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A Journey Through Time: From the Dawn of Psychiatry to the Golden Age of Neuroscience

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Nancy C. Andreasen, MD, PhD

Professor Andreasen is Andrew H. Woods Chair of Psychiatry and Director of the Psychiatry Neuroimaging Consortium at The University of Iowa Carver College of Medicine.

Her primary research interest is neuroimaging. She is also actively researching genomics and the natural history and neural mechanisms of schizophrenia. Her achievements include the first quantitative Magnetic Resonance study of schizophrenia, the development of the first scales to measure the positive and negative symptoms of schizophrenia, and the first study to combine genomic with neuroimaging techniques. She has served on both the DSM and DSM IV task forces.

Prof. Andreasen was Editor-in-Chief of the American Journal of Psychiatry for 13 years and has written three widely praised books for the general public: 'The Broken Brain: The Biological Revolution in Psychiatry' (1984), 'Brave New Brain: Conquering Mental Illness in the Era of the Genome' (2001), and `The Creating Brain: The Neuroscience of Genius' (2005). She has also authored, co-authored, or edited 12 other scholarly books and over 500 articles.

This publication is a summary of a recent presentation by Professor Nancy Andreasen, Andrew H. Woods Chair of Psychiatry and Director of the Psychiatry Neuroimaging Consortium at The University of Iowa Carver College of Medicine, Iowa, USA. Prof. Andreasen addressed psychiatrists in Wellington, Dunedin, Hamilton and Auckland, during September 2011 on the importance of mental illnesses and mood disorders such as schizophrenia and their impact upon individuals. The presentation reviewed scientific advancements in neuroscience that have led to important insights into the diagnosis and treatment approaches for mental disorders, offering hope for remission and recovery in the era of modern treatments.

An historical overview

Notably, the award of the 2000 Nobel Prize for Medicine to Arvid Carlsson, Paul Greengard and Eric R. Kandel highlighted the significant advancements accomplished by their research in psychiatry and the neuroscience that supports psychiatry. Much of the framework that we work with comprising the diagnostic systems used in psychiatry was defined by Emile Kraepelin and Eugen Bleuler. Kraepelin is specifically credited with developing the concept of dementia praecox, with the implication that this was a dementing illness or Alzheimer's-like disease that occurred in young people. Bleuler had a more optimistic view; he renamed the illness "schizophrenia", referring to the fragmented thoughts, the "split mind" (schizo phrene) that occurs in the illness, and maintained that the illness has a less grim prognosis than dementia praecox. However, he also stated that people with schizophrenia never make a full recovery (a full "restitutio ad integrum").

Over the next 50 years, schizophrenia was indeed a grim prognosis. Lifelong institutionalisation was the model and the knowledge underlying our understanding of schizophrenia was very primitive. All of this changed dramatically with the introduction in the 1950s of chlorpromazine, a treatment that had a huge impact upon the lives of patients with schizophrenia, producing improvements that seemed astounding at the time. This represented huge progress. Prior to the serendipitous discovery of chlorpromazine, originally identified as an anaesthetic agent, treatments consisted of leucotomy, insulin coma, and reserpine. Importantly, this first effective antipsychotic paved the way for a new era in the development of other compounds that would prove to be equally effective in schizophrenia. The prescribing guidelines for chlorpromazine seem primitive today (e.g., it was recommended to increase the dose until the patient developed parkinsonian symptoms, at which point this was thought to be the therapeutic dose). Side effects associated with chlorpromazine were – and still are – problematic.

Worldwide efforts to develop a brain-based scientific pharmacology have been led by Arvid Carlsson, whose Nobel Prize was awarded for his development of the dopamine hypothesis as well as for his investigations into Parkinson's disease. He devoted his efforts to synthesising more effective agents that would block dopamine D_2 receptors and treat schizophrenia.

An early belief prevailed that "new" antipsychotics such as chlorpromazine could produce remission and cure if used early and consistently. However, those hopes were slowly dashed over time, as it became evident that mild psychotic symptoms could still persist and that negative symptoms have an important role in social and cognitive impairments. The introduction of "second generation" medications (atypicals) and creation of long-acting forms raised expectations again and encouraged people to hope that relapses may be prevented and remission may be possible. While atypicals have a similar blocking effect on D_2 receptors, some also have additional effects on serotonin receptors, the combination of which could reduce side effects and improve symptom reduction.

