SCIENCE

VOL. 94 FRIDAY, AUGUST 1, 1941 No. 2431

SCIENCE: A Weekly Journal devoted to the Advancement of Science, edited by J. MCKEEN CATTELL and published every Friday by

THE SCIENCE PRESS

Lancaster, Pa. Garrison, N. Y.

New York City: Grand Central Terminal

Annual Subscription, $6.00 Single Copies, 15 Cts.

SCIENCE is the official organ of the American Association for the Advancement of Science. Information regarding membership in the Association may be secured from the office of the permanent secretary in the Smithsonian Institution Building, Washington, D. C.

THE METAMORPHOSIS OF DRUG RESEARCH[1]

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THE topic which has been assigned to me for discussion is a broad one, and I am going to consider it from its broadest aspects. It is only a small exaggeration to say that any one who takes as much as an aspirin tablet for himself engages in drug research. I can speak then as one of 130,000,000 drug researchers in this country, but even at that I can only speak with the deepest humility. A short time ago our colored maid developed a cold and with it a cough. I was called upon to do something about it, and I gave her what I considered to be the best medicines available for a cough due to a cold. But the maid had more faith in a medicine of her own selection which I noticed she took to the exclusion of mine. Her faith in her medicine was its own reward and in due course of time her cough fortunately disappeared. I would have exposed myself to polite but silent scorn if I had tried to tell her that neither my prescription nor hers cured the cough—that it would have disappeared anyway, or, as some one put it, "Nature cures the disease while the remedy amuses the patient." I might have tried to show her that man has been subject to colds and coughs since the dawn of civilization and that they have come and disappeared for countless generations before her medicine or mine had been discovered. But it would have been useless. If colds and their coughs hadn't made a habit of coming and going in precisely the same way regardless of what we did for them, man would long since have coughed himself off the face of the earth.

The element of faith has for centuries been one of the most important active ingredients in every medi-

[1] An address delivered before the American Drug Manufacturers Association, May 7, 1941.

cine—even though it is not declared on the label and Congress has completely overlooked it in the Food, Drug and Cosmetic Act.

Drug research had its start about a thousand centuries ago. It began before the dawn of what we choose to call civilization. For more than 995 centuries of this time the scientific method as applied to drug research was unknown. When we consider the empiricism, the "post hoc ergo propter hoc" reasoning, the stupidity that still passes for science to-day, perhaps we should find some comfort in the realization that sound scientific inquiry in this field has been practiced for less than five centuries—less than the twinkling of an eye in man's history on earth. But it is also discouragingly evident that in a thousand centuries we haven't learned much about drugs.

For untold ages disease and death were considered to be caused by evil spirits and supernatural forces. Obviously, the function of early researches was to find some sure way of warding off these spirits or placating the gods that sent them. Since disease was the doing of the gods, the only qualified experts in such matters were the tribal medicine men, who were, of course, religious functionaries. We see a hang-over of this idea even to-day, particularly in our system of medico-legal jurisprudence which looks upon schools of healing as if they were endowed with some divine right to use human bodies for the practice of their fantastic notions of therapeutics.

The first conception that disease was caused by external spirits acting by remote control later changed to the notion that the evil spirit gained access to the body and resided within it. And with it the job of the medicine man changed, too. He prescribed charms and fetishes such as amulets, rattles or the beating of drums to prevent the evil spirit from entering, or, once having entered, he tried to get rid of it by prayers and incantations. If these didn't effect a cure, he resorted to more demonstrative forms of elimination therapy such as blood letting, catharsis, leeches and opening holes in the skull. Although several thousand years have passed since these ideas predominated, they, too, still influence the therapeutic thinking of to-day. As the mind of primitive man began to free itself from the conception that disease was due to the evil eye or the wrath of the gods, he began to look around for other causes and with it other ways of dealing with them. He thought he observed that illness could be cured by many strange and wondrous means. For instance, a flannel cloth worn around the neck was believed capable of curing sore throats and whooping cough, provided the cloth was red. A horse chestnut was thought to be good as a preventive for rheumatism.

While the royal touch had only a limited vogue as a cure for scrofula, many peasants were certain that all forms of tuberculosis could be warded off by wearing earrings. It was once believed by generations of country folk and a few that I know who were born in Brooklyn that warts were caused by toads and cured by touching them with pebbles or milkweed. Bags of asafoetida were worn around the neck to ward off asthma and croup. While most of us are now pretty sure that there is no danger of lunacy if the moon should shine on us during sleep, it is no mere ancient myth that moonshine causes plenty of trouble. But some of the ancient observations on the cause and cure of disease happened to be right. For instance, savages in widely separated countries learned of the effects of the poppy for various conditions, and cinchona for malarial fevers. The virtues of cod liver oil were recognized long before the word "vitamin" had been thought of. The diuretic effect of foxglove was known to a housewife in Shropshire before the physicians of the time recognized its merits. But all in all early experiences with drugs were empirical in nature and followed a pattern something like this:

An individual is sick.
A drug is given.
If the individual recovers, the drug effected the cure.
If the patient dies, it is easy to excuse the failure by reasoning that not enough of the drug was given, or too much was given, or it was not given early enough.

