

LISTENING TO THE PLACEBO, OR HOW TO FIND OUT WHY TREATMENTS WORK

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El efecto placebo es poderoso y ha demostrado su eficacia en múltiples estudios, compitiendo incluso con tratamientos bien establecidos. Esto pone de manifiesto un efecto en absoluto inerte o inespecífico. Tiene una naturaleza ubicua y da razón de todo tipo de tratamientos, si bien es la psicología el ámbito que le hace comprensible. Desgranar y conocer qué le hace tan eficaz es una tarea útil e ilustrativa de cómo operan los tratamientos al uso. En este sentido hay que destacar que para que opere debe ser construido en términos contextuales, no requiere de engaños y sí de una persona con problemas, en desequilibrio homeostático. El estudio de las condiciones en que el efecto placebo ocurre ha sido útil para delinear qué aspectos son importantes en los tratamientos, a saber: la facilitación de información y el sentido de ésta, las experiencias previas y las creencias del paciente, la aplicación del tratamiento en condiciones favorables y el uso de tratamientos bien reconocidos y aceptados en sus fundamentos y procedimiento.

Palabras clave: Placebo, Efecto placebo, Tratamiento, Psicoterapia.

The placebo effect is powerful and has been proved effective in multiple studies, competing even with well-established treatments. It is absolutely not an unspecific or inert effect. It has a ubiquitous nature and accounts for all types of treatments, although psychology is the area that makes it comprehensible. Discussing and discovering what makes it so effective is a useful and illustrative task regarding how treatments work. In this sense, it must be emphasized that in order for the placebo effect to operate, it must be considered from a contextual view, it does not require deception, and it does require a person with problems, in homeostatic imbalance. The study of the conditions in which the placebo effect occurs has been useful in delineating which aspects are important in treatments. These are as follows: the provision of information and its meaning, the patient's previous experiences and beliefs, the application of the treatment under favorable conditions, and the use of well-recognized and accepted treatments in their foundations and procedure.

Key words: Placebo, Placebo effect, Treatment, Psychotherapy.

The placebo is a well-established treatment. In other words, there are enough good quality, empirical studies to state that the placebo is an effective treatment and even more effective and efficient than other alternative treatments. This cannot be said for all disorders or problems but, as you will see, it can be said for some of particular importance. What is beyond doubt is that if you search any scientific database (PsycInfo, Medline) or even Google, the number of entries for the word «placebo» is similar to others (psychotherapy, psychopharmacology, etc.) relating to conventional treatments. This is an indication of the number of studies in which the placebo participates and it is its empirical support, hence the statement at the beginning of this paragraph.

This can be said to be natural because any worthwhile scientific study must have a placebo group, which normally obtains worse results than the treatment or intervention being studied. True, but there is a small catch here—even discounting the studies in which the placebo is as effective or more effective than the alternative treatment—which is that the

studies in which the placebo is used as a control ensure beforehand that its effect will be reduced.

PLACEBO STUDIES VS. PLACEBO EFFECT

Studies in which the placebo is used as a comparison with another treatment focus on the substance (the medicine or therapeutic procedure). This is done in the traditionally valued RCTs (randomized clinical trials). The following is an example of instructions from an RCT: «You may receive a medicine or an inactive agent or placebo»; this highlights the substance administered. In contrast, in the studies on the placebo effect, the type of instruction is: «You are going to receive a treatment that has been shown to be effective in solving your problem» after which you will be given, for example, a medicine or a placebo. What is relevant here is not the substance, but the expectation of efficacy induced by the previous instructions.

