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Editorial paper

Concerns about depression*

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Summary – Biological depression research can boast of a number of significant achievements over the past 35 years. Yet, in spite of those achievements, the field is in danger of desiccation. Five reasons are discussed herein: 1) short-comings of the DSM-based depression classification; 2) the ever increasing number of, generally poorly validated, diagnostic categories; 3) desubjectivation of psychiatric diagnosing; 4) the lack of a dimensional (better: functional) component in diagnosing depression; and 5) horizontalism, *ie* the absence of attempts to group symptoms "vertically" according to their diagnostic weight. The issues are in need of urgent scientific attention, lest biological depression research will stagnate and ultimately whither. We have indicated ways to approach the issues.

depression / biological research in depression / nosological and dimensional depression classification / primary and secondary symptoms in depression

THESIS AND ANTITHESIS

Videtur quod non; such was the formula often used by mediaeval theologians in launching a debate. *Videtur quod non:* it would appear that such and such is not. The scholars thus frequently initiated their discussions with arguments militating against their thesis (Vermes, 1983).

In the case of my thesis, this approach seems most appropriate. It would appear, that biological depression research is in no way a subject to be concerned about. It can indeed boast of a number of significant achievements over the past 35 years. I mention four major ones.

1) Until recently, no standardized and operationalized classification system for depression existed. Diagnostic criteria and definitions varied by psychiatric school, by language group, by textbook. The publication of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) in 1980 concluded this epoch, by providing psychiatry for the first time with a standardized, operationalized and now generally accepted classification system.

2) With the introduction of the antidepressants, psychopathological and diagnostic research of mood disorders started to flourish as it had never before and the bloom shows no signs of waning.

3) The antidepressants represented a new pharmacological principle. Up to then electroconvulsive therapy was the only specific biological treatment of (certain types of) depression. With the introduction of the antidepressants many more patients could be treated in a non invasive way.

4) Before 1958, the field of biological depression research was virtually untrodden. At present, a wealth of biological findings has been reported, biochemical, endocrinological, and physiological in nature. Wherever one digs, it seems, new findings emerge.

Yet, in spite of all the achievements, this presentation will be, no hymn. Within the four domains I mentioned, I will caution, rather than praise, caution for growth that went awry, for deceitful-growth, that is for motion in the wrong direction, leading to stagnation and even decline. Recognizing one's weaknesses is a better posture to make headway than self-sufficiency. A priori I want to

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underline is that my argument pertains particularly to research, less to clinical practice.

CLASSIFICATION

Shortcomings of the DSM depression classification

The classification of depression, as proposed by the DSM-III, is standardized, operationalized and generally accepted. As much as it obviated the existing chaos, it created a new one of its own making, less obvious than the old one but no less detrimental to biological depression research. In the DSM-III the "choice principle" was introduced. For the diagnosis of a particular syndrome the presence of X out of a list of Y symptoms suffices, no matter which ones. Hence, the various disorders that are distinguished are symptomatologically ill defined. In fact, many different syndromes carry the same designation: major depression and dysthymia. Based on nosological principles as the DSM-III is, depressive syndromes are coupled to non-symptomatological variables, particularly to severity, duration and premorbid personality structure, in an attempt to delineate discrete diagnostic entities characterized by multiple criteria. The utility of the categorical constructs, however, is questionable. Our studies at least have failed to validate them (van Praag, 1989). Duration, severity and personality structure vary across the various depressive syndromes and offer no support to anchor discrete mood disorders. For those reasons, I consider these concepts unsuited for depression research, particularly biological research, requiring as it does well-defined and assessable diagnostic concepts.

Another fundamental shortcoming of the present system is the lack of an etiological axis. The rationale for this is the wish to be "atheoretical". But, as I have argued elsewhere, with today's methodologies, one can arrive at an etiological hypothesis with no less reliability as one can regarding the presence or absence and severity of particular psychopathological symptoms.

For biological research, the absence of an etiological axis is counterproductive since biological variables might very well vary with the etiological conditions under which a particular depressive syndrome emerges.

Another factor which has not been approached satisfactorily, is that of comorbidity, *ie* the concurrent presence of depression and other psychiatric disorders, considered to be independent. To face this situation, the latest editions of the DSM utilize the hierarchical principle, according to which psychiatric disorders are rank ordered according to severity and the more severe disorder takes precedence over the less severe. For the diagnosis of major depression, psychotic and organic conditions have to be ruled out. The diagnosis of generalized anxiety disorder cannot be made in the presence of a mood disorder.

