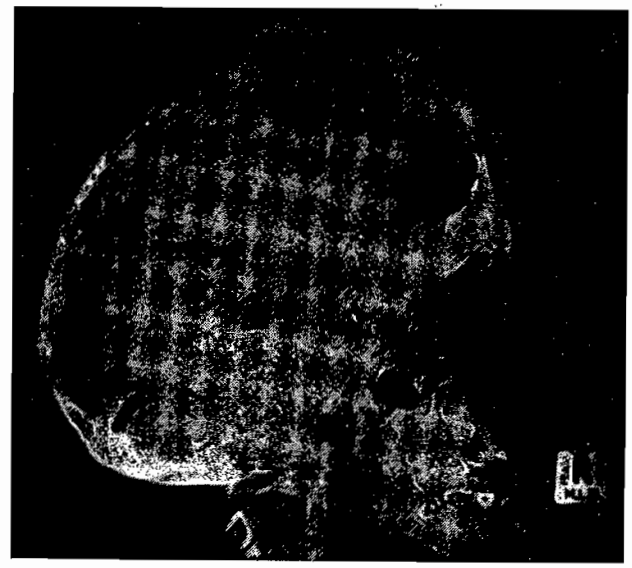

Fig. 4. Lateral view. Note towering frontal region of the skull, shallow orbits, hypoplastic maxilla with the relative prognathism of the mandibula.

DISCUSSION

Aetiology and Genetics of Crouzon's Syndrome

Some authors cite heredity as being one of the essential features of Crouzon's disease. Crouzon himself initially believed that the disease was familial and hereditary, but later changed his original assertion. There is much evidence of the disease being familial. Kushner *et al.*[21] described 3 families in which 2 or more members of the immediate family were affected by the disease. A family reported by Vulliamy and Normandale[32] illustrates how a family can recognise and even accept such an unusual appearance as this cranial and facial abnormality, since it did not compromise the average lifespan and did not result in much disability. Schiller[29] reported considerable variations in 4 generations of a family in which, probably incidentally, the oldest affected persons were the least deformed and the youngest the most. Flippen[12] showed that this disease can be an expression of a heterozygous, dominant trait. Most authors suggest that the disease is autosomally dominant,[30,31] but Gorlin and Sedano[14] suggest that it is autosomally dominant without complete penetrance.

Apparently considerable variation exists in the expression of the dominant gene for craniofacial dysostoses. For instance, sporadic cases with disfiguring cranial and facial abnormalities can readily be diagnosed, but cases that resemble mildly affected members of the family, particularly when normal functions are maintained, may not be so obvious. Flippen[12] mentioned recessive determination as a theoretical consideration. Juberg and Chambers[18] presented a case in which they concluded that the typical findings of the disorder in 2 siblings were probably genetically determined by a single autosomal recessive gene.

More recently, chromosomes have been found to be normal in those children who have inherited this defect from their parents.[5] Sporadic cases without a hereditary background do occur, and have been described.[5,7,18,31] These cases may represent a new mutation.[18,23]

The aetiology of premature closure of cranial sutures is unknown. A faulty development of the blastomal mesenchyme which is destined to form the sutures was postulated by Park and Powers,[24] and is a plausible explanation. Fleischer[11] estimates that the disturbance takes place at about the seventh week of embryogenesis.

Experimentally the condition of craniodysostosis has been produced by mechanical trauma to the sutural area[22] and by giving large amounts of vitamin D to pregnant rabbits.[33]

Some authors have found abnormal serotonin biochemistry in various syndromes, which include mental retardation as one of their manifestations.[25,26]

Differential Diagnosis

The 'frog-like' appearance of patients with Crouzon's disease resembles those with Apert's syndrome[30] (acrocephaly, associated with hypertelorism and syndactyly), and also the Rubinstein-Taybi syndrome.[27] Kushner *et al.*[21] even went so far as to suggest that Apert's, Crouzon's and Rubinstein-Taybi syndromes could be various manifestations of the same genetic disease.

Other craniofacial dysostoses, such as the Russell-Silver syndrome,[16] must be excluded, as should other syndromes comprising both mental retardation and osteofacial anomalies.[4,17,19,20,28] A classification with a brief description of cranial abnormalities clearly separated Crouzon's disease from other dysostoses of the cranial bones.[26] Disorders in which ocular defects present in association with mental retardation must also be excluded.[8,22]

Treatment

The threefold **surgical therapy** for Crouzon's disease is directed towards the prevention of constriction of the brain's growth, prevention of increased intracranial pressure, and improvement of the facial appearance.[21] Craniectomy is advocated in some cases and may be repeated up to 3 times.[1]

Psychiatric awareness and availability of treatment are important, as illustrated by the case presented.

