The persistence of the excellent clinical results in these limbs, in spite of the reappearance of the reflexes in most, signifies that the new nerve path is functionally less efficient than that present before operation.

Once more, we acknowledge our gratitude to Prof. J. R. Learmonth, Mr. P. Fitzgerald, and Mr. J. S. Loughridge for putting us in touch with their patients; Mr. D. B. Smith for technical assistance; and the Medical Research Council for defraying expenses.

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A METHOD OF TESTING ANALGESICS

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EARLY in 1947 Messrs. Roche asked the Central Middlesex County Hospital to perform a clinical trial of their analgesic preparation 'Saridone.' * This paper describes an attempt to judge the effectiveness of these tablets by as impartial and accurate a method as possible. It is notoriously difficult to assess the power of different analgesics. There are three main methods—animal experiments, experiments on human volunteers with artificially produced pain, and clinical trial on patients with naturally occurring pain.

Animal experiments are useful in initial tests to select a substance for further trial, but they assess properties only remotely connected with the purpose of an analgesic. A patient wants a tablet that makes his pain better and not only one that stops a rat from twitching its tail away from a painfully hot lamp (a common laboratory test for analgesic properties is to measure the time taken before a rat moves its tail from an increasingly hot beam of light).

Experiments on artificially produced pain have disadvantages too. First, the subjects have not the same mental attitude to the pain as ordinary patients have. It is a pain of their own choosing, and so they suffer none of the anxiety, resentment, and irritability that usually attend naturally occurring pain. Their discomfort is somewhat modified too by the pleasure of feeling slightly heroic and by the curiosity of being experimented on.

Clinical Trials

The danger of clinical trials is that a perfectly controlled test is so hard to arrange. Also, the more elaborate the arrangements, the less closely do the conditions of taking the tablet resemble normal bedside administration. For any fair trial a control inert tablet should be given, but if the identity of the tablet is known to the doctor supervising the tests or to the nurses giving the tablets, their own attitude may much influence the attitude of the patients and so corrupt the results. Consciously or unconsciously a nurse giving a substance she knows to be inert may convey her distrust of the tablet to the patient by manner, gesture, or word. The way people can be unconsciously influenced by a word is well shown by the results of an American bureau of salesmanship who found that when a salesman said "Ice-cream, sir? Large?" he sold over 50% more large ice-creams than when he said "Ice-cream, sir? Large or small?" It is therefore essential that the identity of substances under trial be not known by anybody until all the tests are completed. As well as a control tablet and the substance being investigated, it is useful to include a substance of established reputation so that we can answer two questions: (1) does the substance work? and (2) does it work any better than what we are using at present?

In the present trial three kinds of tablets were used: saridone, an inert tablet, and tab. codeine co. (N.W.F.), which is perhaps better known as 'Veganin.' Messrs. Roche kindly made up these three substances in tablets of identical appearance, except that they were coloured red, white, and blue (not necessarily respectively). For the second half of the experiment they supplied another set of tablets in which these colours were changed round. There was no possible way of knowing which colour corresponded to which tablets. The key to the identity of the tablets was provided in a sealed envelope which was kept locked in a drawer until after the whole trial was completed, when it was publicly opened by the chairman (Dr. Avery Jones) at a meeting of the clinical society of the Central Middlesex County Hospital. Messrs. Roche also printed for me a corresponding number of cards bearing on one side instructions to the nurse and on the other side instructions to the patient. The instructions to the nurse were as follows:

These tablets are to be given for the relief of pain, not for sleeplessness without pain. Two tablets of the same colour are to be given. Only one pair of tablets may be tried by each patient. Please hand this form to any patient who is given these tablets.

Please complete this side of the form first and see that the patient fills in the other side properly.

Name of Patient .....

Ward .....

Description of Pain and/or Diagnosis .....

Colour of Tablets Supplied .....
(Different coloured tablets may not be given together.)

The instructions to the patient were as follows:

You are asked to try these tablets which are for easing pain. Please help us to judge them by filling in this form. Do not fill it up for at least two hours after taking the tablets.

1. Was the pain (*a*) Slightly eased? .....
(*b*) Completely relieved? .....
(*c*) Not changed at all? .....

Put a cross against one of these answers.