This principle is not applicable in biological psychiatry. One can and should not simply discart the possibility that a biological variable observed in a psychotic condition is linked to a concurrent depression, or one found in depression is in fact related to an anxiety disorder (Van Praag, 1995).

Another approach to handle the problem of comorbidity is to provide one and the same patient with multiple diagnoses. In that case, however, one finds oneself unable to decide to which of the diagnoses a particular biological variable relates.

Finally, the ever changing definitions of depression in the successive DSM editions lead to a confusion of tongues, and incomparability of data collected under the various DSM editions.

All in all, our efforts to come to terms with the classification of depression have produced a system, seemingly scientific and sophisticated, but in fact seriously handicapping progress in biological depression research.

To remedy the situation, diagnostic methodologies in biological depression research have to be drastically changed.

Starting point should be a sharply defined syndrome, *eg* the syndrome of vital or endogenous depression. Patients not meeting all symptomatological criteria should be excluded. This approach probably leads to many false negative cases, but has the invaluable advantage that the object of study is unambiguously defined.

Since no predictable relations are known between depressive syndromes and such non-symptomatological criteria as severity, duration and premorbid personality structure, these variables should be assessed on independent axes.

Next, the syndrome has to be dissected in its elementary components, *ie* the psychological dysfunctions, that are to be assessed and measured with the appropriate instruments (see Biology section).

Finally, the diagnostic analyses should comprise an etiological component (or hypothesis, if one so wishes) so that the impact of etiological heterogeneity of the syndrome on its pathogenesis can be studied.

Nosologo-mania

Another concern I entertain, with regard to classification, is the present exaltation with nosological categorisation. I am alluding to the urge to discover ever and again new disorders, without much evidence that they are singular, that they are more than slight variations of the disease categories that were distinguished thus far. The DSM-I contained 106 psychiatric diagnosis, the DSM-II, 182; in the DSM-III the number of disorders had grown to 265 and in the DSM-III-R a total of 292 diagnostic categories was reached.

The diagnostic splintering did not pass by the group of mood disorders. One reads about major depression, minor depression, double depression, dysthymia, unipolar and bipolar depression, depressive personality, depression not otherwise specified, brief recurrent depression, subsyndromal symptomatic depression, mixed anxiety depression disorder, seasonal depression and adjustment disorder with depressive mood (though not all these categories have as yet been sanctioned by the DSM). Seeing so many trees, one searches desperately for the forest.

Nosology reigned supreme in Kraepelin's days and in the time of his immediate successors. This diagnostic approach witnessed another upsurge with psychiatry's move towards the empirical sciences. Psychiatrists aspired to become scientists. Scientific physicians study concrete and discrete diseases. So we grouped psychopathological phenomena accordingly. But yet, though psychiatry's conversion to empiricism could explain the revival of nosology, it does not account for the proliferation of disorders prior to and in the wake of the publication of the DSM-III. Did we notice too little in the past, or too much in the present? The latter is likely to be true. It is the way it was decided to categorize mental disorders that boosted the nosologomania.

1) Diagnostic concepts are essentially symptomatologically based while each of those – thanks to the "choice principle" – can encompass a variety of syndromes. This approach causes marked overlap between diagnostic categories and so encourages delineation of novel entities. For instance, mood- and anxiety-disorders strongly overlap and thus the DSM Work Group seriously considered a new diagnosis *ie:* mixed anxiety depression disorder, a diagnosis that was indeed adopted by the ICD 10.

2) To conceptualise genuine "disorders", syndromal concepts were coupled to non-symptomatological criteria, such as duration and severity. For instance, to qualify for the diagnosis major depression the depression has to be severe, time-limited, but having lasted for at least two weeks. Depressions, however, differ markedly both in severity and in duration. Moreover, what "severe" means is not further specified. So a variety of new diagnoses was born, such as dysthymia, minor depression, brief recurrent depression and subsyndromal symptomatic depression.

3) Many patients with depression suffer in addition from personality disorders, some do not. If they do, the border between mood- and personality-disorder is often hard to draw. This prompted the consideration of a new diagnostic category: depressive personality disorder.

4) The present taxonomy of psychiatric disorders has not incorporated criteria for severity. Hence we do not dispose of guide lines to discriminate disorder from distress. This permits a diagnosis like "adjustment disorder, with depressed mood" and eight additional types of adjustment disorder.

There are, however, many more ways in which distress can be expressed, thus permitting that in the future a lot more of human misfortune and misery could be brought under the denominator of a mental disorder.