The atypical antipsychotics did create another paradigm shift. Within a decade, they became the most widely used class of antipsychotics for the treatment of schizophrenia.[1]

Neurological underpinnings of schizophrenia

Based on their observations of patients, Kraepelin stressed that people with schizophrenia have "*a peculiar destruction of internal connections of the psychic personality*", while Bleuler's coining of the term schizophrenia emphasised the fragmenting of thoughts. When considering schizophrenia in the 21st century, those insights are very relevant but they must be recast within the language of neuroscience and neurobiology. The current thinking is that patients with schizophrenia have somehow developed an abnormality in connectivity in the brain and this abnormality is not in a specific brain region. Rather, the most up-to-date thinking is that this disease affects the entire brain and instead of being an illness in a single region, it is an illness involving the inability of multiple brain regions to communicate with one another effectively. These misconnections explain both the cognitive and emotional impairments and the other clinical symptoms. For example, a misconnection leads the person to misinterpret information: a delusion arises because a percept is linked to the wrong association. It is believed that two different kinds of misconnections are occurring:

- Structural misconnections: impaired links between nodes in anatomic networks and circuits
- Functional misconnection: An abnormality in the functional interaction between two or more components or nodes in a brain network, conceptualised as a distributed system.

Prof. Andreasen emphasised the importance of integrating information from multiple levels, if we want to understand schizophrenia and also most of the other mental illnesses that we deal with. When we see patients we are thinking at the clinical level in terms of symptoms, while the language of neuroscience holds that we are working at the systems level. At the neural systems level, tools such as neuroimaging can track neural changes and progression over time.[2]

Of increasing importance is the ability to understand an illness at the cellular and molecular level; genomics may be used to identify genetic mechanisms of neural changes that underlie an illness such as schizophrenia.[3]

Thus, in the 21st century, neuropsychiatry and neuroscience is considering what lies behind the patient's symptoms – disturbances at increasingly finer levels:

- Genes
- Molecules
- Cells
- Neural circuits and systems
- Cognitive and emotional processes
- Symptoms: disturbance in any and all of the above leading to the manifestation of a disease process.

Increasingly, psychiatrists will need to be able to know about all of these levels in the various illnesses; i.e. how genes, molecules or cells produce the symptoms of mental illness.

According to current understandings as to the genetic, molecular, and cellular basis of schizophrenia:

- The misconnection is due to an impairment in neuroplasticity that affects the healthy development of synapses, spines, and dendrites in cerebral gray matter (GM)
- This is reflected in the neuropathology of schizophrenia
- Schizophrenia arises due to an impairment in the processes that regulate activity-dependent modeling of the pattern and strength of synaptic connections
- This can be studied by examining the relationship between genes that regulate neuroplasticity (e.g., brain-derived neurotrophic factor, or BDNF) and measures of brain structure using sensory motor rhythm.

Morphometric analysis has identified distinct neuropathology in the schizophrenic brain. The normal brain has normal-sized cell bodies and a rich arbor of dendrites, spines and synapses extend up from the soma. In the schizophrenic brain, the cell bodies are smaller, the dendritic arbors are smaller and the cortical thickness is thinner than in the normal brain.[4] These findings have been repeatedly replicated by MRI studies.

One of the challenges in studying schizophrenia and trying to understand its cellular and molecular mechanisms is that this is an illness that extends over a long period of time and that apparently begins at an early point, in the prodrome period – by the time patients present to the psychiatrist, they have already been ill for some periods of time with symptoms such as anxiety and negative symptoms. The illness progresses for years, sometimes leading to a residual state and sometimes to a better outcome, such as remission.

For almost 20 years, Prof. Andreasen has been accumulating longitudinal evidence on schizophrenia, in an effort to understand its natural history. A key question is "*When does the brain become broken in schizophrenia?*"[2] The first symptoms usually appear in the prodrome period and florid symptoms present between about age 16 or 18 through about 30 years; the typical age of onset is in the early 20s. Normal brain development is characterised by an overgrowth of GM during childhood and adolescence that is pruned back at around age 15; thereafter, GM decreases up to around age 25, after which it levels off. In parallel, white matter (WM) increases during the same time period and peaks at about age 25. Given that the onset of schizophrenia is that same time period during which the normal brain is developing myelination, it seems likely that the processes that shape neurodevelopment must have gone awry in schizophrenia.