You might think that there is little difference between the two types of instructions, but there is not. In analgesia there is a big difference, as Vase, Riley, and Proce (2002) show. The effect size in the RCT studies is 0.15 (-0.95 to 0.57) while in the case of the studies on the placebo effect it is 1.41 (0.12 to 2.51). It seems that the expectation of efficacy plays an important role. Furthermore, if two well-established analgesic treatments and their corresponding effect size are taken as a reference, such as non-steroidal anti-inflammatory drugs

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NSAIDs (0.61) or cognitive behavioral therapy CBT (0.61), as pointed out by Forsberg, Martinussen, and Flaten (2017), the placebo effect (1.14) far exceeds that of the well-established treatments. In other cases, a similar efficacy to CBT or antidepressants is found (Gould et al., 2020). Therefore, in the treatment of pain, the placebo effect would be the most ethical option, in line with the scientific evidence indicated. The statement with which I began this article is true in this case. As will be seen below, the placebo effect has proven effective in the treatment of pain, irritable colon, allergies, dermatological problems, depression, anxiety, ADHD, addictions, etc. This may allow us to understand more about the effectiveness of treatments for these problems.

THE WELL-KNOWN PLACEBO EFFECT

The placebo effect is not a newcomer. It is a classic and permanently open research topic, especially in the field of pain; and it corresponds to the psychological domain. The pill, the injection and the white coat, or the clinic, are personally and/or socially associated with the improvement or resolution of health problems. There is, therefore, a learned associative link that confers a value beyond the substance or procedure itself. Classic conditioning processes and the role of outcome expectations give good reason for these placebo effects, whose neurophysiological routes have been well described. The question is to learn from these phenomena, which are present in every intervention, in order to better understand the efficacy of the therapies. On the other hand, if the placebo effect is so powerful, and of a psychological nature, how can we manage it?

DECEPTION OR DISAPPOINTMENT

It seems that telling someone to take a tablet (simply sugar) with all its appearance of a pill, to solve a problem: (1) is a deception and, moreover, to be effective (2) it must be. With regard to the first point, it would only be a deception if the person in question has no personal or social experiences that relate the pill to a therapeutic procedure. If he or she has such an experience, it would not be a deception, but rather a way of activating the associative and/or cognitive processes

related to the efficacy of drugs. This activation does not have to be explicit, although—and here comes the answer to the second question—it does not have to be hidden either.

The placebo effect does not require the person to be misled. The truth can be told clearly, these are the procedures called open-label placebo, where it is indicated that the procedure or the drug being administered is a placebo, perhaps explaining what the placebo effect consists of. Moreover, once the placebo effect is generated and obtained, for example, analgesia, it does not disappear when the patient is told that no drug was administered and is even informed in detail of the placebo procedure (Schafer, Colloca, & Wager, 2015).

A MATTER OF INFORMATION

When a placebo is used explicitly, specific information may be provided. For example, Shaefer, Shan, and Berstecher (2018) provide information in the context of treating allergic rhinitis. They informed the participants that «placebos are inactive substances without any medication, but nevertheless have powerful effects. The body can respond automatically when the placebo is taken, like Pavlov’s dog salivates when it hears the bell. A positive attitude can help the placebo effect but is not necessary for it to work.” However, these instructions did not afford greater efficacy in allergic symptoms than the mere instruction that «the placebo contains no medication and is like a sugar pill”.

Information that explains the placebo effect in terms the patient can understand and thus helps to make the «deception» more digestible does not necessarily improve the effects of the deception. An example of alternative instructions can be seen in Table 1.

There is conflicting evidence about the usefulness of detailed explanations of how the placebo effect operates. In some cases, they are not necessary (Shaefer et al., 2018; Kam-Hanse et al., 2014) whereas in others they are (Locher et al, 2017; Wei et al., 2018). However, it is clear that for the explicit (open-label) placebo effect to work they are not essential, although they can be useful when they fit in with people’s previous beliefs (Leibowitz et al., 2019).

THE LIMITS OF THE PLACEBO

Can any inert element or procedure generate a placebo effect? Obviously not. In the first place it must be associated, as has been said, with a procedure of proven efficacy and experienced directly or indirectly by the subject, but there is another element, it requires certain conditions of the system, of the body. Let us look at an example that had some relevance more than 10 years ago: activity bracelets, more specifically the Power Balance®. It promises to improve balance, strength, and flexibility. However, none of these effects have been observed when comparing its use, with the use of a conventional bracelet, or with the absence of a bracelet (Verdan et al., 2012).