The validity of many of those diagnostic concepts is unproven, uncertain or even questionable. Imagine that one day they would be shown to lack validity; suppose a concept like dysthymia would strongly overlap with and insensibly merge into diagnoses such as major depression, generalized anxiety disorder, adjustment disorder, and various forms of personality disorder; our persistent efforts to find biological markers of these disorders, to elucidate their genetics, their epidemiology, to unravel the differential therapeutic effects of the various biological and psychological interventions, would have been largely futile.

I do not profess this somewhat gloomy scenario to necessarily come true, but I do maintain that validity studies should have taken precedence over all others. Research of non-validated concepts runs the risk of generating non-valid results, however great its methodological sophistication.

Inflationary pressures on mental disorder

The absence of anchor points distinguishing distress from disorder, I mentioned as a contributor to the proliferation of diagnostic categories in psychiatry. One could easily imagine that this deficiency could, in addition, lead to overestimation of the frequency of mental disorder in the general popu-

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lation. This indeed seems to have happened, as exemplified by the recent National Comorbidity Study, carried out in the USA (Kessler *et al*, 1994).

In that study, a cohort of approximately 8,000 people randomly selected from the normal population, aged between 18-54 years, was studied as to the occurrence of mental disorder, presently or in the past. Nearly 50% of respondents reported at least one lifetime psychiatric disorder and close to 30% reported at least one 12-month disorder.

The latter figure comes close to that reported by the NIMH Epidemiological Catchment Area Program (Regier *et al*, 1993). After 20,000 household diagnostic interviews in 1980, follow-up data were collected from more than 16,000 individuals between 1981 and 1985. Of that cohort 28.1% were reported to have (DSM-III) diagnosable disorders during a one year period, but only 28.5% of them had sought professional help.

These results lack credibility. Half the population having been mentally ill at least once during their life time? Imagine what these figures would have been if subjects up to 75 years of age would have been included. Prevalence figures approaching 100% could have been expected.

The reason for those, I believe, grossly inflated frequency figures is that emotional states like stress, distress, discontentness and bewilderment are mistaken for mental disorders. Since clear differential diagnostic criteria are lacking, it is absolutely mandatory that psychiatric interviewing in epidemiological studies is done by experienced clinicians. This has not been the case in the studies under discussion. In Kessler *et al's* (1994) study, for instance, interviews were carried out by lay interviewers, after a course of one week and using a standard interview, *ie* the Composite International Diagnostic Interview.

Like the Catchment Area study, the Co-morbidity Study furthermore concludes that many people with, alledgedly, psychiatric illnesses did not get psychiatric treatment. "Even among people with a lifetime history of three or more comorbid disorders, the proportion who ever obtained specialty sector mental health treatment is less than 50%." The authors plea for more outreach and more research on barriers to professional help-seeking. They, apparently, did not consider the possibility that not seeking help might have been conditioned by the fact that those people were not mentally ill, did not feel mentally ill, and therefore did not try to obtain psychiatric treatment. To me, however, this seems a valid option.

How could one conceive of arriving at a meaningful demarcation between distress and disorder, between the point where normality comes to an end and pathology commences. It is hard to imagine absolute criteria, but even in hard-core somatic medicine these are frequently lacking. There is nothing absolute in the agreement that a blood pressure of 120 over 80 is normal, and one of 160 over 110 is pathological. Pathology in this case is defined in terms of diminished life expectancy, *ie* an increased risk of being struck by brain, cardiac and some other disorders.

In the same vein, the transition of mental distress to mental disorder could be defined and operationalised on the basis of prognostic criteria, *ie* the risk that a particular behaviour or experiental state will lead to vocational or social disability or to a significant and sustained drop in quality of life.

So far the earlier stages of mental pathology have hardly been studied in a systematic and probabilistic way. Yet this seems to me an inevitable, though cumbersome and time-consuming exercise in order to eventually acquire realistic estimates of the occurence of mental disorder in a given population.

DIAGNOSIS

Psychopathological research flourishes as it never has before. Great strides have been made towards the assessment and differential diagnosis of depressive phenomena. Subtyping of the DSM-III proposed mood disorders is the order of the day. All this is remunerative; yet there is a definite debit to the account, *ie* that psychiatric diagnosing is de-subjectivized and de-historysized (Van Praag, 1992a).

Contrary to diagnostic studies in bygone days, it is now required that diagnostic criteria are operationalized, *ie* well-defined; that diagnostic concepts are standardized, *ie* linked to clear criteria; that diagnostic criteria are essentially measurable, both the symptomatological and the etiological criteria. In other words, objectivity is the catchword in psychiatry today.