Genetic counselling is of importance to both parents and patients. If a child with Crouzon's disease is born to parents who show no signs whatever of the disorder, risk to subsequent siblings is probably low — perhaps 1 in 30.[31]

CONCLUSION

A sporadic case of Crouzon's disease was presented. There appears to be a correlation between advanced parental age and the occurrence of the disease. The most important feature is the absence of mental defect — to what extent this was due to early surgery deserves consideration. In addition, reactive depression and temporal lobe dysfunction were diagnosed. Sterilisation was recommended, since the expectancy of recurrence of Crouzon's disease is 1 in 2.

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Briewerubriek : Correspondence

Die menings gelug in die Briewerubriek van die Tydskrif *is nie noodwendig dié van die Mediese Vereniging van Suid-Afrika nie.*—Redakteur.

The views expressed in the Correspondence published in the Journal *are not necessarily those of the Medical Association of South Africa.*—Editor.

SICK UTOPIA

To the Editor: During the third quarter of 1974 I was locum tenens at the general hospital in the Seychelle Islands. The patient population seen by me consisted mainly of local Seychellois, a mixture of East African, Indian and Caucasian races. The following are some of my more interesting and important observations.

Hypertension is prevalent. In over 700 patients presenting at my outpatient clinic, which was equivalent to a general practice, 18% were hypertensive. Hypertension was diagnosed on a diastolic pressure of over 100 mmHg, and in most cases multiple readings were taken on various visits. Bearing in mind that between 10 and 15% of patients were children between the ages of 2 and 15 years, who attended the clinic primarily for worm treatment, the incidence of hypertension among adults rises to well over 20% of patients. Of the hypertensive patients, 76% were symptomatic, 69% were females, 43% were obese and 36% admitted to being nervous or anxious.

Unlike westernised populations, only 6% of the affected patients were professional or skilled people, the other 94% being manual labourers or unskilled workers.

Asthma was a common finding. Many patients had had their first attack as early as at the age of 2 months. More cases presented during the South East Monsoon period, when most allergic conditions occur. Some authorities have suggested childhood infestation with helminths as a predisposing factor in the aetiology, but in the present series, equal numbers of patients had and had not received regular worm treatment such as piperazine during their lives. Only a few patients had signs of infection such as a temperature or lung parenchymal pathology. Of the patients seen, 85% had a positive family history, no sex difference was found, and there was no positive correlation with anxiety. It would therefore appear that most of the patients had a primarily allergic aetiology.

For a so-called Utopian island, the incidence of mental illness was surprisingly high. A factor which may contribute to this seemingly high incidence is that only a select number of patients are institutionalised, because many patients are kept by their families at home, while their medical treatment is handled on an outpatient basis. Many schizophrenic patients were seen. A great many patients with anxiety neurosis were seen, many of whom presented with somatic conversion symptoms, of which pain down the whole of one side of the body was the commonest. Mongolism, epilepsy and specifically temporal lobe epilepsy were common.

Venereal disease is common on the islands. Cases of primary, secondary and tertiary syphilis were seen, in addition to gonorrhoea, lymphogranuloma venereum, and *Trichomonas vaginalis* infection.

The discovery of arcus senilis was very often incidental, and, in addition, many young patients had arcus juvenilis, with no other evidence of disease.

Alcoholism too, was common. There is a high consumption of beer but toddy or calou, an alcoholic beverage which is the fermented sap of the coconut palm tree, is also popular.

Worm infestation was one of the most common conditions seen, including parasites such as helminths, *Giardia*, and hookworm. Hookworm is probably the most common cause of anaemia in children.

As expected, amoebic dysentery or amoebic hepatitis were seen fairly often. Similarly high incidences of tonsillitis, upper respiratory tract infections and dyspepsia were also seen.

There are numerous avenues of research that present themselves. Venereal disease, because it is so common compared with our society (despite the 'silent epidemic') fascinated me particularly, as did the mental illnesses, hypertension and asthma.

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Briewerubriek : Correspondence

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MARITAL DISCORD IN FEMALE PSYCHIATRIC PATIENTS

To the Editor: While working in the Psychiatry Department of the Johannesburg General Hospital I noticed the extremely high incidence of marital discord in psychiatric inpatients. I therefore decided to investigate this fact further and to determine whether a similar situation existed in patients with organic disease and, if so, whether any statistically significant difference could be proved. The following results are the essentials of this study.

Three hundred female inpatients treated at the Johannesburg General Hospital were included in this study. All patients, apart from being matched for age and sex, were of the same racial and socio-economic groups. The study group consisted of 100 consecutive inpatients in the female psychiatric ward, whose diagnoses were predominantly personality problems and neurotic reactions, or both. As control subjects, 2 groups of 100 inpatients were interviewed in the medical and gynaecological wards. The presence of marital discord was assessed in patients who had had unhappy marriages, who were separated or divorced, and in widows who had been unhappily married. Statistical significances were evaluated using Pearson's χ^2 method.