The placebo effect occurs most likely when the person is not in homeostasis, that is in individuals with pain, depression, stress, immune response imbalances, etc. It is precisely the placebo effect that restores homeostasis (Flaten, 2013), so if

**TABLE 1
INSTRUCTIONS FOR THE USE OF OPEN-LABEL PLACEBO**

«Okay, I’m going to put some cream on your arm. This is a placebo treatment. I don’t know if you know what it is. It basically doesn’t have any active ingredients, but we know that placebo creams are effective for allergic reactions like yours, making the allergic reaction go away faster. There are several reasons for this. One is that it creates positive expectations that can cure you. These are not conscious expectations. We know that the human body can respond with physiological changes to situations associated with healing, such as taking a pill or applying a cream. This is the placebo effect. We know that the cream acts on the parasympathetic nervous system to reduce stress, this decreases inflammation. There are powerful and diverse reasons that support the usefulness of the placebo cream and justify its usefulness. (Leibowitz, Hardebeck, Parker Goyer, & Crum, 2019, p. 616).



the organism is in homeostasis the placebo effect is non-existent or minimal. This fact is probably related to the state of imbalance of the system, as stated in Wilder's law of initial values (1962). The perception of pain, discomfort, etc., when it no longer has an adaptive function must be deactivated. Moreover, its deactivation is required. Moseley and Butler (2015) consider that informing about self-regulation mechanisms is a way for the organism to «recognize» the nonsense of the imbalance, as applied in the procedure called "Explain Pain". The placebo effect would therefore be fertile ground for action. The analgesia generated by the placebo effect is greater in pain patients than in healthy people (Forsberg, Martinussen, & Flaten, 2017).

BUILDING THE PLACEBO EFFECT

As it has been mentioned, the placebo effect does not come out of nowhere, it must be built according to each person's personal experience, including the socio-cultural context. Both elements, the personal and social factors, are always present and must be taken into account. If a person does not know what morphine or Prozac is, nor have they had any experience with them, it will not be possible to generate any specific placebo effect on them. Put another way, from the moment a person has experience with a specific drug or therapeutic procedure, it is possible to generate the placebo effect. Note that as stated about RCTs, if the drug being administered is not known and/or there is no experience with it, the placebo effect will be minimal; this will contribute to the «success» of the RCT but from the moment the drug enters into circulation the placebo or nocebo (negative placebo) effects will do so as well.

The genesis of the placebo effect (Liu et al., 2017) begins with the belief in the (direct or indirect) efficacy of a treatment. It continues with the presence of a pain or discomfort that is close to appearing or increasing. The expectation is then created that the pain or discomfort can be reduced by the placebo effect, which involves negative reinforcement of the placebo. It is the expectation of reduction that generates the placebo effect. In sum, there is no placebo effect (1) without belief in the treatment; (2) without signs of pain or discomfort that can be reduced. Thus, the anticipation of discomfort shapes subsequent placebo responses. The degree of discomfort is an indicator of the intensity of the placebo effect. This discomfort may also be increased by the treatment itself when it is invasive (surgery, etc.) or aversive (exposure techniques). In these cases, there may be an overlap between the clinical discomfort present and that generated by the procedure. When the discomfort created by the therapy ends, it could produce a carry-over effect on the associated sensory experience, the clinical element. There is considerable leeway here that allows the development of unique therapeutic techniques, such as the one developed by Klingler et al. (2017) for the treatment of low back pain.

THE CONTEXTUAL KEY

At this point it becomes clear that the placebo effect depends on the personal and socio-cultural context, it is not surprising

that the belief in the efficacy of a certain treatment and/or procedure is socially determined. It is based on a general agreement and mutual knowledge, as well as specific preferences also accepted by all (Chiffi & Zanotti, 2017). A striking example is the meta-analysis by Chen et al. (2017) on the placebo effect in the treatment of fibromyalgia. It turns out that in different studies, as befits a meta-analytic study, a positive correlation ($r=0.7$, $p<0.0001$) is obtained between the effect size of the main treatment (which is supposed to be the most empirically supported one) and the placebo treatment. This is that the size of the placebo effect varies proportionally and positively to the effect size of the chosen treatment. Since the studies are independent, it can only be assumed that some type of communication must have existed between the participants of the studies (experimental group and placebo group) and with a univocal direction, the better the treatment applied, the better the response of the associated placebo. Interestingly, there seems to be a sympathetic connection between the two treatments.

