Dr. Jack Killen, Deputy Director of the National Center for Complementary and Alternative Medicine (NCCAM), opened the meeting and spoke about NCCAM perspectives on the conference. The hope of the NIH sponsors of the workshop is that discussion by the participants will inform a forward-looking agenda of research aimed at providing the evidence needed by clinicians and policy makers in addressing questions about whether placebo-based approaches can and should ever be employed in clinical practice.

**PLACEBO AND HEALING: IMPLICATIONS FOR PRACTICE, RESEARCH AND POLICY**

Dr. Wayne B. Jonas, President and CEO of Samueli Institute, used the story of a patient to illustrate the opportunities and challenges that placebo creates. The patient asked about acupuncture to help with lower back pain. The physician looked into the literature and found that acupuncture is superior to the best current conventional therapy, but sham acupuncture (where the needles were not inserted and the location of the needles did not follow acupuncture theory) caused the same improvement. What recommendation and actions should the physician take in this situation? With regard to placebo pills (in contrast to a placebo procedure such as acupuncture), there are other concerns and, indeed, formal changes to the rules of clinical practice. Thirty years ago the prescribing of inert (e.g., sugar) pills was common. Today this is considered unethical, so many physicians instead prescribe actual medicines that are known to be ineffective for the condition at hand but thought to be benign—but these may still produce problematic side effects. Such behavior by physicians who want to harness the power of placebo is understandable, but still unfortunate, and also considered unethical by many. We need better ways to engage the power of meaning and context in the service of healing.

**MEMORY FOR DRUG ACTION: A KEY MECHANISM IN PLACEBO RESPONSIVENESS**

Dr. Fabrizio Benedetti: What are the mechanisms that underlie the collection of effects that we call “placebo?” There are many psychobiological factors that underlie reactions to placebo-based treatments, including genetics, expectation, and learning. Within “learning” there are also subdivisions, including social learning, reinforced expectations, and classical (“Pavlovian”) conditioning. This presentation focused on the classical conditioning in the context of analgesic drugs to promote pain tolerance in exercise. Actual analgesic drugs (morphine or ketorolac) are used to demonstrate the behavioral consequences of an analgesic when performing an increasingly painful endurance task. When other drugs (naloxone to block morphine receptors, or rimonabant to block ketorolac induced actions) are given to block the action of the analgesics, the increases in pain tolerance go away. When placebos are given after several days of the drug-induced analgesia, strong effects are seen—but these effects go away if the blocking drugs are also given. Thus, it is clear that the physiological last stage of placebo induced analgesia is via the very same channels that decrease pain via drugs.

This conference examined key issues associated with a future agenda for placebo research aimed at addressing these and related questions. Scientific presentations formed a backdrop for wide ranging discussions on next steps in the field of placebo research.

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**PRESENTATIONS**

**CHARTING THE PATH FORWARD**

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CONDITIONING AND PLACEBO RESPONSES: WHAT HAVE WE LEARNED FROM MECHANISTIC AND CLINICALLY-ORIENTED RESEARCH?

Dr. Luana Colloca, a scientist at (NCCAM), National Institutes of Health (NIH), reported studies that chart the path from molecular and animal research to enable a full understanding of the biochemical pathways for conditioned placebo responses. A potential model of translatable of molecular and animal findings into preclinical and clinical areas has been illustrated by presenting recent advances in the field of immune system modulation via/involving placebo interventions. By using a conditioned strategy of pharmacotherapeutic effects, some argue that it is possible to harness placebo effects in therapeutic paradigms.

Dr. Ulrike Bingel, a neurologist, investigates pain and cognition. In addition to behavioral evidence for the changes in subjective pain during placebo analgesia, there is also evidence from functional brain imaging. In one such imaging study, Dr. Bingel and colleagues showed evidence that now extends down to the level of the spinal cord systems. Dr. Bingel emphasized the value of imaging studies in addressing one of the traditional objections to placebo research—that subjects might be responding in ways to “please” the experimenter—perhaps reporting more change than they truly feel. Now that we can see objective changes in brain activity in parts of the brain and spinal cord known to be involved in pain processing, it is not likely that the effect is solely an artifact of trying to please the experimenter.