Diagnoses are preferably based on phenomena in observable behavior which may be diagnosed independent of verbal communication and on symptoms unambiguously agreed to upon direct questioning ("Yes, indeed, I feel depressed"). Diagnoses are preferably anchored to etiological variables that leave little room for doubt, such as definite family loading, demonstrable brain lesions and life events with "absolute" valence, that is with traumatic impact for the average individual.

Diagnoses are preferably assessed with so-called objective instruments, *ie* instruments that are minimally influenced either by the patient who exhibits the symptoms or by the investigator who registers them.

In the process of objectification a great deal of relevant information is being lost. First, the phenomena closer to the subjective pole of the psychopathological spectrum. I refer here to two types of phenomena. Firstly, those that are confined to the patient's experiential world, are not expressed in observable behavior, and are "atmospheric" rather than "factual" in nature, that is, not manifesting themselves as delineated mental phenomena and not verbalised as such. The quality of the depressed mood is an example.

A second group of psychopathological phenomena can be described as purely subjective, not because they are "diffuse" and remain confined to the patient's experiential world, but, because they are conceptualized in the interviewer's/observer's mind. The meaning of a particular behavior or utterance, or of habitual attitudes of the patient are examples. Those are construct generated by the interviewer/observer and not communicated, as such, by the patient.

How diagnostically important is subjective psychopathology? As said, the question is largely ignored in experimental psychiatry. On face value, I am inclined to consider it of crucial not of marginal diagnostic importance and our own, very preliminary data support this view (van Praag, 1992b).

Another victim of today's diagnostic reductionism is the notion of psychogenesis: the weighing of psychological factors in the occurrence of a particular psychiatric disorder. The DSM-III based classification system is the main culprit. First, it has refrained from an etiological axis. Second, it permits independent assessment of axes I and II diagnoses, and does not require a statement, hypothesis if one so wishes, about the connection of transient psychopathology and stable personality pathology.

In mood disorders, this interconnection seems particularly close and cannot be ignored with impunity; not with regard to treatment and prophylaxis of depression and not with regard to the interpretation of biological data. A biological disturbance observed in a depressed patient should raise the question whether it relates to the depression as such, to components of the depression, to a concomitant (underlying) personality disorder or to particular personality traits. Moreover, one cannot resolve the crucial question whether the relation between the personality pathology and the depression is coincidental or causal, by simply ignoring it.

Finally, I consider the evaluation of life events to be unsatisfactory. Admittedly, axis IV, provides an opportunity to assess the pathogenic valence of a psychosocial stressor. The rating should be based, however, on the clinician's assessment of the stress an "average" person in similar circumstances and with similar sociocultural values would experience from the particular psychosocial "stressor". In other words, the factor personality vulnerability is ignored and only "absolute" events are recorded, not the "relative" events, those that a normal individual can cope with, without detrimental effects, but are harmful for dysfunctional personalities. With the latter we deal in psychiatry, not with "average persons". Not recording relative life events is bypassing a lot of potentially important pathogenetic life experiences.

The practice of judging axes I, II and IV independently ignores the possibility – probability, I gather – that in depression those three domains are broadly overlapping, and does not invite to formulate hypotheses and corresponding research. In psychodynamic psychiatry, relationships between mood, personality and life events have been taken for granted. In experimental psychiatry, belief in the self-evident has been lost, but with the diagnostic approach it champions, the remedy could become as serious as the disease.

BIOLOGY

A lot of "biology" has been uncovered in the various mood disorders. Frequently one can observe disturbances in monoamine metabolism and functions, endocrine irregularities, disturbances in sleep-architecture, to mention only a few examples. The diagnostic specificity of these findings for the group of mood disorders is low, the specificity for a particular mood disorder even lower. In other words, in spite of an intensive search for more than 35 years, no biological markers for depression, have been spotted; no biological variable that can be utilized for diagnostic purposes.

What could be the reason for this disappointing state of affairs? First, we could have been barking up the wrong tree, studying biological systems irrelevant for depression. This seems unlikely. Little doubt exists that monoaminergic neurons are involved in the regulation of emotional systems like mood, anxiety and aggression. Systems that are in a major way unsettled in mood disorders. Endocrine systems contribute to preservation of

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homoeostasis if a person is exposed to psychological or biological stressors. Though we do not know the exact relation between depression and stress, it seems likely that the two conditions are strongly intertwined. Sleep disturbances are a prominent feature of most depressions, so it is hard to imagine that sleep research in depression would be besides the point.

A second reason, why biological markers of depression have so far been elusive, could be that the diagnostic concepts studied, are too ill-defined and therefore too heterogeneous. This explanation could make sense. As mentioned before: the various mood disorders, as presently defined, are syndromally extremely heterogeneous and wrapped in nosological "packages" with little validity. Concepts like major depression and dysthymic disorder are but broad basins for a wide variety of depressive conditions.