The contextual aspects are also relevant to the value-adding elements associated with any treatment. The therapeutic rituals, and the therapeutic relationship itself, are classic elements in the explanation of the placebo effect, from the Latin *placere* (to like, to please). The warmth and competence of the doctor, for example, have been shown to be decisive in assessing patients' responses to allergic reactions (Howe, Goyer, & Crum, 2017). In reality, any interpersonal interaction, which also has a personal and social experience and has an effect on health, would be framed as being capable of becoming an effective treatment and therefore a placebo effect.

CLUES TO MANAGING THE PLACEBO EFFECT

The placebo effect is multi-faceted and ubiquitous in the way it is generated and enhanced. It affects all types of intervention and its scientific domain is psychology, since it is relevant to the processes of conditioning, the importance of verbal aspects, interpersonal relationships, expectations, and their fulfilment. It should therefore be noted that every intervention is impregnated with the placebo effect. Its magnitude will depend on various factors. For example, the field of pain treatment is one of the most prominent, where the placebo effect has been studied the most and its effectiveness has been proven, as well as its perceptual, behavioral, cognitive, and physiological effects. In fields where the functional or idiopathic is more relevant, the placebo effect plays a greater role.

With empirical reference to studies on the treatment of non-neoplastic pain, several factors have been identified that are related to the presence of the placebo effect (Bishop et al., 2017). This gives us clues about which factors, related to the placebo effect, point to what is relevant for a treatment to be effective. From the extensive work of Bishop et al. (2017) I will highlight, in order of importance, the first five factors, as follows: (1) that patients know their evolution during treatment, through information on the measures used (self-reports, tests, etc.); this will certainly allow them to know to what extent the expectations



of results are being fulfilled; (2°) that people know that their treatment is part of an investigation, i.e., that they are contributing to improve the knowledge about the problem and to help other people in the future; this gives a sense of value to the treatment and reduces the focus on oneself; (3°) that the treatment is adjusted as much as possible to the conditions and rituals that are characteristic of it (the form of administration, aspect, visual appearance, etc.); this will favor a connection with the treatment considered and accepted as true, which strengthens the belief necessary for the placebo effect to be generated; (4) formal obtention (written or verbal) of the patient's informed consent; this adds an element of truthfulness, information, and commitment to the most appropriate treatment; and (5) the treatment should conform to strict inclusion criteria, taking into account the clinical history so that it fits the particular patient. The interested reader can consult the taxonomy proposed by Bishop et al. (2017) as it includes more data than those selected here and enables us to understand why the treatments work.

The recommendations of Klinger and Flor (2013) to promote the placebo effect in the field of chronic pain are of particular interest in understanding what works in both medical and psychological treatment. Thus, to obtain the therapeutic effects associated with the intervention they indicate: (a) advising the patient, when ingesting a drug, to pay attention to its appearance, the taste, smell, and sensations perceived; focusing in detail on the elements of the technique or therapy associated with the positive experience in the treatment of the problem, or similar problems (b) taking the drugs under benign conditions, together with other interventions that may reduce the pain, or at times when the pain is less intense; associating the therapeutic measure with other positive ones will enhance it; (c) treatments reactivate past experiences, it is necessary to know these to enhance the positive ones and minimize the negative ones. On the other hand, and with respect to the expectations related to the treatment, these authors suggest: (a) emphasizing the positive aspects of the treatment, realistically explaining its effects and not overestimating the negative effects; (b) explaining the mechanisms of action of the treatment (remember what was said about the Explain Pain procedures); (c) explaining the foreseeable course of the treatment, avoiding unrealistic promises.

