ranges from 0.24 to 5.2 percent of administered testosterone-4-C^{14} activity and from 0.19 to 4.3 percent of administered progesterone-4-C^{14} activity. This activity is correlated with the amount of fat present in the animals.

Figure 1 shows the total radioactivity of C-19 steroids plotted against grams of fat for goldthioglucose obese mice and nonobese controls given 10 μc of testosterone-4-C^{14}. This activity was measured 18 hours after injection. It is evident that retention of labeled hormone is proportional to the amount of fat, or to obesity per se. The same picture was found in goldthioglucose obese mice given 5 μc of testosterone.

Similar results were obtained with the obese-hyperglycemic mice—that is, retention of testosterone-C^{14} was proportional to the amount of fat present in obese and nonobese mice. In addition, C^{14} retention per gram of fat (1800 count/min per gram of fat for animals given 10 μc) was the same for both types of obese mice and their nonobese controls. For the various types of mice at the two doses studied after 18 hours, retention of testosterone was represented by the formula: percentage retention $= 1.3 + 0.05 \times 10^{-3} f$, where f is total body fat in grams.

Figure 2 shows the radioactivity present in the progesterone fraction plotted against the grams of fat for goldthioglucose obese mice, obese hyperglycemic mice, and their respective nonobese controls measured 18 hours after the injection of progesterone-4-C^{14}. As in the testosterone study, retention of labeled hormone is correlated with the amount of fat present regardless of the type of obesity or whether the mice are obese or nonobese. Carbon-14 retention per gram of fat is the same for all animals (1600 count/min per gram of fat in the progesterone study). Thus, although the obese-hyperglycemic mice and goldthioglucose obese mice differ markedly in fatty acid and cholesterol synthesis, retention of administered steroid hormone appears to be a physical phenomenon common to both groups because of their increased fat content. A large amount of excess fat in obese animals favors the retention of injected steroid hormones. This may have physiological consequences in that obese animals (and obese patients) may retain larger amounts of their own steroid hormones. It may also have therapeutic implications in that it appears likely that steroid hormones administered to obese patients may be stored in appreciable amounts in their fat depots (*11*).

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5. Goldthioglucose hypothalamic mice become hyperphagic and obese as a result of the destruction of the ventromedial area of the hypothalamus by a single injection of 1 mg of goldthioglucose per gram of body weight (*2*). No abnormality of carbohydrate or fat metabolism (outside of those secondary to hyperphagia) is present.
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20 October 1958

Nervous Pathways of Cutaneous Pains

Abstract. In discussing the reality of a peripheral duality of pain-afferent systems, which she attributes to an artifact [*Science* 128, 713 (1958)], M. H. Jones rejects as valueless data concerning differences in the velocity of conduction of nerve impulses as determined by reaction times. Yet precise data tend to show the reality of these differences in velocity.

I found it very strange that Margaret Hubbard Jones should maintain, on several occasions (*1*), solely on the basis of subjective data, that the duality of cutaneous pains is an artifact.

For a long time now the dissociation of cutaneous pain systems has been established, as I reported in detail in 1935, in an article in *Traité de Physiologie* (*2*).

Supporting data obtained from an analysis of reaction times were deliberately rejected by Jones, who cited a study by Lele, Sinclair, and Weddell (*3*) in support of her position.

Answering Libet (*4*), she declares, "Libet's emphasis on reaction time is unfortunate. None of the studies meet the minimum requirements for work in the field."

Actually, research studies of Lele *et al.* have shown that these reaction times do vary—something which has been known for a century. It was through variations in reaction time that Helmholtz measured, for the first time, in 1850, the velocity of the nerve impulse in afferent tracts, with an accuracy which afterwards proved satisfactory.

Of course, measurements should be planned under very precise conditions and made on trained and sufficiently coherent subjects (this was not the case in the research of Lele *et al.*); it is then possible to get mean values which are stable enough to be significant. A most important point lies in the use of constant physiological intensities, for reaction times depend on the intensity of the sensation, showing rapid variability around the threshold. For touch, a margin of about 230 msec between threshold intensity and an intensity 150 times greater (*5*) is found; narrower margins are sometimes met with, however, (*6*).

But Lele *et al.*, when comparing reaction times to stimulation consisting of equal pressures on a finger and on a toe, took no account of differences in the sensibility of their subjects and did not establish threshold values; hence, their comparison loses all its significance and their conclusions all their value.

In 1930 (*7*) I made a series of measurements of reaction times to such stimulations as painful pricking, burning, and pinching, the stimulations being so graded as to cause sensations of seemingly equal pain on the forehead (or the temple), the wrist, and the ankle.

Under such conditions (the dispersion indices of means computed on series of 20 being usually less than 10 percent), I found, for two nerve pathways each 80 cm long (between forehead and hand and between hand and foot), reaction-time differences of 235 and 216 msec for burning (by contact for forehead and hand, by immersion for hand and foot); differences of only 49 msec for pricking (either between forehead and hand or between hand and foot); and, finally, differences of 135 msec for pinching between temple and foot (that is, 68 msec for a pathway 80 cm long).