2. How soon after taking the tablets did you get any benefit? .....

3. Did you notice any other effects from the tablet? If so write them here. .....

EXPERIMENT I

Two hundred pairs of tablets from the first set were distributed to the wards with the same number of cards, and an explanation of the experiment was given to the nurses. They were asked to give the tablets to patients to whom they would normally have given aspirin or codeine tablets, but not to patients with severe pain needing morphine. They were not told that any of the tablets were inert, but most of them guessed that at least one colour of the three kinds would be inactive. They were only told one deliberate lie—that different wards were being given different sets of tablets. I did not want rumours, such as "blue are the duds," to spread from ward to ward; so I left them believing that what was blue in one ward might be white in another. Further I feared that tablets might be lent by one ward to another, which would muddle results if different sets were used (and this actually happened). It was interesting to hear the different reputations of the various colours. In one ward the sister told me "I am sure the white have nothing in them; so I only give them to patients I don't think have really got a pain." In an adjacent ward the sister swore by the blue and restricted their use to the

* Saridone, according to the makers, is an effective and balanced combination of analgesics, rapid in action and free from disagreeable effects. It is recommended for headache, toothache, rheumatism, &c. The formula is:

Isopropyl antipyrine ..	150 mg.
Phenacetin	250 mg.
'Persedon'	50 mg.
Caffeine	50 mg.
Weight of tablet	600 mg.

patients with the worst pain. It became more and more obvious what a good thing it was that nobody really knew which tablet was which, and that the different wards thought they had different tablets. Until both lots of tablets were all used I did not add up the results from the cards, and so I had no idea which were the inactive tablets.

Of the 200 cards issued 141 were suitable for analysis. The others had been lost or were inadequately or ambiguously complete. The results of these tablets are shown in table I. The column marked "strict" gives a strict criterion of relief, and the column marked "wide" gives a wide one—i.e., in the "strict" column relief means that "completely relieved" was recorded, and no relief that "not changed at all" or "slightly eased" were recorded; in the "wide" column relief includes both "completely relieved" and "slightly eased," and no relief means "not changed at all."

From the total results at the bottom of the table it is easy to see, without statistics, that the pink tablets are far less effective than the other two—i.e., over half the patients got no relief from them, whereas from the other tablets more than nine-tenths got relief (in its widest sense). Taking relief in the strict sense the conclusion is the same though not quite so obvious (the pink tablets gave 31% complete relief compared with 55% and 65% for the other two). I was thus almost certain, after adding up these results, that the pink were the neutral tablets. The other deduction is that the blue and the white tablets do not significantly differ in power, for they give 92% and 94% relief (wide criterion) and 55% and 65% relief (strict criterion) respectively. Statistical analysis of the figures confirms these self-evident results.

TABLE I—RESULTS OF TRIALS OF ANALGESIC TABLETS (EXPERIMENT I)

Ward	Effect	White tablet		Pink tablet		Blue tablet	
		Criterion of relief		Criterion of relief		Criterion of relief	
		Strict	Wide	Strict	Wide	Strict	Wide
Annexe	Relief ..	..	..	1	1	1	2
	No relief..	..	..	0	0	1	0
C3	Relief ..	5	6	0	3	4	4
	No relief..	1	0	5	2	1	1
D2	Relief ..	1	2	0	1	1	2
	No relief..	1	0	1	0	1	0
C4	Relief ..	3	5	2	2	4	5
	No relief..	2	0	0	0	1	0
D3	Relief ..	3	3	0	0	1	3
	No relief..	0	0	5	5	4	2
B4	Relief ..	4	5	2	2	0	4
	No relief..	2	1	2	2	4	0
A2	Relief ..	2	2	0	0	1	3
	No relief..	1	1	3	3	2	0
A1	Relief ..	4	5	3	3	3	4
	No relief..	1	0	1	1	2	1
O2	Relief ..	2	5	0	1	3	5
	No relief..	3	0	4	3	2	0
O1	Relief ..	2	4	4	4	3	5
	No relief..	2	0	1	1	2	0
D1	Relief ..	1	4	0	1	2	4
	No relief..	4	1	4	3	2	0
C1	Relief ..	5	5	1	3	4	4
	No relief..	0	0	4	2	0	0
Total	Relief ..	32 (65%)	46 (94%)	13 (31%)	21 (49%)	27 (55%)	45 (91·8%)
	No relief..	17 (35%)	3 (6%)	30 (69%)	22 (51%)	22 (45%)	4 (8·2%)
	Total ..	49		43		49	

