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Review

Dal 1963 al 2013, da Umberto Pallotta, Pompeo Capella e Edoardo Turchetto in poi: "I lipidi in 50 anni di ricerca"

Massimo Cocchi

"Paolo Sotgiu" Institute for Research in Quantitative & Quantum Psychiatry & Cardiology, L.U.de.S. University
Department of Veterinary Medical Sciences, University of Bologna

«From 1963 to 2013, from Umberto Pallotta, Pompeo Capella and Edoardo Turchetto to the future: "Lipids in 50 years of research»

Summary. After 40 years since I entered the glorious Institute of Biochemistry, University of Bologna and began to deal with lipids, fatty acids and their tissue and cellular metabolism. That was the time of the demonization of saturated fat and cholesterol; substances that were considered "hurt" the body. I must say, for intellectual honesty, that our "School" never for a moment believed in this axiom, as documented in the long sequence of scientific papers produced. Even science as politics is often dominated by movements of thought and leadership affected by interests that have little to do with the knowledge of phenomena, with a genuine scientific speculation, documented and critics. However, it is not this, the time of polemics but to restore some truth, that not only give confidence to those who believe in science, but that lead back the thought and knowledge in the right direction. This is the case of fatty substances, of the lipids that with the daily eat, with the worry of mind, almost religious, committing sin. Even in science, with the economic power and the misuse of the mathematical discipline called statistics, you can prove everything and support it in the face of scientific, complacent, communities. Well, Aseen Malhotra, says in his "observations" in the British Medical Journal: "Correlation" does not mean "Cause". Lipids, fatty acids and cholesterol are living a new course, their roles and functions are restoring, roles and functions that, too often and superficially, have been addressed and discussed. During those glorious years in the Biochemistry of Bologna we realized that most of the phenomena related to the "lipid handling" should be interpreted through the behavioral study of biological membranes and the relationships that they contracted between the inside and outside of the cell. We were, from the beginning, convinced that it was inappropriate to make excessively fluid the cell membranes and that it was also inappropriate to demonize saturated fats and cholesterol. Even, and especially from them, depended the functioning of regulatory activities, in the biochemical sense, of the cellular traffic. Today, with searches that investigate the man and the animal, with a simple blood test, and with the aid of complexes mathematical tools, which can not be manipulated, many of the phenomena which was convinced are confirmed for a role of saturated fat and cholesterol as essential agents in the control of the correct function of the membrane which, however, does not tolerate nor extreme excesses or deficiencies, to the detriment of dysregulation of the entire biochemical system. The drastic elimination of the visible fat from foods of animal origin and the push for more and more desired reduction in serum cholesterol will dispense, with both hands, rebound of clinical problems, to say the least, devastating. The different chapters of research addressed, faced the lipid and fatty acids research in various experimental conditions: cell culture, animal, man. Below is summarized the search path made up to the latest experimental evidence in areas that have proved indispensable links with lipids and in particular with fatty acids. The study of lipids, and of the fatty acids of tissues and cells, allows important nutritional and diagnostic interpretive skills, as well as has been proved essential, on some occasions, the use of complex mathematical functions (Artificial Neural Networks) to the understanding of phenomena that otherwise would not have been possible, and that led to the opening of new frontiers of knowledge in biological and clinical conditions of high complexity. They involve the heart and the brain.

Key words: Lipids, omega 3 fatty acids, omega 6 fatty acids, cholesterol, ethanol, platelets, mood disorders, ischemic heart disease