Psychiatric inpatients demonstrated a strikingly increased incidence of marital discord over medical and gynaecological inpatients matched for age, sex, race and socio-economic group, and this was statistically significant ($P<0,01$).

The incidence of marital discord among subjects in the psychiatric ward was 66%, which is significantly higher than the 16% and 24% in the gynaecological and medical wards respectively. Thirty-two per cent of psychiatric subjects were single, while only 15% of gynaecological subjects and 17% of medical subjects were single. Moreover, 18% of the single subjects in the medical ward had previously received psychiatric treatment. Both these figures indicate that patients with a psychiatric history are less likely to get married. In addition, there were far more single subjects of over 30 years of age in the psychiatric ward, who are less likely to get married in the future.

Significant factors contributing to the marital discord included the following: (*i*) previous psychiatric illness; (*ii*) parental marital discord; (*iii*) history of psychiatric illness or alcoholism in the subject's close family. It must be stressed that only the wives of the couples were interviewed; yet, despite this, the figures were significant. In this study physical illness and parity were not significantly correlated with marital discord.

The findings of the present study would appear to confirm the data of other authors such as Renee,[1] who found that people with a past history of psychiatric illness, specifically depression and alcoholism, have an increased likelihood of an unsatisfactory marriage. Eshleman[2] found that there was a high correlation between mental health and a healthy marriage. Ovenstone[3] pointed out that the spouses of neurotic patients tended to develop neurotic symptoms and that the more neurotic the marriage, the higher the marital tension.

Although happily married patients in all 3 groups of this study had a slightly higher incidence of children, this difference was of no significance. However, other workers such as Renee[1] and Figley[5] found that childless marriages are associated with more happiness, while Ryder[6] found the opposite. In the present survey more subjects who had had discordant marriages had experienced physical illness, but this was not significantly so. Renee, however, found that there was a correlation between physical illness and marital dissatisfaction.

It can therefore be concluded that there is a significantly increased incidence of marital discord in the marriages of psychiatric patients, who, in fact, are also less likely to get married. Contributory factors to the marital discord were the subjects' personal previous psychiatric history, parental marital discord and close family psychiatric history, all of which were statistically significant. It is therefore suggested that it is the psychiatrically sick personality which causes marital discord.

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Hepatoma Presenting as a Bone Tumour

A Case Report

A. F. THOMAS, M. M. ROBERTSON, F. GOTTSCHALK

SUMMARY

Osseous metastases from hepatoma are rare. One patient who had a lesion in the upper humerus is presented.

S. Afr. med. J., 52, 899 (1977).

Primary carcinoma of the liver, although having a relatively low incidence in Europe and the Americas (roughly 1,5% of all carcinomas), is prevalent among the Black people of South Africa. The patient usually presents with abdominal pain, jaundice, malaise, splenomegaly, and, invariably, an enlarged nodular liver. Metastases in the regional lymph nodes or lungs occur in about one-third of cases. The ribs and vertebrae are less common sites for metastatic deposits. Other metastases are rare, and carcinoma of the liver presenting as a tumour in a long bone is extremely unusual.

CASE REPORT

A 38-year-old Black man was admitted to hospital with a swelling of his left arm, which had caused him considerable difficulty in moving the arm for 2 months before admission. He also stated that he had had problems with walking and passing urine more recently, and that vague abdominal pain had been present for some months. He denied excessive alcoholic intake and the history was otherwise non-contributory.

On examination there was a large mass involving the upper end of the left humerus. It was bony hard, obviously arose from bone, and measured approximately 15 × 10 cm. There were a few small, shotty lymph nodes in the left axilla. Systematic examination revealed a liver that was enlarged 4 cm below the right costal margin, hard, smooth, but not tender. There was no ascites and the spleen was not palpable.

Neurological examination revealed diminished sensation below the level of T4, with extensor response of the left foot, and some loss of power in both lower limbs.

Special Investigations

Radiography. An X-ray film (Fig. 1) showed a markedly destructive expansile lesion involving almost the entire upper half of the shaft of the left humerus. The tumour was surrounded by a thin shell of cortex which in places appeared to have been breached, and the radiological appearances suggested a malignant tumour.

Fig. 1. Destructive lesion of upper humerus.

Needle biopsy showed tumour cells with intensely eosinophilic cytoplasm arranged in cords and sheets. The nuclei were fairly regular, round and generally pyknotic, the overall appearance being that of a well-differentiated metastatic hepatoma.

Liver scan. This showed a major defect in the lower zone, involving both right and left lobes. The features were consistent with a hepatoma and liver biopsy confirmed this.

