Experimental Pharmacology and Measurement of the Subjective Response

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The Field

Boundaries. Experimental pharmacology in the past has dealt largely with phenomena that can be measured objectively in response to drug administration, with changes in heart rate, rises or falls of blood pressure, neuromuscular action, and so on. Such experimental studies have usually been carried out in animals, and the basic controls have been observed in most cases. On the other hand, relatively little attention has been given to the nature of the controls that are essential in order to elicit true and clear information concerning subjective responses to drugs. Such work must usually be carried out in man.

The need for measurement of subjective responses can be seen by taking a look at the general growth of medicine in recent years. Besides its direct benefits, this growth has served indirectly to emphasize areas where development has lagged. Notable, for example, is the slowness of enduring growth in experimental psychiatry. This is not to say that advances have not been made. They have been, of course. But it is possible that growth in this field has been retarded because pharmacology as it deals with the subjective response has not been given the attention it deserves.

The experimental biochemistry, physiology, and pharmacology of the future will more and more concern man, and in studies of man answers will be sought to questions that involve man's subjective responses. For success here we must recognize the needs of this kind of investigation; they differ from those that deal with objective responses.

Definitions. Objective responses in the sense in which we use the term here are made evident in physical change (or can be made evident) to the senses of an onlooker (a physical sign). They can be mechanically recorded. Subjective responses are evident only to the individual experiencing them (a symptom). They can be imparted to an onlooker only through a cooperative statement by the subject. We are not at the moment concerned with the fact that subjective factors can play a part in producing objective manifestations. Fear, for example, produces dilated pupils. Except for a special consideration of certain physiological and mental performances, we are limiting our interest here to subjective change as just defined.

Some subjective responses studied. We (*1–8*) have had experience in quantifying, after drug administration, the following subjective experiences: headache, difficulty in concentrating, difficulty in focusing eyes, fatigue, relaxation, drowsiness, sleep, neutral effect, unpleasant effect, pleasant effect, warm glow, sensation of drunkenness, sensation of heaviness, sensation of ataxia (without objective sign), dizziness, faint feeling, sensation of weakness, light head, fullness in head, heavy head, tinnitus, increased "nervous" tension, paresthesias, itching, anorexia, nausea, and pain.

We have also worked in related areas where subjective reactions exert powerful influence, and where, if one is to work, controls must be set up as if subjective responses are to be measured—that is, with certain types of physiological performance and mental performance following drug administration (*9*).

Identifying the presence or absence of the above-mentioned sensations is less difficult than it is to get clean-cut measurement of drug effects in special cases of physiological performance (*9*), such as impairment of highly coordinated neuromuscular function—for example, in tapping speed and auditory reaction time —and, in the field of mental performance, attention, memory, association and, insofar as possible, critical judgment. Our chief interest in the kinds of physiological and mental performance mentioned in response to drug administration has been to elicit them in terms that permit accurate comparison of the subtle effects of one agent with another.

Presence, duration, and intensity of subjective responses. We have had good success in identifying the presence or absence, and duration, of the subjective responses mentioned. We have been able to differentiate between these effects as produced by drugs and between a given drug and a placebo. We have had some success in measuring the types of physiological and mental performance mentioned as they are altered by drugs. There are, however, many difficulties in the way of measuring *intensity* of subjective responses. There are practical, as well as theoretical, reasons why measurement of the intensity of pain, say, is very important. Hardy, Wolff, and Goodell (*10*) think they have measured the intensity of pain. We question this, as described in the ensuing section on *"Natural" Sources vs. Experimental Sources.* For the present, at least, the question of whether one can measure intensity of pain or the intensity of any of the types

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of subjective responses mentioned above must be left open. We (*11*) are obtaining promising measurements on the severity (intensity) of pain by comparing the percentage of effectiveness of the early doses of a proved narcotic with later doses in two series of patients: (*a*) those whose pain is easy to relieve (few doses of narcotic required), and (*b*) those whose pain is difficult to relieve (many doses of narcotic required).