Riassunto. Sono trascorsi 40 anni da quando entrai nel glorioso Istituto di Biochimica dell'Università di Bologna e cominciai ad occuparmi di lipidi, di acidi grassi e del loro metabolismo tissutale e cellulare. Era quello il tempo della demonizzazione dei grassi saturi e del colesterolo, erano considerate sostanze che "facevano male" all'organismo. Devo dire, per onestà intellettuale, che la nostra "Scuola" mai per un momento ha creduto in quest'assioma, com'è documentato nella lunga sequenza dei lavori scientifici prodotti. Anche la Scienza come la politica è sovente dominata da movimenti di pensiero e da leadership che risentono d'interessi che poco hanno a che fare con la conoscenza dei fenomeni, con la speculazione scientifica vera, documentata e critica. Comunque, non è questo tempo di polemica ma di ripristino di alcune verità, che non solo diano fiducia a chi nella scienza crede, ma che esse riconducano il pensiero e la conoscenza nella giusta direzione. È questo il caso delle sostanze grasse, dei lipidi che quotidianamente assumiamo con il patema d'animo, quasi religioso, di commettere peccato. Anche nella scienza, con il potere economico e con l'uso scorretto di quella disciplina matematica che si chiama statistica, si può dimostrare ogni cosa e sostenerla di fronte a comunità scientifiche compiacenti. Ben dice Aseen Malhotra nelle sue "observations" sul British Medical Journal: "Correlazione" non significa "Causa". Lipidi, acidi grassi e colesterolo vivono un nuovo corso, si stanno ripristinando ruoli e funzioni che troppo spesso e superficialmente sono stati affrontati e discussi. Durante quei gloriosi anni nella Biochimica di Bologna capimmo che la maggiore parte dei fenomeni legati alla "movimentazione lipidica" doveva essere interpretata attraverso lo studio comportamentale delle membrane biologiche e delle relazioni che esse contraevano fra interno ed esterno della cellula. Fummo, fin dall'inizio, convinti che fosse inopportuno rendere eccessivamente fluide le membrane cellulari e che era anche inopportuno demonizzare i grassi saturi e il colesterolo. Anche, e soprattutto da loro dipendeva il funzionamento delle attività regolatorie, in senso biochimico, del traffico cellulare. Oggi, con ricerche che indagano l'uomo e l'animale, in modo incruento, e con l'ausilio di strumenti matematici complessi e non manipolabili, molti dei fenomeni di cui si era convinti trovano conferma per un ruolo dei grassi saturi e del colesterolo come agenti imprescindibili nel controllo della corretta funzione di membrana la quale, tuttavia, non tollera né eccessi né carenze estreme, pena la destabilizzazione dell'intero sistema biochimico di regolazione. La drastica eliminazione del grasso visibile dagli alimenti di origine animale e la spinta alla sempre più auspicata riduzione della colesterolemia dispenseranno a piene mani problemi di rimbalzo clinico a dire poco devastanti. I diversi capitoli di ricerca affrontati affrontavano il problema lipidi e acidi grassi in varie condizioni sperimentali: colture cellulari, animale, uomo. Di seguito è riassunto il percorso di ricerca effettuato fino alle ultime evidenze sperimentali in settori che hanno rivelato legami imprescindibili con i lipidi e in particolare con gli acidi grassi. Lo studio dei lipidi e degli acidi grassi tissutali e cellulari consente importanti capacità interpretative di tipo nutrizionale e anche diagnostico, così come si è rivelato imprescindibile, in alcune occasioni, l'utilizzo di funzioni matematiche complesse (Reti Neurali Artificiali) per la comprensione di fenomeni che altrimenti non sarebbe stata possibile e che hanno portato all'apertura di nuove frontiere conoscitive in condizioni biologiche e cliniche di elevata complessità, coinvolgendo esse il cuore e il cervello.

Parole chiave: Lipidi, acidi grassi omega 3, acidi grassi omega 6, colesterolo, etanolo, piastrine, disordini dell'umore, cardiopatia ischemica

Summary of research

1) Ethanol and lipid metabolism

The effect of ethanol on lipid homeostasis has been studied in rat liver. The phospholipid pattern and the correlated fatty acid modifications were in dose relation to the entity of ethanol intake. At an early stage, this phenomenon was reversible, as ethanol was excluded from the diet, but if at the same time animals received an hypoproteic diet, which worstened the biochemical damage, it could not return to a normal sta-

tus. The influence of ethanol on cultured cells has been studied by evaluating the cell growth and respiration in the presence of different ethanol concentrations.