Does brain tissue loss progress after onset?

The most recent analysis of data from research being conducted by Prof. Andreasen and colleagues draws on a large sample of first-onset patients from a longitudinal MR study begun in 1989:

- Examines a total of 898 sMR scans from 211 patients ascertained at onset and 102 controls
- On average subjects had at least 3 scans (at least 2 and as many as 6) with an interval of approximately 3 years
- Analysis covers a time period from baseline up to 12 years, with a mean follow-up time of nearly 7 years
- This analysis focuses on a crucial period in brain development: adolescence and young adulthood.

The findings reveal that brain tissue in patients is lost and cerebral spinal fluid (CSF) is increased at a faster rate than can be accounted for by normal ageing in multiple brain regions: in total cerebral tissue and GM, frontal GM and WM, temporal and parietal WM, sulcal, frontal, temporal, and parietal CSF, and in the thalamus and caudate.

Possible explanations for brain tissue loss (prior to and after onset of schizophrenia) include:

- Early environmental factors (birth injuries, viral infections, paternal age)
- Later environmental factors (substance abuse, smoking, protective factors such as cognitive reserve or social support networks)
- Disease characteristics: age of onset, duration, symptom severity, relapse, differential treatment effects
- Effects of genes that regulate neuroplasticity and neurodevelopment, epistasis, GxE interactions.

A recent analysis of treatment effects of data from the Iowa Longitudinal Study revealed that follow-up duration (intrinsic disease progression in the brain) was highly significant and that antipsychotic treatment intensity also had independent significant main effects on nearly all MRI brain volumes. Illness severity and substance abuse had minimal or no effects.[6]

These findings raise concerns about the use of neuroleptics in people who do not have schizophrenia and in vulnerable populations such as children and the elderly. They also suggest the importance of conservative dosing in all patients. However, Prof. Andreasen noted that these results also have to be weighed against the clinical benefits of neuroleptics in schizophrenia.

There is a clear need for innovative drug development, with a focus on brain effects as a critical component in drug screening. There is also a need to "personalise medicine" in order to identify individuals who may be differentially sensitive to antipsychotic medications.

Is remission possible?

The standard remission criteria introduced by Prof. Andreasen and colleagues in 2005 require a level of severity of mild or less for at least 6 months for all of the following 7 symptoms (Positive and Negative Syndrome Scale [PANSS] items): the psychotic symptoms of delusions, hallucinations, disorganised speech and disorganised behaviour, and the negative symptoms of alogia, affective flattening, and avolition. This definition was readily adopted and has since been used in hundreds of studies worldwide investigating remission in schizophrenia.

The remission criteria have been applied to patients in the Iowa Longitudinal Study of First Episode Schizophrenia, with data available for 395 patients who have been followed for at least 2 years (an average of 9 years):

- 51% were able to achieve remission using the 6-month criteria
- 44% were able to achieve remission for 12 months
- 34% were in remission for at least 2 years
- Among those who were in remission for 2 years, the average remission time was actually 5 years.

Thus, the outcome of schizophrenia is not as grim as we used to think!

How to predict later remission?

Analyses of data from the Iowa Longitudinal Study reveal that several factors at illness onset predict later remission:

- Better premorbid adjustment
- Absence of problems in school such as delinquency or being held back
- Good school performance
- Higher IQ
- Close relationship with friends
- Close relationship with family
- Being female.

The concept of remission has been validated with follow-up data examining relevant outcome measures in patients from the Iowa Longitudinal Study:

- People who have a long period of symptomatic improvement also have better psychosocial function
- E.g., many are employed
- They are significantly better in other areas – closer to family, more recreational activities, more friends, and better overall quality of life
- They also had less brain tissue loss.

Defining remission based on symptoms is therefore clinically meaningful, since people who have less severe symptoms also have happier lives and healthier brains.

Is relapse neurotoxic?

A prevailing viewpoint is that active psychosis (i.e., the presence of hallucinations and delusions) is neurotoxic. In studies of initial untreated psychosis, long delays in seeking treatment have been associated with poor clinical outcome. However, Prof. Andreasen noted that the evidence in support of an association between untreated active psychosis and neurotoxicity is very weak.