The resulting probable velocities of nerve impulses are about 4.50 m/sec for burning, 16 m/sec for pricking, and 12 m/sec for pinching, whereas for touch the velocity is about 40 m/sec, according to determinations which von Wittich established as early as 1868 (*8*) through study of reaction times.

In 1939, Zotterman (*9*), using tactual percussion, contact, pricking, and burning as stimulations on a cat's tegument innerved by the saphena, recorded four types of action potentials in this nerve: the fastest (30 to 60 m/sec) were correl-

ative with tactual percussion; the slowest, of the C group (2 to 5 m/sec), were related to burning; those generated by pricking had a velocity 20 to 30 m/sec; and finally, those due to irritative slight contacts which Zotterman thought might induce itching had a velocity of 8 to 17 m/sec and were related to the A group, δ type fibers.

As I pointed out (*10*), it appears to me that there is remarkable agreement between these data and the velocities found in man through measurement of reaction times: 40 m/sec for touch, 4.5 m/sec for burning, 16 m/sec for pricking, and about 12 m/sec for pinching.

This finding that there is dissociation of afferent systems for painful excitations of the skin has been shown to be in agreement with numerous other data, some of which were reported by G. H. Bishop and W. L. Landau (*11*); it can be considered to be a definitively established fact (*12*).

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2 January 1959

Due to limitation of space, I shall limit my discussion to the reaction-time studies which are assumed to prove the duality (or even plurality) of cutaneous pain systems.

I have stated (*1*) that none of the studies of reaction time meets the minimum requirements for reliable results. I repeat, none of them do—not excluding the study of Lele, Sinclair, and Weddell (*2*). But the work of Lele *et al.* was technically superior to most, and it did show that, even in studies of the sense of touch (far easier to deal with than pain), variability of results is the rule. The conclusion I draw is that more than ordinary caution is required to demonstrate a reliable difference in reaction time between two areas.

In the study of pain, proper control of stimulus has been a vexing problem. With needle stimuli, even when properly applied, there is a variation in time lag before stimulation because of the appreciable amount of time necessary for the needle to penetrate to its maximum depth (*3*), and because of the varying depth of the receptors. With heat stimuli, the time lag is both greater and more variable because of variation in the thickness and character of the epithelium in different areas of the body (*4*). And the difficulties involved in precise control of heat stimuli are many (see *5*).

The study which Piéron cites as definitely establishing the dissociation of pain systems is his own (*6*). In this study, on one test subject, a needle was used to produce pricking pain, with pressure of 15 g on the temple, 25 g on the wrist, and 25 g on the ankle. As far as one can ascertain from the report, 24 trials were made at each point. There is no information about pretraining on this type of response (and in any event, the learning curve for reaction-time data does not level off until at least the 100th trial) or about the subject's "coherence" —or, indeed, about how much he knew about what the experimenter expected to find. The intensities used are greatly above those of the pain threshold, and a statement that they were approximately equated for the three areas is not convincing, in the absence of experimental data, in view of the great variability in pain threshold of various pain spots (*7*) and of the extreme difficulty of making that type of psychophysical judgment. Further, there is no measure of the significance of the differences in reaction time used to calculate conduction velocities in nerves.

In the same study, burning pain was produced by application of a metal container filled with water at 70°C (or 60°C?) to the forehead and the back of the hand (four trials each). Since this stimulus gave reaction times for the foot which were too long to be "useful," the difference in reaction time between hand and foot was determined by plunging them into a hot (60°C) water bath (11 and 4 trials, respectively). In neither case is the stimulus constant over time, nor does it bear any observable relation to the threshold for heat pain. In the latter case, even the areas vary. Heat stimuli, to be even moderately controlled, must be constantly monitored, and even then changes or differences in blood flow, color of skin, and chemical changes within the tissues (particularly upon repetition) may render the control superficial.

Heat of this order penetrates tissues more slowly than a needle, and the slower reaction times to heat pain are certainly correlated with the time lag between application of the stimulus to the surface of the skin and the stimulation of the underlying receptors. Furthermore, the differences in the epithelium in various regions of the body would lead one to expect a greater time difference in the response to heat of forehead, hand, and foot than in the response of these areas to suprathreshold stimuli produced by a needle.

McKenna (*8*) found that neither surface temperature nor increase in surface temperature is critical for stimulation of pain by heat, but, rather, that the important factor is either the critical temperature at the receptor or the temperature difference between receptor level and deeper fibers. Thus, the depth and thermal characteristics of the epithelium would seem to be important determinants of absolute reaction time, as well as of the differences in reaction time between various regions of the body.

Until a slow pain ("subjective" because perceived) in the absence of the afore-mentioned artifacts can be demonstrated, there exists no body of data to be related to the physiological data regarding cutaneous C-fiber function.

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27 March 1959

Separation of Hydrogen Isotopes by Gas-Solid Chromatography

Abstract. Conditions are described for the chromatographic analysis of mixtures of H_2, HT, and T_2 on a "molecular sieve" column. This technique may find valuable applications in various kinetic investigations.

Isotope effects in gas chromatography have been observed previously (*1*). We have found that this phenomenon can be used to analyze mixtures of H_2, HT, and T_2. Samples were prepared by