2) Studies concerning unusual fatty acids

Studies performed both in experimental animals and in men confirmed perplexity concerning the use of oils containing a large percentage of erucic acid (C 22:1 n-9), which is responsible for some biochemical, functional and anatomic changes in the heart, where large intake of this acid might induce histiocitary infiltration. These investigations had shown the presence of C 22:1 n-9 in rat heart, both <in toto> and in phospholipidic fractìon. Studies performned on serum had pointed out that the dietary intake of colza and rapeseed-oils) ifluenced the acidic composition of the plasma lipids, changing their normal pattern also in man. The results obtained with these experimental studies have been submitted to the Ministerial Committee, to determine the utilization rules for the use af the above mentioned oils. Moreover, the influence of trans fatty acid intake on the acidic composition of different organs (adipose tissue, heart, liver ecc.) has been studied. The increased consumption of dietary hydrogenated fats, containing these non-physiological isomers, has motivated these studies. The results have notably evidenced a trans fatty acid accumulation in the considered organs, even though in different percentages, not proportional to the dietary intake of these isomers. The administration of a large amount of trans fatty acids also affected essential fatty acid and cholosterol level) in the plasma. Regarding the influence of these stereoisomers on the respiratory activity of heart mitochondria, it has been noted that, in particular stress conditions, mitochondrial activity was decreased, probably in relation to the presence of trans fatty acids in the heart phospholipids.

3) Dietary lipids and tissue lipids

Research about dietetic and tissue lipids correlations have been performed on rats for different times (60, 120, 180 and 360 days) until the maximum of 540 days, in order to evaluate the effects of long term treatmentIt has been pointed out that not only stored lipids were influenced by dietary modifications, but also cellular lipids may be affected later on. Even brain lipids, generally considered as constant, changed in function of the different dietary fatty acids. This concerned not only the gliceride but also the phospholipid fraction. The same modifications were observed in heart, liver, muscle and blood. Significant modifications in total lipids, phospholipids and in fatty acid composition were observed in mitochondria, in microsomes and, to a less extent, in the hepatocyte nucleus. In order to elucidate the lipid and coenzyme Q10 modifications, were used different diets, such as alipidic (Dewel), hypercholesterolemic (Peifer) and vitamine E deficient (Edwin). All these diets caused a notable decrease of coenzyzne Q10, especially in the heart. The lipid content and the fatty acid pattern have been also studied in Rinolophus ferrum aequinum during hibernation. Results showed a decrease in total lipid content, with detectable percent modifications in the fatty acid composition. In particular, essential fatty acids (EFA) and oleic acid decreased while saturated fatty acids increased and no modifications were observed in the brain.

4) The long chain fatty acid metabolism in ruminant

Some studies performed on sheep have shown that the fatty acids present in rumen are different from those present in the diet, and that dietary linoleic and linolenic acid hydrogenation and new odd ramificated fatty acid biosynthesis are operating. The «in vitro» calculation of long chain fatty acid biosynthesis in the ovine rumen was possible using an alipidic diet. It showed not only the presence of odd ramificated fatty acid, but also linoleic acid biosynthesis.

5) Fatty acids of the n-6 and n-3 series

The most recent knowledge about polynsaturated fatty acids was concerned with the problem correlated to n-6 and n-3 fatty acids. These acids are very important not only for their role in cellular and sub cellular structure composition, but also as precursors of prostanoids, which have important and differentiated physiological functions. In particular, gamma-linolenic acid (n-6) is very effective in modulating the balance

between aggregating and non aggregating prostaglandins, by supporting PGEI synthesis in spite of PGE2. The higher fatty acids of the gamma-linolenic family (n-3) have a fundamental structural function in brain, retina, gonads, etc. Research performed in this field has provided greater knowledge abaut n-6 and n-3 fatty acid metabolic turnover, the dose correlations among fatty acids of the two series, as well as their competition towards the specific elongation and desaturase enzymes. In particular, some differences in the organ acidic composition of rats fed with diets having different n-6 and n-3 fatty acid amounts have been reported. Such differences were noted also in mitochondria, but they had no influence on normal function, as the mitochondrial respiratory activity appeared to be normal. Dietary alfa-linolenic acid supply seems to be very important for the nervous system. Following alfa-linolenic intake, some structural modifications are detectable, both in the brain «in toto» and in single structures such as optic and trigeminal nerve. C 18:3 n-3 metabolism has been observed also in the chick embryo. It has been reported that the area of biosynthesis of specific fatty acids in the maturation stage shifts towards particular organs at the end of embryo growth period.