The same type of fallacious therapeutic reasoning is still commonly practiced to-day by laymen and many physicians.

It was not until the nineteenth century, a gestation period of some 999 centuries, that drug investigators fully realized that therapeutic research was not so simple a proposition. It was not enough to give a medicine to some one who was sick and see what happened. Things often did happen, but how could one be certain that the drug was responsible? Scientists gradually set up criteria by which they could distinguish coincidental occurrences from those that had a cause and effect relationship. These criteria took into consideration six fundamental propositions. They are:

(1) Many diseases and symptoms are self-limited, regardless of what is done for them.

(2) Nature heals and cures; drugs at best are merely adjuvants.

(3) Chronic diseases are characterized by spontaneous remissions and exacerbations.

(4) Symptoms are often entirely due to and almost invariably aggravated by worry and emotional disturbance.

(5) Symptoms regardless of their cause are often temporarily improved through the expectation of therapeutic benefit.

And finally,

(6) The fallacy of *post hoc ergo propter hoc* reasoning.

The tendency of the human mind to indulge in *post hoc ergo propter hoc* reasoning was said by the philosopher Kant to be the cause of all human error.

An understanding of these six fundamental propositions is basic to sound therapeutic research. The failure to take them into consideration and to set up proper controls toward this end has led to an enormous amount of misspent research. As far as the drug industry is concerned, it simply means that millions of dollars are being wasted on drug research that is unsound in its conception. It leads to the promotion of drug products on the basis of fallacious therapeutic claims which is an even greater economic waste for all concerned.

Now it is evident that when the scientific method is applied to drug research and therapeutic claims, it is possible to establish a therapeutic representation as a fact. It is something that can be demonstrated and proved with the same degree of certainty as any other factual material presented in our courts of law. But our courts, which look backward to precedent, still regard therapeutic representations as matters of opinion. Perhaps we can't blame lawyers too much for throwing up their hands in hopeless confusion when one considers the rubbish that is presented to them in the name of science. But we have available nowadays well-recognized techniques for testing the correctness of therapeutic claims. Where there is a diametrically opposed difference of opinion, it is self-evident that one opinion is right and the other wrong. Honest differences of opinion arise only because some one has failed to take into consideration the fundamental principles that apply to drug research in human beings. Where there are such differences of opinion it should not be an insurmountable difficulty to show wherein the evidence supporting one of the conflicting opinions is faulty. And in my judgment our courts have a responsibility to look behind the opinion and critically examine the evidence supporting it. Perhaps this is expecting too much of our lay courts, and the ultimate solution may be in the designation of expert tribunals to judge these admittedly difficult questions.

In the metamorphosis of modern drug research certain interesting trends are evident. Drug research started as the effort of individuals. In the eighteenth and nineteenth centuries we find contributions to drug research made largely by individuals in the course of their medical practices or as by-products of their functions as teachers in universities. From the middle of the nineteenth century, drug research has been gradually taken over by workers in universities, foundations and institutions. The medical practitioner has become increasingly aware of the fact that the ordinary practice of medicine does not provide sufficient time, material and specialized instruments for fundamental and well-controlled experiments. As medical research developed as the function of universities, there came into existence the so-called university hospital or the medical center, as an adjunct to the university. Here there have become available human subjects in sufficient numbers to permit well-controlled scientific studies on the cause and treatment of disease. These institutions were and still are largely private organizations supported by the philanthropy of private individuals. But we are now witnessing a gradual but nevertheless tremendously significant change in this situation. It appears to be only one phase of a vast economic movement that is sweeping over the world. Private philanthropy seems to be rapidly disappearing. A few institutions have been able to coast along on what they managed to hang on to during the economic depression, but by and large they are unable to grow and prosper on endowments that are not augmented. Instead, drug research is being increasingly supported by funds from two sources: (1) the drug houses; (2) the government, using the term in its broadest sense to include states and municipalities. And not only are the funds from these sources flowing into the coffers of our universities, but both the drug houses and governmental units are undertaking increasingly important drug research themselves. They are as never before drawing promising investigators away from the universities into their own laboratories.