BELIEFS, EXPECTANCY AND CLINICAL OUTCOME

Dr. Irving Kirsch is the Associate Director of the Program in Placebo Studies and the Therapeutic Encounter at the Beth Israel Deaconess Medical Center and Harvard Medical School. Expectancy, argued Dr. Kirsch, is the heart of all learning and cognition. We are constantly trying to learn how to predict the next thing that will happen in the world. Whether it is conscious and slow, automatic and fast, innate or learned, we are always generating expectancies. One can usefully think of placebo effects as being produced or modulated by such expectancies.

PLACEBO EFFECTS AND IMPLICATIONS FOR THE DOCTOR-PATIENT RELATIONSHIP

Dr. Howard Brody, the Director of the Institute for Medical Humanities of the University of Texas, described some of the best and worst medical uses of placebos in current medical practice. The good news is that physicians have a healthy respect for the powers of mind-body interactions in medical practice. The bad news is that some physicians feel justified in prescribing drugs with potential side effects in order to stimulate a placebo response. He emphasized the two main approaches to eliciting placebo responses: the use of pills or other inert treatments and the utilization of the doctor-patient relationship. The latter is the oldest and also largely immune to the many ethical challenges associated with prescribing medications whose specific actions are not connected to the target medical problem.

PLACEBOS AND RITUALS

Prof. Ted Kaptchuk is the Director of the Program in Placebo Studies and the Therapeutic Encounter at the Beth Israel Deaconess Medical Center and Harvard Medical School. He began his presentation by examining the role of rituals in placebo effects. This discussion was used as a lead-in for presenting patients’ own words about how they experienced being subjects in an experiment where they didn’t know if they were getting the real medical treatment or a placebo. Their comments led Prof. Kaptchuk to design and conduct experiments using “open-label placebo” groups (i.e., groups of subjects who are told very clearly that they are being given placebos, and who know what the term means). Placebo effects were still seen, even in this condition.

NOCEBO RESEARCH: IMPLICATIONS FOR CLINICAL TRIALS AND PRACTICE

Dr. Luana Colloca spoke about “nocebo” effects in experimental and clinical settings. Expectations derived from beliefs, previous experience, and the clinical encounters can produce negative effects, known as “nocebo effects.” Research on the nocebo effect indicates that information disclosure and the manner in which information is divulged, can contribute to producing adverse effects. One surprisingly clear finding, across a number of studies, is that verbal suggestions inducing nocebo effects (e.g., telling a subject that they are likely to experience pain or other negative side effects) are more powerful and longer-lasting in than analogous suggestions for a positive placebo response.

ETHICAL ISSUES IN PROMOTING PLACEBO RESPONSES

Dr. Franklin (Frank) Miller is a Senior Faculty member in the Department of Bioethics at NIH. Dr. Miller discussed ethical issues relating to the use of placebo treatments in clinical practice. He argued that placebo treatments can be legitimate if they are based on solid evidence of therapeutic benefit, they are low risk and modest cost, and they are presented to patients without deception and consistent with informed consent.

IMPLICATIONS FOR HEALTH POLICY AND PRACTICE

Dr. Josephine Briggs is the Director of NIH's NCCAM. Her brief closing comments were addressed to the big picture associated with placebo and health care at a national level. Dr. Briggs oriented her talk around the importance of “words” and of “symptoms” in the future use of placebo. The discussion about “words” (which was extensively explored by the audience after her talk) had to do with the use of “placebo” as a term to describe these context and meaning effects. The discussion about “symptoms” was related to the distinction between “illness” (how you feel) and “disease” (what is wrong in your body), as previously mentioned by Dr. Brody, and how important that distinction is when evaluating both research and funding in placebo.