6) Studies about Essential Fatty Acid (EFA)

Some investigations have tried to determine the EFA requirements The results obtained in experimental animals (rats) pointed out that the largest EFA requirement corresponded to the central period of life, being higher far men than for women. This has allowed toevaluate the EFA requirements on the basis of the tissue lipid homeostasis and of the total fatty acid pattern. Large intakes of EFA, at first, determined an increase af lipid fatty acid unsaturation in all tissues, including the brain, and in subcellular structures, like 1iver mitochondria. Afterwards, the phenomenon decreased and the biochemical aspect of these structures returned to normality. This seemed to show a tissutal defence mechanism against too high EFA amounts. The adipose tissue also had its own homeostatic control and didn't store up, in these experimental conditions, essential fatty acids beyond a definite limit. On the contrary, collateral research using EFA deficient diets has shown alterations of spontaneous and provoked motility in experimental animals and, moreover, a decrease in learning ability and in recent and remote memory.

7) Cellular nutrition

This research line has been performed on cultured heart ceils from chick embryo. The effects of different nutrients, like glucides, ethanol and phospholipids on the proliferation and the respiratory activity of chick embryo myocardial cells, cultured in hanging drop, have been evaluated. The addition of phospholipids to the cultures, aL low concentrations, has shown a positive effect on cell growth, both in basal and in stress conditions while at higher concentrations, phospholipids appeared to be negative. These results differed in relation to the organ from which phospholipids were extracted, and this well correlated with some clinical studies based on enteral or parenteral phospholipid supply in men. Briefly, it has been shown that exogenous phospholipids, at adequate concentrations, can stimulate the rate of macromolecular synthesis processes, by potentiatìng the action of serum growth factors in cultured cells. As far as the mechanism of action of phospholipids is concerned, this appears to be exerted through the modulation of some endogenous factors, such as cyclic nucleotides (AMPc e GMPc) and poliyamines (putrescine, spermidine, spermine), closely involved in the regulation of biochemicai processes notable linked to the rate of cell growth and division.

8) Changes in lipid metabolism during development and growth

The tissues of the developing chick embryo display particularly high levels of C20 and C22 polyunsaturated fatty a.sids. These fatty acids are derived during yolk lipid uptake by synthesis within the yolk sac membrane and preferential absorption of phosphatidyl ethanolamine. The yolk contains a finite level of vitamin E. The marked increase in double bonds associated with polyunsaturated fatty acid accumulation in the embryo tissues therefore poses the question whether adequate levels of vitamin E are maintained thrcughout yclk lipid absorption to afford protection against peroxida-

tion. The relationship between vitamin E and polyunsaturated fatty acid levels in the yolk contents, yolk sac membrane and tissues during development of the chick embryo was studied.

9) Platelet Fatty Acids in Depressive Disorder and in Ischemic Heart Disease

In 2005 he started, with Lucio Tonello, to study the platelet fatty acids in groups of patients (Depressive and Ischemic) realizing a combination between Biochemistry and Artificial Neural Network which has allowed to identify subjects with Major Depression from Bipolar Disorder and the ischemic subjects from the apparently normal people.
On the argument many papers, meetings and conferences have been hold.

Recent advances on fatty acids metabolism and functions
BMJ 2013 Letter to the Editor

Platelet's Fatty Acids Secrets in Coronary Artery Disease (CAD)

Dear Editor,

the aim of this letter is to highlight the role of platelet's fatty acids (FAs) in CAD pointing out some considerations about saturated fatty acids in diet. In previous works on different groups of subjects, the platelets' fatty acids analysis (GC-MS) evaluated with a Self Organizing Map (a competitive artificial learning network) has allowed a strong classificatory property of subjects with a coronary plaque with respect to apparently normal subjects (1, 2). A further set of subjects [n=83, male=54, female=29, age=66.7±10.4 (m ±SD)] with a coronary plaque, diagnosed with coronary angiography, has been investigated. For each recruited subject, the following data have been collected: Biometric parameters (age, gender, weight, height, BMI), Health status parameters [CVD risk factors: Total Cholesterol (Tot C), HDL, LDL, Triglycerides (TG), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP)], platelet membrane fatty acid profile (C14:0, C15:0, C16:0, C16:1, C17:0, C18:0, C18:1, C18:2 n-6, C18:3 n-3, C20:0, C20:1, C20:3 n-6, C20:4 n-6, C20:5 n-3, C22:4 n-6, C22:5 n-3, C22:6 n-3) and drug assumption (ACE-I, Sartan, Statin, ASA, Clopidogrel, Warfarin, other anti-coagulants). In order to find possible linear relationships among biometric and health status parameters, a full correlation matrix have been evaluated (Pearson's Linear Correlations). The parameter with the greater number of significant ($p<0.05$) correlations is HDL. So, what should be noted is its peculiar position: HDL is the only parameter linked with five others. A graph representing all the significant ($p<0.05$) correlations can summarize and be clearer. All of the parameters are depicted as a square node of the graph, while each of the significant correlations will be reported as an edge linking the involved nodes. In particular, positive correlations ($r>0$) will be green colored while negative correlations ($r<0$) will be red. The resulting graph (Fig. 1) clearly shows the "central" position of the HDL. It's linked (i.e. correlated) with biometric data (on the top-left of the graph) and with the other cholesterol parameters (on the top right) as well as triglycerides and blood pressure (indirectly) on the bottom.