Others have argued that the experience of psychosis is neurotoxic via a variety of proposed theoretical mechanisms (e.g., hyperglutamatergic neurotoxicity), but as yet, no studies have directly examined the relationship between relapse and volumetric MR measures over a reasonable time period (e.g., 1–5 years).

The "Csernansky Definition" of relapse

No consensus definition of relapse in psychosis exists. The clinical drug trial literature has traditionally defined relapse with very simple measures, e.g., re-hospitalisation. The problem with this definition is that reasons for hospitalisation are socially dependent and admission rates differ between places. Another standard definition for relapse is an increase in severity of 25% on a standard rating scale. The problem with this definition is that while such an increase may be clinically meaningful with a baseline low severity measurement, it may be difficult to achieve an increase of 25% in a case of high severity. In an attempt to improve upon this situation, John Csernansky created a more extensive definition for use in short-term clinical trials. It requires at least one of the following: hospitalisation, an increase of 25% on a standard rating scale, deliberate self-injury, suicidal or homicidal ideation, violent behaviour resulting in clinically significant injury, clinical deterioration defined as a change score of 6 or 7 on the CGI.

This definition is well-suited for short-term studies in which time to relapse is the outcome measure, but poorly suited for long-term trials in which duration of relapse may be more meaningful. The definition has been applied to a study that compared risperidone with haloperidol, which demonstrated less relapse with risperidone.[9]

When Prof. Andreason and colleagues sought to determine whether relapse is neurotoxic, they created a symptom-based definition that includes relapse duration:

- Initial clinical improvement (typically at the time of discharge from hospital)
- Subsequent worsening of symptoms to a moderately severe level as rated by the Scale for the Assessment of Negative Symptoms (SANS) and Scale for the Assessment of Positive Symptoms (SAPS)
  - Any one symptom: delusions, hallucinations, disorganised speech, disorganised behaviour
  - Two symptoms required for negative symptoms: alogia, anhedonia, affective flattening, avolition, or attentional impairment.

The definition has been applied to 202 first-episode subjects from the Iowa Longitudinal Study, with up to 15 years' follow-up, MR scans at intake, 2, 5, 9, and (occasionally) 12 or 15 years, and in 108 neuroleptic-naïve subjects at intake, with a mean age of 25.3 years, 73% male. The analyses revealed that relapse duration had a highly significant effect upon brain volume, whereas number of relapses had no effect (see Figs. 1 & 2 on page 3).

Figure 1. Effect of relapse duration on brain volume

Brain Measure	Maximum Likelihood	SE	Z	P-value	
Total cerebral	-2.1202	0.7899	-2.68	0.0073	**
Cerebral GM	-1.1177	0.417	-2.68	0.0073	**
Cerebral WM	-0.8862	0.7104	-1.25	0.2122	
Cerebral CSF	1.7505	0.665	2.63	0.0085	**
Total frontal	-1.0729	0.3753	-2.86	0.0043	**
Frontal GM	-0.6178	0.2464	-2.51	0.0122	*
Frontal WM	-0.4296	0.2735	-1.57	0.1162	
Frontal CSF	0.9092	0.356	2.55	0.0106	*
Total temporal	-0.3299	0.1551	-2.13	0.0335	*
Temporal GM	-0.1585	0.1019	-1.56	0.1199	
Temporal WM	-0.1424	0.0949	-1.5	0.1334	
Temporal CSF	0.2325	0.1047	2.22	0.0264	*
Total parietal	-0.4917	0.1855	-2.65	0.008	**
Parietal GM	-0.2622	0.1111	-2.36	0.0182	*
Parietal WM	-0.1953	0.1606	-1.22	0.224	
Parietal CSF	0.3905	0.1586	2.46	0.0138	*
vbr	0.0239	0.0112	2.13	0.0333	*
Surface CSF	1.4213	0.5109	2.78	0.0054	**