NUANCES

The above and subsequent conclusions are subject to nuance, depending on the problem being addressed and the personal characteristics of the patient. This does not invalidate the general information provided but it does require alternative considerations. Take, for example, the first element of the taxonomy of Bishop et al., (2017). It is known and accepted that if patients know their evolution during treatment, through information on the measures used (self-reports, tests, etc.) it potentiates the placebo effect. Geers et al. (2006) already indicated this, however it does not seem to work for patients with obsessive-compulsive disorder (OCD). Interestingly, in these patients the placebo effect is less than in other anxiety disorders (Sugarman, Kirsch, & Huppert, 2017), possibly due to the excess of information received. Indeed, continuous observation,

in addition to being congruent with OCD, helps these patients attribute the reduction in their discomfort to the rituals they perform to reduce it. This destroys any possible external attribution (antidepressants, or other techniques), so the placebo effect diminishes. Furthermore, the rigidity of the rituals and compulsions make them more resistant to change. This lack of flexibility seems to be related to the chronicity of the disorder. This may be the case with OCD, which has an earlier onset than other anxiety disorders, leading to greater chronicity and inflexibility. In the case of fibromyalgia, too, it has been observed that people with greater chronicity generate less of a placebo effect (Chen et al., 2017). It should therefore be borne in mind that in these cases promoting an increase in psychological flexibility not only has positive effects specifically speaking, but would also enhance the placebo effect; and that an excess in the reception of information is not positive but contributes to patterns of inflexibility.

WHAT DOES THE PLACEBO EFFECT TEACH US ABOUT THE EFFICACY OF TREATMENTS?

From what we have seen so far, it is possible to summarize the aspects that, being related to the placebo effect, would justify at least in part the efficacy of the treatments. We refer to treatments in the most general sense: medical, psychological, formal, informal, etc., although the knowledge comes basically from medical and psychological treatments. By way of a decalogue, the main factors include the following: (1) personalized and adjusted treatment to the patient, with specific personal references and taking into account his/her beliefs and previous experiences with other similar treatments; (2) explicit, clear, and formalized information on the treatment, indication, effects, and foundations, as well as its general functioning; (3) explicit information that the proposed treatment is the most appropriate and recommended, as well as the adjustment of this treatment to the standards and procedures accepted and known by the scientific community; (4) continuous and precise information on the monitoring of the treatment; (5) the patient's intervention in therapeutic decisions; (6) application of the techniques when the discomfort, pain, or interference from the problem is less intense or disabling; or when improvement is expected or there are other concurrent effective measures or treatments; (7) intervention to improve something specific (something must be wrong), if there is anticipation of discomfort it is better, as it will serve to contrast the expectations of the result; (8) ensure that an improvement is achieved, using successive approximation procedures; (9) promote a context rich in elements accepted as therapeutic (importance of multi-component treatments); and (10) do not rule out treatments that may generate discomfort, provided that it is justified and can be understood and assumed by the patient.

To conclude this article I would like to add the consensus on the use of the placebo and nocebo effect published by *Psychotherapy and Psychosomatics* (Evers, et al., 2018) and which consists of five recommendations and two warnings (see Table 2). These points summarize and integrate the knowledge on the subject that has been considered in this article.

CONFLICT OF INTEREST

There is no conflict of interest.

TABLE 2
RECOMMENDATIONS, PSYCHOTHERAPY CONSENSUS 2018
(EVERS ET AL., 2018, P. 206)

1. Consider the placebo effect as a regular part of treatment
2. Inform the patient about the placebo and nocebo effects, to maximize the former and reduce the latter
3. Enhance trust, warmth, and empathy, to achieve no. 2
4. Train professionals in the use of no. 3
5. Opt for open-label rather than concealed placebos, provided there is evidence of their efficacy and their prescription is legal
6. **Do not** risk using invasive treatments to maximize the placebo
7. **Do not** consider deception as a necessary component of the placebo