A second correlation matrix has been built for FAs and the parameters investigated. The result, added to the graph (Fig. 1), shows how Palmitoleic Acid (C16:1), Stearic Acid (C18:0) and Oleic Acid (C18:1)

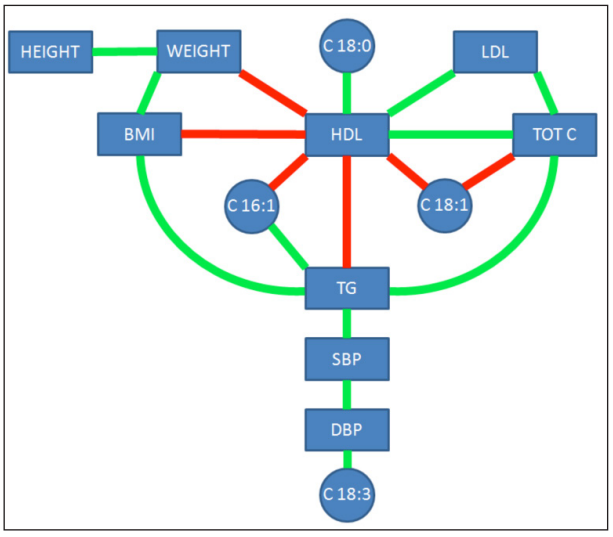

Figure 1. The graph reports the correlations found among FAs, biometric and health status parameters.

could rule the dynamics of the whole system and, in any case, how they could play a leading role. Acting directly in most cases, or indirectly in the others, the three FAs seem to be able to orchestrate the whole system. C18:3 (n3) is involved as well but with a marginal, less influencing power.

A third correlation matrix has been calculated, in order to find internal linear relationships among all the FAs. 17x17 correlations (289 correlations) have been evaluated crossing all FAs. Many of them turn out to be significant. So, in order to summarize the results focused on C16:1, C18:0 and C18:1, a graph has been realized (Fig. 2):

What this result seems to suggest is that, C18:0 and C18:1 are the ones with the higher number of significant correlations. They are correlated with almost all of the FAs. Moreover, each FA correlation has opposite sign with C18:0 and C18:1 in all of the cases. The FAs which are not correlated with C18:0 and C18:1 (i.e. C14:0, C15:0) are correlated with C16:1, a part from C17:0 and C18:3 (n3).

In other words, the three fatty acids (C16:1, C18:0 and C18:1) seem to act as an interface between the whole FAs profile and the CAD parameters. In fact, the three FAs seem to summarize the dynamics of all the FAs profile (Fig. 2). Note that C18:3 (n3), which is one of the 2 FAs not linked to the three FAs, is the only FA reporting a significant correlation with health status parameter, not linked to HDL, as previously shown in Figure 1. It's a sort of outsider, involved independently.

As a further analysis, has been investigated the relationship of drugs assumption on the relevant FAs

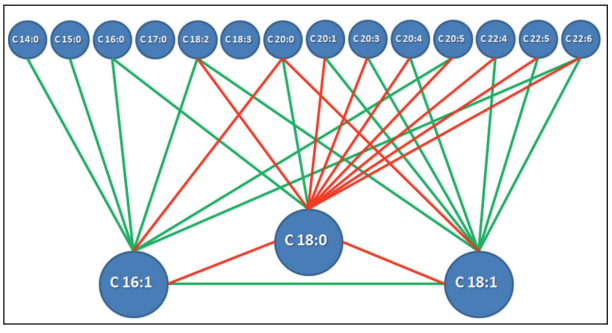

Figure 1. Significant correlations of all the FAs profile and C16:1, C18:0 and C18:1. Red edges represent a negative Pearson's r, while green edges represent a positive one.

in order to understand if the system dynamics could be drug driven or, anyway, drug dependent. So an Analysis of Variance has been performed comparing the level of C16:1, C18:0 and C18:1 for each known drug assumption. The FAs level shows no significant differences.