Goals. Pharmacology involving the subjective response is concerned largely with the individual's sensations as modified by the inconspicuous effects of drugs on sensory phenomena, mental state, attention, learning, association, memory, and critical judgment. The goal here is to elicit these imponderables in terms that permit accurate statements of change, that permit accurate comparisons of the effects of one drug with another. It is evident that precise work here is of as much interest to fundamental psychiatry as it is to basic pharmacology. It is evident also that attack on the problem of measuring the effects of a drug on, say, sensory reaction must be very different from that of counting the change in heartbeat in response to a drug. In the latter case few would fail to control temperature. Oddly enough, many have shut their eyes to the complex controls necessary if one is to deal successfully with the difficult problem of measuring subjective responses, and we see investigators plunging into studies of pain without giving attention to the nature of the essential controls.

In this report we shall examine the conditions necessary and the nature of the controls that are required for study when subjective responses to drugs are to be considered. The agents of principal interest here are at present the central nervous system depressants, and man is the essential animal for most of the experimental investigations.[2]

The desired effect with these agents is subjective change. To achieve the purpose desired, in the dosages employed in man, the agents often produce no objective alteration. (The antitussives and the anesthetics are of course exceptions.) Large doses of the central nervous system depressants usually give rise to objective, easily detected toxic signs. It is also true that the therapeutic dose is sometimes inseparable from these undesirable side effects. For example, morphine relieves pain, but the dose that does this satisfactorily also depresses the respiration. Although our primary interest is in the subjective response, it is thus not possible to avoid the necessity of assaying the side reactions that accompany them. These can be evaluated only if doses that produce identical therapeutic effects are compared—an obvious factor that is often overlooked. Thus the power to equilibrate agents in terms of equal therapeutic power is a necessary preliminary to a comparison of their toxic effects.

Accuracy. Experience has shown that with sound controls we can achieve at least the same degree of accuracy in measuring some subjective responses as can be attained with objective responses. For example, we (*6*) dealt with several unknown solutions in the treatment of real (pathologic) pain. One group of these solutions was found, at the end of the experiment, to contain always 10 mg of morphine per unit volume, whereas the other solutions pitted against it contained varying concentrations of morphine (not known at the time of the experiment). In the end we found we had equilibrated 10 mg of morphine with 10.8 mg of morphine, for equal pain-relieving power, an 8 per cent error. This is within the 10 per cent accepted for most biological work.

Experimental Material for Study

Man, the "animal of necessity." From the definition of subjective response given above it is evident that man must be in most, if not all, cases the final experimental subject. This emphasizes the importance of the hospital in work in this field. For the protection of the subject, much human experimentation must be carried out in a hospital; incidentally, this is generally the source of material when the subjective response to be measured arises in disease or trauma.

Lower animals. It is not clear at present just how useful animals really are or can be. For instance, new analgesic agents are commonly screened in animals. All tests yet developed of these substances in animals depend upon reflex phenomena. What the connection is between pain-relieving power and depression of the various reflexes tested is not altogether clear. When questions such as these are raised, it is customary to state that the animal methods have been successful in the past. That statement will bear critical examination; there is need for fresh thought here.

A group of new, possibly analgesic, agents is made by the organic chemist in such a way that most of the new compounds bear a more or less close relationship to the chemical structure of known analgesics. (In the powerful ones a tertiary nitrogen is always present, etc.) These agents, which are generally far from random choices, are then sent to the biologist for "screening" in animals. There may be some element of chance in the fact that two or three fairly active agents are pulled out of the twenty or so under test. This "successful" screening may in part be coincidence. We are examining the possibility mathematically at the present time. Such a matter cannot be settled finally by mathematics, but the data appear interesting, for there is,

[2] For some years we (*2–9, 12*) have been concerned in our laboratory and clinic with the central nervous system depressants: the sedatives, the sleep-producing agents (the hypnotics), the pain-relieving agents (opiates, narcotics, and others), the antitussives, the ego-depressing substances (agents from many chemical classes, used in narcoanalysis), and the anesthetics. The diverse substances used to produce the effects mentioned have some common characteristics: They depress the central nervous system. The boundaries between them often are not clean-cut. Agents from one of the groups, merely by changing the dosage, will often produce effects common to another of the groups referred to. A small dose of a barbiturate has sedative effect, a little increase in dosage has good hypnotic power and some analgesic effect; with a further increase in dose the same agent becomes an ego-depressant, useful in narcoanalysis; and with a final increase in dosage, an anesthetic. The close relationships within these several categories, the stimulation and cross-fertilization of ideas that arise, justify, we believe, a broad attack on the problem of measurement of the subjective phenomena that arise from use of these agents as a closely related group.

indeed, the possibility that as many good agents produced by the chemist go down the sink as are pulled out of the new lot by present screening procedures. Whatever the final outcome may be as far as these questions are concerned, certainly animals do have a field of usefulness in screening new agents. Also, toxic organic effects must first be sought in animals.