The rest of the investigations, including a full blood count, erythrocyte sedimentation test, alpha-fetoprotein estimation, liver function tests, protein electrophoresis, and calcium and phosphorus estimations were largely non-contributory.

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DISCUSSION

Although primary carcinoma of the liver is common in African countries, especially south of the Sahara (in Nigeria it is one of the commonest malignancies recorded in the cancer registry of the University College Hospital, Ibadan), associated skeletal metastases are rare.

Bolker *et al.*,[1] in a review of the literature up to 1936, could only find 9 reported cases. More recent reports show that the incidence is higher than was previously thought. Charache[2] found osseous metastases in 18 out of 1 125 cases, and Green,[3] in a 10-year collective review, found that of 386 proven cases, 8% had metastasized to bone. Carnahan[4] found that out of a total of 1 391 cases, 45 (3,23%) showed long bone involvement.

It is evident from these reports that osseous metastases from primary carcinoma of the liver are uncommon, for the carcinoma to present as a lesion in a long bone is excessively rare. We were unable to find any other report of hepatoma metastasizing to long bones in South Africa, although the occurrence is well documented. The purpose of this article is two-fold. Firstly, to report this uncommon site of presentation of secondary carcinoma of the liver, and secondly to emphasize that in an area where carcinoma of the liver is prevalent and where skeletal metastases are the presenting feature, the liver should not be forgotten as a possible primary site.

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Osteitis Deformans in the South African Negro

A Report of 3 Cases

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SUMMARY

Osteitis deformans is a relatively common disease in Caucasians, but rare in the indigenous people in Africa. Three cases of Paget's disease occuring in South African Negroes are reported here. Gene marker studies confirmed the absence of Caucasoid genes in these patients.

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Osteitis deformans was described in some detail by Sir James Paget[1] in 1877 and is now generally known as Paget's disease. It is certain, however, that the condition was known before then and that the original name had been proposed by Czerney in 1873. The disease occurs widely among humans and has been identified beyond doubt in horses and monkeys. However, reports of its occurrence in African Negroes are rare, and even these lack information on the genetic identification of the affected individuals. The present article describes 3 cases of osteitis deformans in South African Negroes treated at Baragwanath Hospital in Johannesburg.

CASE REPORTS

Case 1

A woman aged 52 years was admitted to hospital after an assault. On routine examination it was noted that she had an enlarged skull, she was deaf, and there was bilateral bowing of the tibiae. Investigations at the time revealed no abnormalities except for an alkaline phosphatase of 75 units (King-Armstrong). Radiographs of the skull, pelvis and lower limbs showed the classic features of Paget's disease (Figs 1 - 3). Gene marker studies and blood grouping showed no evidence of characteristic Caucasoid genes.

Case 2

A 58-year-old Black woman complained of low backache for several years. Radiographic examination showed osteitis deformans affecting the pelvis and lumbar spine (Fig. 4). Further investigations revealed no abnormalities except for a raised alkaline phosphatase of 31 KA units. Genetic studies showed no evidence of characteristic Caucasoid genes.

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Fig. 1. Radiograph of the skull, showing loss of differentiation between the outer and inner tables, with sclerosis and thickening. There is also osteoporosis circumscripta in the frontal region.

Fig. 2. Radiograph of the pelvis, showing characteristic changes with thickening, sclerosis and protrusio acetabuli.

Case 3

A 53-year-old woman complained of generalized joint pain of about 2 years' duration. Examination did not reveal any clinical evidence of osteitis deformans. However, radiographs of the pelvis showed changes typical of the disease. The serum alkaline phosphatase level was raised to