The results obtained confirm two main aspects: first, that the significant reduction of the oleic acid is peculiar with respect to the CAD (1, 2), second, that the stearic acid, significantly high, represents an element of characterization of CAD.

Some considerations must be made on the stearic acid as an element of assessment in CAD. In all cases previously studied (Major Depression, Bipolar Disorder, Scleroderma, Morphea, CAD subjects, young subjects, children, pigs and other animals) the platelet's stearic acid is elevated only in particular conditions: children, pigs and CAD as confirmed in the second and independent experiment.

Being very well known that in young organisms (e.g. children and pigs) there is a low level of cholesterol in membranes that could make them very fluid and therefore jeopardize their functions in CAD, stearic acid, reducing the average platelet volume as well as the activity of the clotting factor VII, provides greater stability of the mechanisms that induce the clotting function (3-7). This leads to consider that, given the characteristics of stearic acid on platelets, it could represent a defense mechanism for the control of platelet activation also in CAD itself. Enzymatic activity such as desaturase and elongase, and gene expression need to be further investigated.

As a final consideration, therefore, it would be confirmed that the membrane of platelets requires a certain degree of saturation to be better protected and that it uses a specific saturated fatty acid to obtain this result. The main nutritional indication remains that of favoring, and is confirmed also from this study, a regular intake of olive oil to supply oleic acid.

In the preventive treatment of CAD, therefore, it must be emphasized that the intake of saturated fat should not be demonized (8) but reasoned, however, not excluded a priori, and that the oleic acid, being the most critical fatty acid in CAD, should be regularly present in order to restore a correct trend towards normalization of the ratio stearic-oleic in platelets, which

must be lower than, approximately, 0.8 (2). To obtain these results, at least, thirty grams of olive oil should be consumed daily.

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Platelet's Fatty Acids Secrets in Mood Disorders

The identification of three fatty acids of platelets (palmitic, linoleic and arachidonic acid), introduced some hypothesis that, over time, they have been recognized in the stability of the experimental data obtained, also with regard to the concept of serotonin uptake, on the basis the viscosity of the membrane, presenting, therefore, the platelets like elements of great similarity with the neuron, not only for its embryogenic origin but also for some molecular aspects (1-14).

This evidence, together with the ability to classify the two major mood disorders (Major Depression and Bipolar Disorder-MD-BD), has led to some reflections on the molecular specificity of Major Depression, understood as a phenomenon that affects only humans, and, in particular, only a part of them. In this situation, we are able to draw the human condition between normality, BD and MD, the latter being considered as a bio-molecular and existential niche. If you keep in mind the unequivocal distinction between depressed and bipolar subjects obtained through the neural network (Self-Organizing Map-SOM) and the chemical index (B2) as indirect assessment of the viscosity of the platelet membrane, you can make more of a reflection:

- The molecular characteristics of the population suffering from MD are completely different from those of many other living beings studied, whether animals (except the dog) or humans. The depressed subjects, therefore, constitute a particular and isolated group that, on the biochemical-metabolic side has enzymatic characteristics (for example, desaturase and elongase) that do not follow the typical conditions of aging.
- On the basis of our considerations, the MD would be, at this point, a real disease, with specific molecular features and expression of consciousness.
- The molecular attitude of bipolar subjects (they are more numerous than the subjects with MD) would seem (although from a pathological point of view, is not less severe than depression), as the alternation of behavioral expressions which in a certain sense may be more easily treated and recovered, although the possibility of dramatic and explosive onset of psychotic symptoms can hardly be controlled.

The use of biochemistry, non-linear mathematics, and the comparison human-animal allows reflections that are not only very close to the interpretation of mood problems in its cultural and biological aspects, but also opens up new perspectives and new diagnostic interpretative models of the condition known as "Mood Disorder".

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Correspondence:
Prof. Massimo Cocchi
Paolo Sotgiu" Institute for Research in Quantitative & Quantum Psychiatry & Cardiology, L.U.de.S. University
Department of Veterinary Medical Sciences,
University of Bologna
E-mail: massimo.cocchi@unibo.it