REFERENCES

- Bishop, F. L., Coghlan, B., Geraghty, A. W., Everitt, H., Little, P., Holmes, M. M., ... Lewith, G. (2017). What techniques might be used to harness placebo effects in non-malignant pain? A literature review and survey to develop a taxonomy. *BMJ Open*, *7*, e015516.
- Chen, X., Zou, K., Abdullah, N., Whiteside, N., Sarmanova, A., Doherty, M., & Zhang, W. (2017). The placebo effect and its determinants in fibromyalgia: meta-analysis of randomised controlled trials. *Clinical Rheumatology*, *36*, 1623–1630.
- Chiffi, D. & Zanotti, R. (2017). Knowledge and belief in placebo effect. *The Journal of Medicine and Philosophy*, *42*, 70-85.
- Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., ... Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics*, *87*, 204–210.
- Flaten, M.A. (2013). Placebo Responses, Antagonistic Responses, and Homeostasis. In L. Colloca, M. A. Flaten, & K. Meissner (Eds.), *Placebo and Pain*. (pp.103-113). Academic Press.
- Forsberg, J. T., Martinussen, M., & Flaten, M. A. (2017). The placebo analgesic effect in healthy individuals and patients: A meta-analysis. *Psychosomatic Medicine*, *79*, 388–394.
- Geers, A.L., Helfer, S.G., Weiland, P.E., Kosbab, K., 2006. Expectations and placebo response: a laboratory investigation into the role of somatic focus. *Journal of Behavioral Medicine*, *29*, 171–178.
- Gould, H. M., Atkinson, J. H., Chircop-Rollick, T., D Andrea, J., Garfin, S., Patel, S. M., Funk, S. D., Capparelli, E. V., Penzien, D. B., Wallace, M., Weickgenanta, A. L., Slater, M., & Rutledge, T. (2020). A randomized placebo-controlled trial of desipramine, cognitive behavioral therapy, and active placebo therapy for low back pain. *Pain*, *161*, 1341–1349.
- Howe, L. C., Goyer, J. P., & Crum, A. J. (2017). Harnessing the placebo effect: Exploring the influence of physician characteristics on placebo response. *Health Psychology*, *36*, 1074–1082.
- Kam-Hansen, S., Jakubowski, M., Kelley, J. M., Kirsch, I., Hoaglin, D. C., Kaptchuk, T. J., & Burstein, R. (2014). Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Science Translational Medicine*, *6*, 218ra5.
- Klinger, R & Flor, H. (2013). The potential of the analgesic placebo effect in clinical practice - Recommendations for pain management. In L. Colloca, M. A. Flaten & K. Meissner (Eds.), *Placebo and Pain*. (pp. 267-275). Academic Press.
- Leibowitz, K. A., Hardebeck, E. J., Goyer, J. P., & Crum, A. J. (2019). The role of patient beliefs in open-label placebo effects. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, *38*, 613–622.
- Liu, T. (2017). Route of placebo administration: Robust placebo effects in laboratory and clinical settings. *Neuroscience and Biobehavioral Reviews*, *83*, 451–457.
- Locher, C., Frey Nascimento, A., Kirsch, I., Kossowsky, J., Meyer, A., & Gaab, J. (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain*, *158*, 2320–2328.
- Moseley, G. L., & Butler, D. S. (2015). Fifteen Years of Explaining Pain: The Past, Present, and Future. *The Journal of Pain: Official Journal of the American Pain Society*, *16*, 807–813.
- Schaefer, M., Sahin, T., & Berstecher, B. (2018). Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. *PLoS One*, *13*, e0192758.
- Sugarman, M. A., Kirsch, I. & Huppert, J. D. (2017). Obsessive-compulsive disorder has a reduced placebo (and antidepressant) response compared to other anxiety disorders: A meta-analysis. *Journal of Affective Disorders*, *218*, 217–226.
- Vase, L., Riley, J. L., III, & Price, D. D. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain*, *99*, 443–452.
- Verdan, P. J. R., Marzilli, T. S., Barna, G. I., Roquemore, A. N., Fenter, B. A., Blujus, B., & Gosselin, K. P. (2012). Effect of the Power Balance® band on static balance, hamstring flexibility, and arm strength in adults. *Journal of Strength and Conditioning Research*, *26*, 2113–2118.
- Wei, H., Zhou, L., Zhang, H., Chen, J., Lu, X., & Hu, L. (2018). The Influence of Expectation on Nondeceptive Placebo and Nocebo Effects. *Pain Research & Management*, *8459429*.
- Wilder, J. (1962). Basimetric approach (law of initial value) to biological rhythms. *Annals of the New York Academy of Sciences*, *98*, 1211–1220.