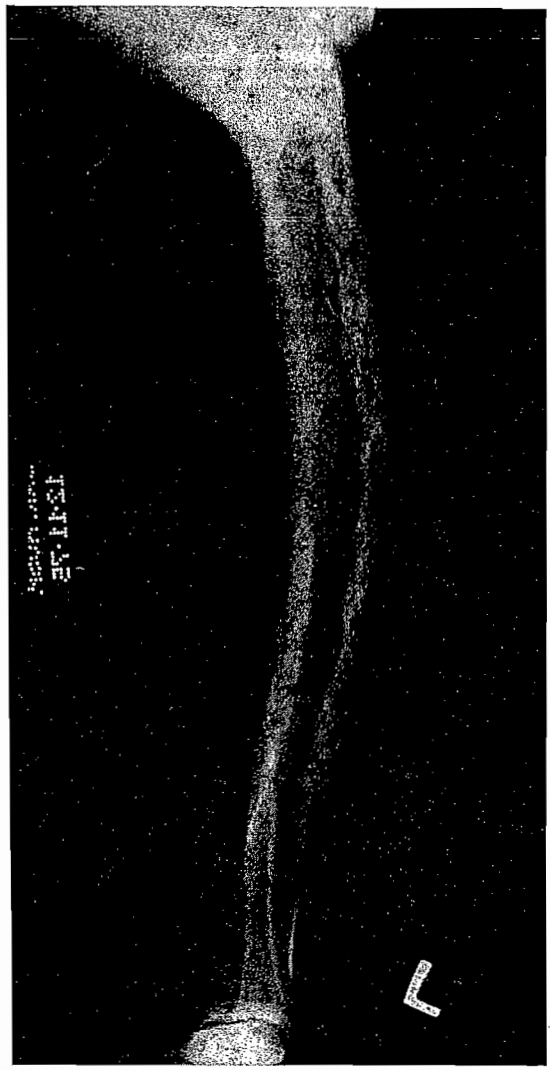

Fig. 3. Radiograph of the tibia, showing anterior bowing with rarefaction, coarse wide trabeculation, sclerosis and thickening.

Fig. 4. Radiograph showing dense sclerotic vertebral involvement due to Paget's disease.

84 KA units. Genetic studies revealed no evidence of Caucasoid admixture.

DISCUSSION

About 45 years after Paget's description of osteitis deformans the apparent incidence of the disease in Western Europe rose sharply. This was just after World War I, when roentgenograms began to be used routinely. It became clear that the clinical picture shown by Paget's original patient was the end result of a long and slowly progressive bone disorder. In patients who are only minimally affected, the lesions are often discovered accidentally during the investigation of other disorders. These patients, with neither symptoms nor signs of any bone disorder, might live the normal span of years without the diagnosis ever being made. It is thus impossible to estimate the true incidence in the population, but it is known to be fairly common in Caucasians. Schmorl[2] found Paget's disease in 3% of necropsies on unselected persons over 40 years of age; a similar figure (3,7%) was cited by Collins[3] on the basis of 650 unselected necropsies on individuals over 40 years of age.

There are striking contrasts in the geographical and racial distribution of the condition. It is considerably more common in the north of England than in Wales, and the prevalence in Britain as a whole is higher than in the rest of Europe or North America. It is also widespread in Australasia among people of Anglo-Saxon origin. Although most of the descriptions stem from the Western world there are well-authenticated case reports from India, Asia and Africa.

The rarity of the condition in African Negroes has often been remarked (Edington and Giller,[4] and Sissons[5])

Bohrer[6] found only 5 cases in over 200 000 individuals who had been examined in the Radiology Department, University College Hospital, Ibadan, Nigeria. However, the possibility of Caucasian admixture was not excluded by specific genetic studies in these patients.

In the 3 cases described here gene marker studies confirmed the absence of any Caucasoid genes. Together with another 5 similar cases reported by Pompe van Meerdervoort[7] they offer renewed evidence that Paget's disease does indeed occur in the African Negro, although its prevalence appears to be much lower than in Western Europeans.

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CASE REPORT

A case of anorexia nervosa with an associated urogenital malformation

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SYNOPSIS A further case of anorexia nervosa with an associated urogenital malformation, namely hypospadias, is presented. The prevalence of urogenital abnormalities in patients with anorexia nervosa is much higher than expected on the basis of coincidence.

INTRODUCTION

A relationship between anorexia nervosa and urogenital malformations has been suggested previously. We report a further case with certain unique features.

CASE REPORT

G.S., a South African of Ashkenazi origin, was born in 1953 at 8 months gestation; her birth weight was 2·2 kg. She was the elder of two sisters. At the age of 12 years, she was extremely fat, a compulsive eater, and was teased at school for her obesity. Her mother seemed to play on her compulsive eating; whenever the patient asked for emotional or physical support or assistance, her mother would offer her some food. She reached her menarche at the age of 12½ years. At the age of 16 years, she weighed 83·2 kg and her height was 170 cm. At this stage she was noted to be very hirsute and was referred to a gynaecologist who, after investigating her, told her that she had a 'fistula' and that she passed urine through her vagina. Her frequent bouts of cystitis were attributed to this anomaly. She began to restrict her diet at the age of 17 years. At one stage she dieted so severely that she lost 13·6 kg in 6 weeks, finally reaching a weight of 54·4 kg at the age of 21 years. At this weight she became amenorrhoeic and remained so for 18 months. She would not eat food unless she saw it being prepared, in order to prevent any fattening substances being added. When her weight dropped to 47·3 kg, she began fainting, had poor concentration span and therefore visited her general practitioner regularly, who explained that she was anorexic.

She was referred to a psychiatrist, and admitted to a psychiatric clinic. At this stage she weighed her lowest, 38·6 kg. She received insulin and other medication, but with little effect. She discharged herself from hospital, dissatisfied with the treatment she was receiving. Independently, she made a conscious effort to help herself and managed to gain some weight.