Figure 2. Effect of relapse number on brain volume

Brain Measure	Maximum Likelihood	SE	Z	P-value	
Total Cerebral	-0.4396	0.4437	-0.99	0.323	
Cerebral GM	0.0163	0.2989	0.05	0.9566	
Cerebral WM	-0.4559	0.3759	-1.21	0.2268	
Cerebral CSF	0.1505	0.3668	0.41	0.6821	
Surface CSF	-0.01329	0.2684	-0.05	0.9606	
Total frontal	-0.2754	0.2219	-1.24	0.2161	
Frontal GM	-0.09409	0.1494	-0.63	0.5296	
Frontal WM	-0.1813	0.1552	-1.17	0.2441	
Frontal CSF	0.08079	0.2106	0.38	0.7016	
Total Temporal_T	0.01287	0.1022	0.13	0.8999	
Temporal GM	0.01089	0.07762	0.14	0.8886	
Temporal WM	0.001976	0.05913	0.03	0.9734	
Temporal CSF	-0.01878	0.05276	-0.36	0.7223	
Total Parietal T	-0.08505	0.1182	-0.72	0.4727	
Parietal GM	0.01292	0.08204	0.16	0.875	
Parietal WM	-0.09797	0.09137	-1.07	0.285	
Parietal CSF	0.04339	0.08852	0.49	0.6246	
vbr	0.01001	0.006076	1.65	0.1009	

In conclusion:

- **Relapse is not good for the brain**
- **Longer duration of relapses are associated with greater GM loss**
- **Simply counting the number of relapses is not predictive of anything.**

Will LAIs improve outcome by preventing relapse?

Long-acting injectable (LAI) antipsychotics are promoted for use in the following patient groups:

- Patients who are acutely and severely psychotic, need rapid treatment, and refuse oral medications
- Patients who have cognitive problems and simply forget to take medication
- Patients who are prone to relapse frequently, perhaps due to nonadherence
- A "last resort" for patients who are nonresponders.

In an attempt to rectify the scant amount of data regarding the use of LAIs in first-episode patients, Prof. Andreasen presented her patients with the advantages and disadvantages of the oral versus LAI medication options. When approached in this way, the patients were not so averse to choosing the LAI.

Only one randomised clinical trial has compared medications in first-episode schizophrenia.[10] That trial compared the conventional antipsychotic haloperidol with the atypical olanzapine (for up to 2 years) in patients with first-episode psychosis and healthy volunteers. Haloperidol was associated with reduced (whole brain and frontal) GM volumes, whereas olanzapine treatment was not significantly associated with GM volume reductions. Instead, olanzapine-treated patients had a modest increase at 12 weeks, a decrease at 24 and 52 weeks, and a small increase at 2 years; controls showed increases at 12 weeks and 1 year. The results of this trial are often used to support the contention that olanzapine is neuroprotective. However, Prof. Andreasen noted that the high attrition rates make these data difficult to interpret. Another problem is that pooled MR data sets tend to be very noisy.

Prof. Andreasen and colleagues have addressed this problem with a 1-year trial that has just been completed (no data have been released as yet), in which long-acting paliperidone palmitate was compared with oral treatment as usual in first-episode patients, with an emphasis on those who were neuroleptic-naive. The study was designed to answer whether a reduction in relapse rates would be associated with less brain tissue loss. MR scans were therefore undertaken at study intake, 6 months, and 1 year. The study has included a wide array of measures: structural measures, fMR, and fibre tracking of white matter (DTI). The power of this study lies in the fact that only two sites are involved (Iowa and Indiana), which have amassed much experience with first-episode schizophrenia; this should reduce scanner noise. Prof. Andreasen believes that if these high-quality data show that patients perform better on LAIs, this will create a paradigm shift in how such patients are best treated.

A possible advance: Personalised medicine?

Many hope that personalised medicine may incorporate genomic information to allow us to predict on-treatment response and guide on-treatment therapy decisions. In regards to schizophrenia, this disorder concerns a misconnection syndrome – one that is thought to be due to impaired synaptic plasticity. Therapy decisions may be improved by considering genes that regulate neuroplasticity, such as BDNF, an important protein that is involved in brain development; affecting neuronal survival and differentiation in the developing nervous system, and BDNF is involved with improvements in learning and memory, by modulating activity-dependent synaptic plasticity in mature neurons.[11]

Notably, a polymorphism in the *BDNF* (*BDNFval^{66}met; rs6265*) gene causes a valine (val)-to-methionine (met) substitution at codon 66 and predicts poorer episodic memory, abnormal hippocampal activation associated with fMRI, and lower hippocampal n-acetyl aspartate (NAA), assayed with MRI spectroscopy.[12-14] *BDNF*-met allele carriers also show smaller hippocampal and frontal GM volumes.[15]