"Natural" (pathological) sources vs. experimental (contrived). During work on pain in 1947, we (*3*) were led to postulate that there is a fundamental difference in what can be learned in studying "natural" pain which arises in a pathological focus (disease or trauma are defined here as "natural" cause) from that produced experimentally (heat to forehead, pin pricks, electric shocks, or heat to teeth, pain deliberately produced with a tourniquet, and so on). The basis for this postulate had its beginning in our attempts to use the Hardy-Wolff-Goodell technique. This involves projecting a measured amount of heat onto the skin until pain is produced. We found with this method that some thresholds were higher after the injection of isotonic sodium chloride solution; some were lower after the administration of morphine; and these discrepancies were common.

We concluded that, for some reason unknown to us, we were not correctly employing the method. An investigator with years of experience with the method was called in and set to work on the problem. He, too, failed. He was completely unable to differentiate between 15 mg morphine and 1 ml normal saline, so long as he was kept in ignorance of which agent the subjects had had. This by no means impugns his honesty. It is our conviction that ignorance of the observer, as well as of the subject, is absolute necessary in work of this kind. The experimenter's enthusiasm, in whichever direction it exists, for or against, must be removed. Failure of such gross differentiation as this forced us to conclude that it was useless to look with this method for subtleties in pain-relieving power —subtleties that might distinguish one narcotic from another.

Inquiry then revealed that our experience was common to many other groups, not only to those employing the Hardy-Wolff-Goodell method, but also to those using the other experimental pain methods as well. (We have no wish to single out the Hardy-Wolff-Goodell method. It is doubtless as good as most such methods. We refer to it particularly because our only firsthand experience with experimental pain methods was with this one.) Not only has there been failure of one man to confirm the work of another with a given experimental pain method, but studies of the same analgesics by different experimental methods failed to check in many instances. There were other disturbing problems: For example, it is widely stated by those who use experimental pain methods that aspirin has no analgesic power! Anyone who has had his tonsils out and who has had to chew five grains of aspirin before he could swallow his food knows that aspirin does have local analgesic power. The man with a headache, with a toothache, with the pain of arthritis, with wound pain, does not need a learned treatise to tell him that aspirin is indeed an analgesic agent, and a fairly good one; yet these experimental pain methods usually failed to reveal what we all know. This was a further significant reason to doubt the validity of the premise on which the experimental pain methods are based. Our conclusion was supported further by the fact that our method of using pain of pathological origin *can* differentiate satisfactorily between aspirin and a placebo, or aspirin and morphine. It seems likely that the chief field of usefulness for experimental pain methods may be in animals.

We (*3–5*) then set about devising another approach to the problem, an approach that included the belief that the use of pain of experimental origin in man is artificial and is particularly unreliable in this complex field. Basic reasons for this belief were observations (*1, 13, 14*) that emotion can block pain, that extrinsic factors and lack of attention to wounds, as in games or during fighting, can block pain (namely, removal from the danger of the battlefield to the relative safety of the military hospital produces euphoria and a disregard for wounds which is very often associated with block of the peculiarly intrinsic experience of pain [*1*]). Finally, there is the widely accepted view that the pain experience consists of the pain sensation (percept) and the reaction to pain (this involves the total concept).[3] Hardy and Wolff have for years rightly emphasized these two aspects of the pain experience. It is because we so heartily agree with them that we believe the use of pain of pathological origin is important in the appraisal of analgesic power.

No one who has worked with problems of pathological pain can doubt the importance in this field of the environment, of emotional factors, on the reaction to pain. Wikler (*15*) brought this out in his superb review. It requires little imagination to suppose that the sickbed of the patient in pain, with its ominous threat against his happiness, his security, his very life, provides an entirely different milieu (*and reaction*) than the laboratory, with its dispassionate and unemotional atmosphere. This is not to say that anxious states cannot be deliberately produced in the laboratory, but they are generally not a part of the experimental technique for the study of pain, nor do we believe they can be as satisfactorily produced there.