At this time she had minimal insight into her condition. She complained of chronic constipation for which she took about 30 laxative tablets daily. She was also drinking apple cider, vinegar and liquid paraffin as an additional purge. As well as this she was taking various diuretics and appetite suppressants. After eating, she used to make herself vomit by putting her finger down her throat.

At the time of admission to our unit she weighed 51·8 kg. She was hirsute with a male distribution of pubic hair. She also had a nest of hair over the sacral area. Examination of her urogenital system revealed a mild urethral hypospadias. Apart from that, the pelvic examination was normal. There was no evidence of facial acne nor of any increase in facial hair.

The only results of laboratory investigations that were abnormal were low urinary 17-

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ketosteroids, which were 4·4 mg per 24 h (normal values 4·5–20·0 mg per 24 h). The following endocrine findings were within normal limits: serum progesterone, testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH) and thyroid function tests. She had a normal female chromosomal complement (46 XX). The X-ray of her spine showed no evidence of spina bifida.

A laparoscopy, performed during the investigation of her hirsutism when she was 16 years old, showed normal ovaries.

DISCUSSION

The opening of the female urethra posterior to its normal site, or into the anterior wall of the vagina, has been termed female 'hypospadias', and the condition probably represents a mild degree of persistence of the urogenital sinus (Gray & Skandalakis, 1972). The meatus may open directly into the bladder neck, the latter case being essentially a vesico–urethro–vaginal fistula with incontinence (Rubin, 1967). About 25 % of the patients with hypospadias have other urinary tract abnormalities (Gray & Skandalakis, 1972); Rubin (1967) mentions an associated enlarged clitoris and views the latter as part of an intersex problem.

Halmi & Rigas (1973) reported 5 cases of anorexia nervosa with associated urogenital abnormalities. They examined hospital files and found 87 consecutive patients with anorexia nervosa, 59 of whom fulfilled the criteria of Feighner *et al.* (1972). Among the 59 patients, 5 had various urogenital anomalies: namely vaginal atresia, malformed vagina, Fallopian tube malformations, a single malformed kidney and bifid uterus. They maintain that the frequency of these abnormalities (5 per 59, or 8 %) is much higher than expected on the basis of coincidence.

Urogenital abnormalities are also found in Turner's syndrome. A total of 10 cases of Turner's syndrome and one with gonadal dysgenesis have been reported as concurring with anorexia nervosa (Lindsten, 1963; Pitts & Guze, 1963; Mellbin, 1966; Kihlbom, 1969; Dickens, 1970; Forssman *et al.* 1970; Liston & Shershow, 1973; Halmi & de Bault, 1974; Theilgaard & Phillip, 1975; Kron *et al.* 1977). These were selected cases; Halmi & Rigas (1973) found one in a consecutive series of 59 cases. This association is higher than would be expected by chance, as the birth incidence of Turner's syndrome is 1 in 2500 (de Grouchy, 1978).

The prevalence of urogenital malformations in the female population is difficult to measure. Minimal abnormalities may not give rise to symptoms and therefore are not recorded. There are series of symptomatic cases, but these are selected and so do not give a true overall accurate picture of the prevalence.

Hypospadias in the female is rare: Rubin (1967) reports the prevalence as 1 in 3000 females. Anorexia nervosa is a common condition. The exact prevalance is unknown, but appears to be increasing (Kendell, 1973; Crisp, 1976; Russell, 1977).

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Cold Injury Caused by Psychiatric Illness: Six Case Reports

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Summary: Six patients are reported in whom mental illness led to severe cold injury. The main contributory factors were cold surroundings, inactivity and neglect. The additional factor of impaired microcirculation in these patients may also be significant.

In the winter of 1979 two instances of cold injury in patients with mental illness came to our attention. A search of the medical records at the Whittington Hospital revealed a further three cases over a period of 14 years. One patient was seen at the National Hospital for Nervous Diseases, Queen Square.

Case Reports

Patient 1—gave an eight year history of schizophrenia, which had required in-patient treatment from 1958 to 1962. In January, 1966, aged 42, he entered a catatonic state and had apparently stood in a stationary position in the street over a period of two weeks. He was admitted to a psychiatric hospital under Section 29. He was described as extremely withdrawn and uncommunicative. On physical examination he was found to have gangrene of the tips of all toes, extensive sloughing of the skin and oedema of both legs. In addition on the right leg there was a large area of necrosis over the medial aspect of the ankle. Subsequently, extensive gangrene of both feet developed and he required bilsteral below knee amputation. He was then given chlorpromazine 100 mg four times daily and his mental condition improved; he was described as 'buoyant and extrovert' and no longer needed to be in a psychiatric hospital. He went to live in a hostel, completed a rehabilitation programme and was fitted with a permanent prosthesis.