Until recently drug houses have confined their efforts largely to laboratory investigations with drugs. They have turned to the universities and their hospitals for their clinical tests. In general, they have exercised little control over the development of these clinical studies except as the aim to please and perhaps attract additional funds may have influenced the investigators. I suspect that this relationship is not always satisfactory from the standpoint of the drug manufacturers, since they pay the money and yet are not in a position to control the direction of the studies. But, on the other hand, it provides what may be said to be a non-partisan, unbiased inquiry into the clinical facts. However, I venture to say that the future will see drug houses obtaining closer and more controlling affiliations with institutions having clinical facilities.

During the last twenty years the tempo of research in the fundamental sciences has been gradually increasing. Those who had a clear vision of the future recognized that the conquest of disease, premature old age and cancer was more likely to be made in the laboratory of the chemist or the physicist than in the clinic where drug research was more often than not practised as a hobby of the medical staff.

During the first quarter of the twentieth century drug research seemed to be suffering from claustrophobia, and chemotherapy in particular was in the

doldrums. But all this suddenly changed in 1932 with the discovery of the clinical usefulness of sulfanilamide. The importance of a close collaboration between laboratory and clinic was reemphasized. Sulfanilamide and intriguing discoveries in the field of endocrinology have unveiled new horizons. The sky seems to be the limit. Scientists are tackling problems of disease, such as the cause of cancer and the prolongation of life, with not only zest and enthusiasm but confident expectation that the achievements of the past are but a minor prelude to discoveries that will transform the whole panorama of life itself.

The enactment of the New Drug Section of the Food, Drug and Cosmetic Act has provided a powerful impetus to drug research. For the first time in our national history a thorough investigation of the safety of drugs before they are marketed has been made compulsory. Thousands of drug investigations are now being conducted where previously there was only a handful. Prominent pharmacologists tell me that this law has provided an incalculable stimulus to a science that was once regarded by some as a sterile cross between physiology and chemistry. Time will show, I believe, that the new drug section of the act is one of the most significant things that has ever happened to drug research in this country and the legitimate drug industry will be among the principal benefactors of its wholesome influence.

There will always be a drug industry and individual drug manufacturers. But some manufacturers will develop and prosper; others will decline. Some will see more clearly than others that the future of their companies rests more than anything else upon the research that is stimulated by them. Others will recognize, as some already have, that we can't make much progress if we have only one, two or three bright young chemists shut up in a laboratory, puttering along on problems that are as vital as health and life, and at the same time somewhere else in another laboratory, one or two other chemists going over exactly the same ground, as out of touch with the first group as if they were working on another planet. The sooner we realize that the day of the brilliant individual investigator working alone in a hermetically sealed compartment is gone forever, the sooner will we solve problems that are far more important than the tensile strength of steel, nylon stockings, synthetic rubber or a horsepower per pound of airplane engine.

The problems of drug research are more complex than they used to be. Progress in the future will come increasingly from the collaborative efforts of groups of individuals, working under the leadership of those who have imagination and minds fertile with ideas. The brilliant investigator is indispensable, but he must have the tools to work with and the help of assistants who will act as test pilots for his ideas. There must also be a harmonious integration of the work of chemists, physicists, physiologists, pharmacologists and clinicians to produce results. I think it is about time that medicine and the drug industry gave up its small-time amateurish attempts at drug research. I think we should go to the du Pont Company, the United States Steel Corporation, the General Electric Company and the Firestone Rubber Company and see how they tackle their research problems. We must enlist the brains, the imagination and the ingenuity of thousands of chemists, physicists, pharmacologists and clinicians to solve these important problems of life and health. They are the problems that count, for without a long life and health, it really doesn't matter much whether we have nylon stockings or synthetic rubber or stratosphere planes or anything else.

ASPECTS OF MODERN PSYCHOLOGY. II

By Dr. CHARLES S. MYERS
ENGLAND

LET us now return to the fate of the psychology founded by Wundt which directly concerned itself in observing mental experience and in reducing it to its elementary terms of sensation and feeling. His former pupil, Külpe, met with Wundt's violent opposition when at Wurzburg he began to study experimentally and introspectively the processes of thought, paying particular attention to the acutely living *acts* of judging, valuing, denying, etc., and not only to the relatively lifeless *stuff*—"bundles" of sensation, percepts, images and thoughts. In Paris, Binet had already detected the occurrence of thinking without images, verbal or concrete. Külpe's school also insisted on introspective grounds that meaning was possible in the absence of images (and hence of sensations). Wundt protested that such inquiries were beyond the scope of introspection, and Titchener, endowed with vivid imagery, maintained that anyhow introspection in Külpe's school must be defective, as he himself could always detect kinaesthetic imagery in all meaning. Meaning, he said, is invariably "context"; it involves a bodily attitude of the individual facing the situation; and psychologically meaning *is* the characteristic kinaesthetic experience aroused by that bodily attitude. Few psychologists will now insist that meaning must have a sensational (or imaginal) basis, or that thought must always have imagery as its vehicle.

Equally important was the experimental evidence