As an indicator of how far psychiatry and in particular, the neuroscience of psychiatry, has advanced our understanding of the pathogenesis of schizophrenia, the tools of MR scanning enable us to address significant questions such as how a single nucleotide substitution in the gene encoding the proBDNF protein possibly affects progressive brain volume changes in schizophrenia. Its probable mechanism comprises the following:

> Met substitution → improper folding of mature BDNF → inefficient BDNF trafficking → reduced BDNF availability → diminished dendritic arborisation and reduced soma size → gross MRI volume changes.

Applying a molecular/cellular approach

Evidence from the Iowa Longitudinal Study suggests that Met allele carrying first-episode schizophrenia patients experience greater progression of GM deficits in the prefrontal cortex and ventricle enlargement than Val homozygous patients over the 3 initial years of disease course.[16] Thus, this study supports the hypothesis that progressive brain change in schizophrenia can be explained in part by a genetic polymorphism in BDNF. The study data also support the likelihood that progressive brain change is a consequence of abnormal neuroplasticity: an impairment in the processes that regulate activity-dependent modelling of the pattern and strength of synaptic connections and spine/dendrite formation. As far as Prof. Andreasen and colleagues are aware, this is the first study to apply a molecular/cellular approach to explaining the mechanisms of longitudinal brain changes occurring at the neural systems level.

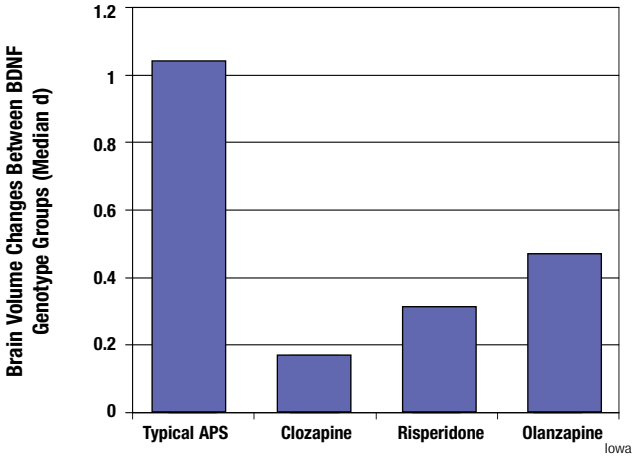
An important component of this study was to consider whether different types of antipsychotics have differential effects on BDNF expression. It is known that chronic administration of typical antipsychotics, such as haloperidol, decreases hippocampal and prefrontal BDNF concentrations in rats.[17] Decreased BDNF synthesis is thought to be mediated through dopamine D_2 receptor blockade. Risperidone and olanzapine are associated with less marked reductions in BDNF expression, while clozapine, which has virtually no D_2 receptor activity, has no effect on or even up-regulates hippocampal BDNF mRNA expression.[18]

Prof. Andreasen and colleagues compared brain volume changes between genotype groupings by `predominant antipsychotic treatment' (i.e. receiving a given antipsychotic for >50% of an interscan interval) for 4 mutually exclusive groups in the Iowa Longitudinal Study:

- typical antipsychotics (n=Met/Val:5/20)
- clozapine (n=Met/Val:6/11)
- risperidone (n=Met/Val:13/23)
- olanzapine (n=Met/Val:11/8).

Analyses showed significantly greater loss of brain tissue in Met allele carriers treated with typical antipsychotics, compared with those given clozapine, risperidone, or olanzapine (see Figure 3 on page 4). These findings require further confirmation in controlled studies where subjects are randomly assigned to antipsychotic treatment. The potential clinical implications are that if genetic screening becomes more routinely available, treatment algorithms may avoid typical antipsychotic treatment in Met allele carriers.