Patient 2—in March, 1979, aged 63, gave a six year history of a mixed affective disorder in a personality described as schizoid; he had made two suicide attempts and had been admitted to a psychiatric hospital three years before. During a spell of very cold weather he spent four days wandering out of doors. He had little memory of this time and was thought to be in a depressive fuge. On admission to hospital he was of neglected appearance and was unable to account for the previous four days. He was retarded in speech and movement but fully orientated in time, place and person. Physical examination revealed that his toes were gangrenous, with demarcation at the level of the metatarso-phalangeal joints. He required amputation of all toes and skin grafting. After the operation he had an uneventful recovery. His feet healed satisfactorily and he was able to wear normal shoes. He has since had several relapses of his psychiatric illness, requiring admission to hospital. During remission he is followed up at out-patients and is able to hold down a job.

Patient 3—had five admissions between the ages of 34 and 47 with a diagnosis of schizo-affective disorder. In February, 1979 she retired to a garden shed where she was found after several days in a neglected state. On admission to hospital she was severely depressed and retarded. On physical examination she had frostbite of all toes necessitating amputation. During the nine months after her operation, she developed passivity feelings and paranoid ideas and at one time refused treatment. It was felt that her continuing retarded state hampered the quick healing of her feet, and although her mental state did eventually respond to treatment, two years later her feet were still not healed completely. She still attends a day hospital.

Patient 4—a Kenyan-Asian, was seen in January 1980, aged 35. He gave a 21 month history of delusions and passivity feelings. During that time he had secluded himself in his room in order to fight off the forces he felt were attacking him. The room was not heated and when he went out he wore open-toe sandals. In the week before his admission to hospital he had spent long periods of time sitting in a chair. On examination, he would strike postures which were maintained for several minutes at a time and he continued to express florid delusions. He had frostbite of all his toes which responded to conservative management of antibiotics and perfusion of his feet. The patient's mental state improved markedly with phenothiazines and his feet healed completely. It was felt that he was unable to look after himself in his own accommodation and he has gone through a prolonged

period of rehabilitation in hospital with a view to being discharged to a hostel.

Patient 5—a Nigerian, aged 45, was working up until four weeks before admission, and gave no previous psychiatric history. He had suddenly experienced delusions of persecution, and complained of pain in his leg. He retired to bed and locked the door of his room as he was suspicious of his neighbours. He remained in the unheated room for three weeks before admission to hospital in January, 1980. On examination he had extensive cold injury to both feet. He appeared to be suspicious of staff and refused food as he felt it was poisoned. His feet continued to deteriorate and all his toes required amputation. Postoperatively his mental state fluctuated and he was reluctant to eat or take medication. Healing of the feet was delayed by these factors and six months later a further operation was suggested. He, however, refused surgery and was therefore fitted with suitable orthopaedic shoes and subsequently discharged to a bedsitter.

Patient 6—required three admissions to psychiatric hospitals between 1950 and 1961. Each time she presented with abnormal involuntary movements and the diagnosis was of a hysterical conversion reaction. Her left hand became progressively 'paralysed' and developed a flexion contracture. At the age of 35, in 1962, she became depressed and made a suicide attempt which necessitated an admission to a psychiatric hospital. She was transferred to the National Hospital, Queen Square, with an abnormal gait, involuntary movements of her head, legs and arms, and a flexion contracture of the left hand. She was noted to spend much time sitting at an open window, exposing her immobile arm to the cold. Her left hand was flexed, discoloured and grossly oedematous which rendered it useless. A diagnosis of hysteria was made. A course of ECT and hypnosis treatment was commenced and her symptomatology virtually disappeared under hypnosis. She improved remarkably but her left hand remained swollen and discoloured. Surgical intervention was felt necessary and a left cervicodorsal sympathectomy was performed to good avail. She was rehabilitated with physiotherapy and discharged from hospital.

Discussion

The problem of cold injury caused by psychiatric illness will be discussed under three headings.

Psychophysiological factors

Several psychotropic drugs have been implicated in cases of hypothermia. Chlorpromazine lowers metabolic rate, probably by interfering with central temperature control. Hypothermia associated with imipramine has also been described. As far as we know, none of our patients were taking such medication prior to their admission to hospital.

Acrocyanosis, thought to be due to cutaneous vasoconstriction (Altshule and Sulzbach, 1949) is a common observation in schizophrenic patients. A number of studies have looked at circulatory changes in mental disorders. One such study showed an increased basal forearm blood flow in schizophrenic patients, but a reduced circulatory response to stress (Kelly and Walter, 1968). Other authors have commented on a diminished autonomic response in chronic schizophrenics (Lang and Buss, 1965) and a reduced hand blood flow (Abramson *et al*, 1941).