The search for a "marker" and eventually a "cause" of major depression is like searching for a marker or a cause of the group of abdominal disorders. Few would deny that in the latter case the chances of success would be slim. The same holds true, it seems to me, in the former case.

A third explanation for the diagnostic aspecificity of biological variables is that we could be operating at the wrong level of psychopathological analysis. For a long time we used to correlate biological variables with nosological entities or syndromes and were left with empty hands. There exists, however, a third level of analysis, the one I have designated as "functional". Syndromes can and should be dissected in their elementary components, *ie* the psychological dysfunctions. In doing so one would obtain a much better idea of what components of the psychic "apparatus" are functioning deficiently, and which are still operating within the normal range. In this way a "psychiatric physiology" would be developed (van Praag, 1992b).

It could be that the biological dysfunctions found in depression are linked to psychological dysfunctions rather than to syndromes or nosological entities. Since psychological dysfunctions are seldomly specific for a particular syndrome or nosological entity, but occur across diagnoses, one would, in that case, expect biological variables to be likewise nosologically and syndromally nonspecific.

Quite some evidence indicates that indeed this might be very well the case and that, for example – as we have suggested – serotonergic dysfunctions are linked to anxiety and aggression, dopaminergic disturbances to motor retardation and hedonic dysfunctions to disturbances in the noradrenergic systems. These relations seem to be not restricted to depression but occur also in other diagnoses. In other words, these biological variables are functionally specific – not syndromaly or nosologically – *ie* related to psychological dysfunctions, across diagnoses.

Two ways then, could make biological depression research more diagnostically meaningful: precise definition of the syndromes to be studied and their systematic functional analysis. Methods to carry out such analyses in a sophisticated way, should be developed in collaboration with experimental clinical psychologists.

ANTIDEPRESSANTS

Over the last 35 years a number of agents have been developed with beneficial effects in depression. Gradually, however, it became clear that their name "antidepressants" is much too restrictive. Tricyclic antidepressants for example, are effective in major depression, in panic disorder as well as in generalised anxiety disorder (Rickels *et al*, 1993); monoamine oxidase inhibitors exert beneficial effects in major depression, atypical depression and panic disorder; serotonin uptake inhibitors have been successfully used in various types of depression, in panic disorder, in obsessive compulsive disorder; lithium is used in the prophylaxis of uni- and bipolar depression and as an anti-aggression agent.

Such astonishing observations could indicate that these so-called antidepressants do not affect so much depressive syndromes or disease entities but components of them, components that also occur in other psychiatric conditions which are *mutatis mutandis* likewise favourably influenced. If that supposition were correct, a second conclusion would logically follow, namely that not all components of depression have equal diagnostic weight. That some symptoms are primary, that is the immediate consequences of the pathogenetic process, while others are derivatives.

In present day's psychiatry we tend to group symptoms horizontally, as if they were all of equal diagnostic weight. The group of mood disorders is no exception to this rule. This approach resembles the internist who, in a case of pneumonia, would attach the same diagnostic valence to the symptom of fatigue as to the symptom of shortness of breath.

Our predecessors, such as Kraepelin, Bleuler and Schneider, had a different approach and grouped symptoms according to their alleged diag-

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nostic weight. Their views were not empirically tested, but yet the approach is important. It is *a priori* unlikely that all components of a syndrome are of equal diagnostic importance. Psychiatric diagnosing should once more develop a vertical momentum, and attempts to weigh psychiatric symptoms should be reinstated as a rightful endeavour in scientific psychiatry.

Our studies of mood disorders are a case in point. They led us to the conclusion that a subgroup of depression exists in which serotonergic functioning is demonstrably disturbed and in which anxiety and/or aggression dysregulation are the primary psychopathological features, and mood lowering is a subsidiary. If true, the proper treatment of such serotonin-related, anxiety/aggression-driven depressions would be an anxiolytic and/or serenic that ameliorates anxiety and/or aggression *via* regulation of serotonergic circuits (Van Praag, 1992, 1995).

Thus the "vertical approach" in diagnosing depression could fundamentally alter the direction of the search for novel antidepressants.

EPILOGUE

The yield of 35 years of biological and psychopathological depression research is on the one hand impressive, but on the other hand it is hard to deny that in several respects we have been marching ahead in a blind alley. If we fail to acknowledge that, progress will stagnate. If we do retrace our steps, if we do discerne the barriers to progress, develop new methodologies and dare to leave behind old and worn out concepts, there is every reason to believe that depression research will continue to bloom.

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