Figure 3. Comparison of brain volume changes between genotype groupings by antipsychotic treatment



Clinical accomplishments: the past 50 years

- The majority of patients with schizophrenia live in the community
- Newer medications effectively reduce psychotic symptoms with minimal side effects
- They may also "energize" the patients and thereby reduce negative symptoms and improve cognitive function
- The concept of remission is not an empty dream – some patients do achieve it
- Of course, we eventually want ALL to achieve it

Scientific accomplishments: the past 50 years

- Steadily increasing rigor in clinical trials – rating scales, longer time periods, more diverse outcomes
- Drug development is based on the expanding knowledge base of neuroscience – the basic science of psychiatry
- Clinical management is based on rational and scientific principles about the mechanisms of drug action

Future directions: clinical goals

- Develop standard methods for measuring psychosocial function and quality of life – equivalent to those currently available for assessing symptoms
- Incorporate psychosocial functions and quality of life measures into definitions of remission and recovery
- Develop standard methods for assessing cognition in clinical trials (e.g., the MATRICS battery)
- Ultimately, aim to achieve full recovery ("restitutio ad integrum") with treatments developed in the future

Future directions: scientific goals

- Identify and develop new neurochemical targets in drug discovery
- Base discovery on the most sophisticated models of the neural mechanisms of schizophrenia – e.g., neural circuit models rather than single site models
- Aim for targets that will be neuroprotective and potentially preventive and pre-emptive

Q&A session

Q: Many general practitioners in New Zealand are prescribing antipsychotics as sleep medications in patients who have no mental illnesses. How acceptable is this?

A: Prof. Andreasen advises that this practice deserves very careful consideration and that we should be very cautious about off-label use of antipsychotics. Prof. Andreasen and colleagues have applied for funding to investigate whether antipsychotics have differential effects on the rat brain, in rats of all ages (child, adolescent, young adult and older). Such a study would determine whether these antipsychotics have differential effects in different age ranges, and the strength of such effects. If the evidence is reiterated across animal species and suggests that antipsychotic medications reduce brain tissue in animals as well as in humans, the indications for these medications will have to be reassessed (i.e., antipsychotic prescribing for sleep, controlling behaviour in children, and controlling behaviour in the elderly).

Q: With regard to brain tissue loss, is BDNF one factor that is associated with this phenomenon, or how much loss does it cause, as opposed to other factors? It seems that the importance lies in the screening for Met allele carrier status and determining which patients are at particular risk for brain loss.

A: We know that brain tissue loss occurs in schizophrenia prior to treatment. It is probably crucial to consider genetic factors in addition to a single gene such as BDNF. Almost certainly, future research will identify the involvement of a large number of genes, each of which has a small effect, with different patterns in different people. Prof. Andreasen added that the majority of schizophrenics are not experiencing brain tissue loss; around only 13% of patients are losing in the region of 1% of brain tissue annually over the first 3 years of illness.

Q: Is it possible to expand on the discussion of compounding effects of dosage intensity and severity of illness? It could be that the higher the dosage, the more severe the illness, but it might also be that when a higher dosage was used, the measures of severity decreased because the patient was being treated more effectively.

A: It is true that the more severely ill patients are likely to be treated with higher neuroleptic doses. Prof. Andreasen believes that this question was adequately addressed with the data from the Iowa Longitudinal Study, in which the statistical analysis independently examined treatment dose and illness severity, controlling for illness severity and treatment intensity, as well as substance abuse. The other question is what is meant by disease severity: the analyses revealed that however disease severity was defined (e.g., level of symptoms using standard rating scales, psychosocial function) made no difference to the findings; there was only a very modest relationship between severity and brain tissue loss.

Q: Can psychological therapies make a difference in different aspects of schizophrenia, such as with misconnections and in neuroplasticity? Would this be worth investigating in terms of effects upon brain volume?

A: Potentially, psychological therapies (e.g., cognitive therapies, supportive therapies) and other kinds of nonpharmacological therapies could be helpful. As yet, we lack sufficient study data to know for certain whether such therapies affect brain volume.

Q: In the study data showing brain loss associated with different drugs, it seemed that clozapine was associated with the least amount, followed by risperidone, and the greatest loss occurred with typical antipsychotics. These findings are difficult to understand when the drug receptor profiles are considered; risperidone is closer than clozapine in pharmacological profile to typical antipsychotics.

A: Several factors need to be considered when assessing the study findings. Prof. Andreasen pointed out that they are derived from a small study sample and need to be replicated with larger numbers. Clozapine, the agent that seemed to have the best effect, has a diverse spectrum of effects and it has not been satisfactorily explained as to how it can behave so effectively as an antipsychotic.

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