A prospective study of cyanosis and vascular responses in psychoses was undertaken by Shattock (1950), who reported disturbances of circulation in hospitalized schizophrenic patients and those with affective psychosis. Shattock studied patients aged between 15 and 65 years. Cyanosis of the extremities, particularly of the feet, was present in about 50 per cent of the female psychotics, despite the fact that they were in a room temperature of between 18.3°C and 27.8°C. At the lower room temperature the average surface temperature of the extremities of the schizophrenic patients was significantly lower than the affective psychotics. In severe cases, the skin below the knee was dry, scaly and inelastic, and there was evidence of chilblains and pressure sores, and in a few cases the tips of one or more toes were missing. At the lower room temperature only 5 per cent of male patients were affected. The only explanation for the greater incidence of peripheral cyanosis among the female patients was the difference in the warmth of the clothing worn by the patients.

In our patients a period of inactivity either due to retardation or catatonia seemed to be an important factor in the development of cold injury, but Shattock found an imperfect correlation between cyanosis and inactivity. Shattock also describes seven female schizophrenics with peripheral cyanosis in whom improvement in mental state coincided with clearing of the cyanosis, and a rise of brachial blood pressure. He suggests that the excessive peripheral vasoconstriction in schizophrenics is part of the normal physiological mechanism for conserving body heat. Prolonged vasoconstriction is necessary in the psychotics owing to their failure to respond to increased bodily requirements during chilling by adequate rises in metabolic level. The body temperature is sufficiently maintained by this means to assure survival, although peripheral structures may be injured by excessive reduction of their blood supply. The lack of spontaneous movement in both catatonic

and retarded depressive patients could also be a factor in slowing circulation as has been described.

It is perhaps surprising that there do not seem to be more reports of gangrene occurring in association with catatonia in the days when the condition was described more frequently. Indeed there are few reports of this problem in the literature.

Low forearm blood flow has been demonstrated in patients with depression and retardation (Noble and Lader, 1971). Brenner (1979) has suggested that peripheral postsynaptic receptor cell subsensitivity gives rise to the sleep and appetite disturbance, fatigue, lack of energy and depressed affect, all of which may contribute to an individual's immobility and susceptibility to cold injury.

Diagnostic considerations

Cold injury may involve freezing of tissues or milder damage from prolonged exposure to lesser degrees of cold. Gangrene only develops in a minority of cases, indicating that factors other than simply low temperature are important.

Physical disorders such as diabetes, dehydration and peripheral vascular disease impair microcirculation and may result in gangrene. Myxoedema may also result in cold injury. None of our patients have had any obvious underlying physical cause for their cold injury and in four, (2, 3, 4 and 5) of the six patients, investigations showed negative cryoglobulins, no ANF, and normal thyroid function tests, blood glucose and full blood count. In the remaining two, all investigations done were normal. Nevertheless, all suffered serious damage.

In one study of 68 patients with hypothermia (Maclean *et al*, 1973), 15 had myxoedema. Of the euthyroid patients, only two had a possible primary psychiatric diagnosis, as their admissions were occasioned by overdoses. The mean age of the patients in this study was 75 years suggesting some selection of patients admitted to a general ward. It is possible that younger patients with a primary psychiatric diagnosis are admitted to a psychiatric rather than a general hospital, and the question of hypothermia ignored.

A recent review of physical illness in psychotic patients (Cutting, 1980) mentions only one case of amputation due to frostbite from self-neglect. Such self-neglect was a large factor in the development of cold injury in our patients.

Meteorological factors

Cold surroundings and very cold weather were important factors in the development of our patients' severe cold injury. We obtained meteorological reports from the London Weather Centre (1981), which confirmed that the four periods during which our patients presented were recognized by the Centre as having been particularly cold. January, 1963 had some of the 'coldest weather this century', with the lowest night temperature recorded at −7°C and the highest day temperature being −2°C. The intense cold was accompanied by strong winds and much snow cover. January, 1966 had a very cold spell lasting two weeks when the maximum daytime temperature did not rise above 3°C and the night average was −5°C. A fresh easterly wind, which aids chilling prevailed throughout. February and March, 1979 was a 'classically cold winter', with a period in mid-February of blizzards and gale force winds. Wet conditions throughout the two months amplified the effects of the cold weather. January, 1980 was a dry cold month, below freezing at night with ground frost.

Conclusion

We conclude that in our patients there was a direct link between abnormal state and the development of severe cold injury. An acute exacerbation of mental illness leading to self-neglect, poor nutrition and reduced movement, together with exposure to cold resulted in the development of gangrene. Patients with psychotic disorders often live in poor accommodation, with inadequate heating, and few social contacts. They are, like the elderly, particularly at risk of exposure to cold temperatures. In elderly people exposed to cold, gangrene is rare. The question of an additional vulnerability of psychotic patients because of defective microcirculation is discussed.

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