We agree that all pain experience consists of pain perception and reaction to pain. However, between experimental and pathological pain there are large *quantitative* differences in the role of each component. In the pathological pain experience, the contribution of reaction to pain (amplified by association pathways) overshadows any differences in the quantities of pain sensation, as we have shown. In the experimental pain experience, the relatively short duration of the stimulation and the experimental situation make the experience primarily one of pain sensation.

[3] In the situations just mentioned, it would be interesting to know whether the pain sensation or the reaction to pain is blocked; perhaps one, perhaps both.

We do not believe that the pathological pain situation with all the diffuse associations of illness, disease, and pain can be satisfactorily reproduced in the laboratory. The differences in the quality and quantity of association between the laboratory situation and the hospital bed are so great that the study of either can probably apply only slightly to the other. The discrepancies in results from similar studies by the two methods support this hypothesis. Since pain is almost always a consequence of disease or pathological trauma, the study of pathologic pain seems to us the more direct and logical approach to an understanding of the pain experience and its relief.

Thus our premise is that the "strategic animal" for the study of pain is man himself in real pain of pathological origin. It must stand or fall on its consequences under further test.

We are concerned with (*a*) which method (pathological or experimental) works; (*b*) if both work, which is better—that is, more widely useful. We are concerned with the nature of the evidence that a given method works; i.e., does it work if the "unknowns" technique is employed, and this includes observer as well as subject. We are concerned incidentally, of course, with simplicity. A method that can function with no apparatus other than a notebook and pencil is manifestly more desirable and more broadly useful, other things being equal, than one that requires complex and delicate apparatus which needs calibration by a well-trained physicist.

This matter has been discussed at some length, because, so far as I am aware, attention has not previously been focused sharply on the question of whether the study of therapeutic agents designed to relieve subjective responses that customarily arise in disease or trauma must be studied there for definitive information. If this is true for pain, it may well be true for other subjective responses that arise in pathology. The breadth of the generalization needs to be determined.[4]

Controls

"Unknowns" technique. When subjective effects are under study, the experimental requirements are, as already mentioned, very different from what they are when the effects of drugs can be judged by objective signs. Some of the essential requirements for dealing with agents that produce subjective changes are these: The studies generally must be carried out in man. To discover what the subjective response is, questions must be asked. It is essential that these be framed with care and posed in a neutral manner. Expert guidance, if it can be obtained, is of great importance. Neutrality can be violated not only by wording, but by inflection, by emphasis, by timing of the questions. True neutrality cannot be preserved when any active participant in the experiment is aware of *when* an agent is tested or *what* that agent is, and to preserve the unknown character of the tests, code numbers must be changed frequently. Investigator's enthusiasm or bias comes out in subtle ways that are hard to detect at the time. It becomes startlingly obvious when data, obtained under conditions where the interrogator or investigator was aware of what the subject had, are compared with data obtained when he was kept in ignorance.

Design of the experiment. The escape from prejudice effected by the use of unknowns involves the administration of agents (capsules or solutions) with an identical appearance. In one case the substance given will be a placebo; in another, a standard of reference —for example, in studying analgesics of the narcotic class, morphine in standard dose, usually 10 mg/70 kg body weight; in still another instance the new agent to be tested will be given. A technique of thorough randomization is essential. Each agent is sandwiched between two doses of another; all three agents are bracketed in turn in this way around each other, and all in the same patient, if economy of time and effort is to be achieved. When the series is large, the need for testing all three agents in the same patient is less important, but it remains the soundest technique. Thus one can control suggestion, inherent or implied, the presence of the investigator, practice effect, learning, motivation, interest, the subject's anticipation of an unknown medication, his drug history. The question of whether "acute tolerance" (*16*) develops during the period of study must be examined and ruled out or controlled, if present.

Sound design of the experiment requires that willing, cooperative, undistracted subjects be used in sufficient numbers to cancel out normal mood swings above and below par. The body's diurnal temperature swings, with their demonstrable effects on performance, also require controls. Male subjects are better than female, for the menstrual cycle requires troublesome controls.

The presence of the investigator, as noted above, requires the type of controls effected by the use of unknowns and the randomization technique. It must further be pointed out that constancy of investigator or investigating team is essential during any given series of experiments. We have found in our own work that a sympathetic woman investigator generally obtained a higher percentage of pain relief from various medications than a colder, more remote, male. Wikler (*15*) has referred to the same thing.

The isolation of a true cause-effect relationship[5] requires that all the interfering factors mentioned be cleared away by the plan of the experiment. Mathematical validation of any supposed differences is

[4] At present we are studying antitussive agents under the two circumstances; it will be interesting to see if the data obtained in each case differ from the other.

[5] Lest this appear too precise, it must be understood that the "effect" half of the relationship includes the psychic modification of the original stimulus. It might be objected that, when the drug is given, the patient says he is relieved or he is not; the same drug is used. The same is true of the placebo; he is relieved by it or he is not. We are obliged to assume that the placebo has at times curative power, not a very risky assumption when one stops to consider the very nature of the subjective ailments and their sensitivity, both ways, to suggestion. Thus the effect side of the relationship must include psychic modification of the original stimulus and psychic effects produced by therapy.

essential. Without facing up to these needs many laboratory investigators, not to mention clinical investigators, have for years attempted to work in this complex field with only the slightest acknowledgment, if any, of the necessary controls. Acknowledgment of the requirements of work with the subjective response to drugs constitutes a first step. It will, in giving orientation, help to clarify the problem.

The special problem of "placebo reactors." For many years, perhaps for centuries, it has been widely recognized that certain individuals with subjective complaints will react favorably to—indeed be cured by—placebos. Far too often, in our judgment, it has been supposed that those who were healed by placebos were either malingerers or neurotics. We firmly believe that placebos can cure in some cases, that they can block pain in normal individuals, for instance. Acceptance of this as fact still leaves a considerable problem.

Individuals who are relieved by placebos we call "placebo reactors." The problem they pose is this: We are interested in studying the pharmacology of a new drug. We try it out on a group of patients; a third to a half of this group will be relieved of their symptoms by a placebo; they react favorably to the syringe regardless of what it contains. Thus they dilute the significant data derived from the other half or two thirds of the group that react only to the drug contained in the syringe. We are not, in studying a new drug, interested in the pharmacology of syringes; we are nonetheless obliged to take into account the placebo reactors; we must screen them out if we are to get an accurate account of what the drug itself does. This can be done (*17, 18*). We are doing it with use of two-by-two tables. It is of great importance in the study of the subjective effects of drugs.

Summary of Established Principles and Practices

The principles and practices that have been established are few, and in several instances they may seem obvious to the casual observer. That they have not been obvious to the majority of individuals working with subjective responses can be demonstrated by examining reports of investigations in this field. In summary, here are the principles and beliefs involved and the unquestionable essentials for most work of this kind.

a) Subjective responses are the resultant of the action of the original stimulus and the psychic modification of that stimulus.

b) Man is the essential experimental subject for a definitive answer to questions in this field, and men are easier to work with than women, for with men the controls are simpler.

c) The investigating staff is constant during any given series of experiments.

d) The "unknowns" technique is employed throughout. The agents tested and the time they are tested are unknown not only to the subjects but to the observers as well. This requires the use of placebos, also as unknowns.

e) When a new agent is to be compared with the agents of past experience, and this is nearly always the case, a standard of reference is required (morphine in standardized dosage is used as the standard for analgesics, etc.).

f) Randomization of new agent, placebo, and a standard of reference is essential.

g) Significant comparisons of side actions of agents can be made only on the basis of doses of equal strength in terms of their primary therapeutic effect.

h) Mathematical validation of supposed difference in effectiveness of the two agents is necessary.

i) The subjective effects of drugs can be quantified accurately and rapidly only when placebo reactors are screened out.

Matters for Further Study

The following unproved "principles" can be indicated as questions as well as any other way. There will be partisans for and against each. A good deal of evidence, not yet conclusive, can be marshaled to give an answer to each question.

a) Can the intensity of any of the subjective responses referred to here be satisfactorily quantified? If it can be, which factors predominate in influencing intensity: the original stimulus, the reaction to it (psychic modification), or both?

b) Can one generalize that maximum subjective effects are produced rather early by the effective agents and that no real increase in effect is produced by increased dosage? (Example: morphine produces nearly its maximum pain-relieving effect at about the 8-mg dose. The dose-effect curve breaks sharply at this point. Larger doses will, at great risk, produce anesthesia and unconsciousness, but these effects are outside of analgesia.) We are checking this for cough, for sleep, for euphoria.

c) What is the usefulness of animals for the study of subjective responses, except as screens for organic toxicity? The question of the validity of animal screening methods has enormous importance to manufacturers.

d) What is the place of subjective responses that are produced experimentally as opposed to those that arise in pathology? We must determine whether, as seems likely from a study of pain, subjective responses arising in disease are mandatory for all studies that deal with the therapy of the subjective response. We do not yet know how inclusive this requirement is.

Conclusions

We have shown what conditions are necessary for proper evaluation of a number of drugs, the therapeutic effects of which are subjective, and we agree they are complex and exasperatingly time-consuming. We wish it were not so annoying as it is to fulfill the necessary conditions.

Tedious as these conditions are, we insist that they are *not* more costly than the empirical method and are

actually far less so. They do permit accurate results to be arrived at more rapidly than is true of the old-fashioned method of simply distributing drugs to practically everybody and gradually, by trial and error, arriving in decades or centuries at an approximation of the truth.

To take an example, after all the centuries morphine (or opium) has been used, "common sense" in this country has arrived at a dose that is twice as large (15 mg) as the one that gives essentially the maximum pain relief (8 mg). It is true that in the common-sense method the cost of the evaluation is borne not by the manufacturer but by the public. It is also true that in the case of morphine (opium) the correct result was approximated in hundreds of years, and the conclusion is about 100 per cent off. I believe we can and should do better than this.

There is a great field for study here, but it is a field where there are many obstacles: legalistics to hamper the investigator; ignorance of the relationships between chemical constitution and biological action to slow him down; chance or coincidence to be forced into the open only by intricate and laborious statistical methods. Painstaking and tedious work is necessary. It is a costly field, but one that promises to yield on cultivation an astonishingly rich harvest.

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News and Notes

Scientists in the News

Frank Aydelotte, for 35 years American secretary to the Rhodes Scholarships, will retire Jan. 1. **Courtney C. Smith,** assistant professor of English at Princeton University, will succeed Dr. Aydelotte. A former Rhodes scholar, Dr. Aydelotte has worked closely with the Rhodes scholarship system and the Oxford plan of education in addition to his duties first as president of Swarthmore College and then with the Institute for Advanced Study. In addition to his duties as American secretary, Dr. Aydelotte, a former editor of the *American Oxonian,* has been president of the Association of American Rhodes Scholars since 1930 and was re-elected last May.

Brian Blades, professor of surgery at the George Washington University of Medicine, is principal investigator on four projects supported by grants totaling $27,099. A grant of $6606 has been received from the U. S. Army Surgeon General's office to permit studies on factors of safety in intra-arterial transfusions. Dr. Blades will be assisted by **Howard Pierpont,** director of the Surgical Research Laboratory of the School of Medicine. A grant of $11,005 from the USPHS will be used for research in the restoration of blood vessels injured by disease or a wound. Other investigators on this project are **William S. McCune,** associate clinical professor of surgery, and Dr. Pierpont. Another USPHS grant of $10,249 will permit research in reconstruction of the aortic arch through surgery and the use of grafts or synthetic materials, and a grant of $9239 from the Veterans Administration will further studies of liver circulation.

Kenneth A. Clendenning has been appointed research plant physiologist on the staff of the Charles F. Kettering Foundation for the Study of Chlorophyll and Photosynthesis at Antioch College. Dr. Clendenning was formerly head of the Plant Science Section, Division of Applied Biology, National Research Laboratories, Ottawa.

Paul L. Copeland, acting chairman of the Physics Department at Illinois Institute of Technology, has been appointed chairman. He has been at the institute since 1937.

William L. Doyle has joined the staff of the Research Institute of Temple University in the capacity of full-time research scientist in high temperature work. An expanding program is planned in this field under an Office of Naval Research project. Mr. Doyle has been consultant at the Research Institute since last January. He was formerly in charge of rocket development at Ohio State University and worked with North American Aviation on liquid rocket fuel development.

John Fletcher, a specialist in varnishes and synthetic resins, has joined the staff of National Research Corporation, Cambridge, Mass. Mr. Fletcher will