TABLE II—RESULTS OF TRIALS OF ANALGESIC TABLETS (EXPERIMENT II)

Effect	Pink tablet		White tablet		Blue tablet	
	Criterion of relief		Criterion of relief		Criterion of relief	
	Strict	Wide	Strict	Wide	Strict	Wide
Relief	22 (42%)	43 (83%)	11 (28%)	28 (70%)	20 (40%)	40 (80%)
No relief ..	30 (58%)	9 (17%)	29 (72%)	12 (30%)	30 (60%)	10 (20%)
Total ..	52		40		50	

When the key to the identity of the tablets was opened it revealed that the pink tablets were inert, the white tablets were codeine co., and the blue tablets saridone. This experiment therefore suggests the following:

(1) Tab. codeine co. and saridone are very effective in relieving various kinds of moderate pain.

(2) There is no significant difference in their effectiveness, but tab. codeine co. was slightly more successful in this experiment (and it is also about a quarter the price of saridone).

(3) An inert tablet can give some relief in 50% of cases.

(4) Small experiments are useless in judging analgesic effects—note the widely differing results in different wards.

It cannot be assumed that the 50% effectiveness of a dummy tablet is due to suggestion; a proportion is doubtless due to spontaneous remissions of pain. It would be impossible to measure this proportion without a further series of patients who were given nothing for their pain—not even a dummy—and such people might be too disgruntled to complete their cards properly.

EXPERIMENT II

When the first experiment had been completed (but not computed), the second lot of tablets were used to confirm the previous findings. In this second experiment, because it was troublesome dealing with many different wards, only the two maternity wards were used. Consequently this series contained a high proportion of "after pains" and "headaches" and is not strictly comparable with the assortment of pains tested in the first experiment. Nevertheless the conclusions were much the same—see table II, which records another 142 trials.

The white tablets were obviously less effective than the pink and blue tablets, giving only 28% complete relief compared with 42% and 40% with the others. White was correctly deduced as being the dummy. The pink tablets were saridone, and the blue tablets codeine co. Therefore, as before, saridone and veganin were about equal in effect, giving complete relief in 42% and 40%, and some relief (wide criterion) in 82·8% and 80% of cases, respectively. All these figures are lower than those of the first experiment and suggest that after pains do not respond so well to analgesics as do other varieties of pain. Nevertheless, these women got much more relief from inert tablets than did the patients in the other series—70% compared with 49%. This may mean that women are gullible and more easily duped, but I think more probably it shows that after pains and headaches very often clear spontaneously.

OTHER FINDINGS

No significant effect from colour was noted—i.e., the relative efficacy of the tablets was the same in both experiments—but there is possible evidence that a dud white tablet is better than a dud pink one (some patent-medicine merchants may be interested to know this).

No significant side-effects were noted with any of the tablets, and no information was obtained about the speed of action of the different tablets, partly because so few patients filled in the sections asking about these matters.

COMMENT

This investigation was fairly easy to carry out, and I suggest that the tricolour method or a modification of it should be used as a standard method of testing various drugs. Uncontrolled tests give results so variable as to be valueless. Such controversies as that about the effect of vitamin E in angina or in the myopathies might well be settled in this way. Any substance deserving to be used by clinicians ought to be discernible from a dummy without its identity being known, and to show some advantage over other active substances serving the same purpose.

My thanks are due to Messrs. Roche, who supplied the tablets and cards; the medical staff who allowed me to try these tablets on their patients; and Dr. George Discombe and Dr. Richard Doll for help in the presentation of the results.

Medical Societies

NORTH OF ENGLAND OBSTETRICAL AND GYNÆCOLOGICAL SOCIETY

Early Stages of Cervical Cancer

AT a meeting of this society in Manchester on Oct. 8, with Mr. J. E. STACEY, the president, in the chair, an address on Early and Precursory Stages of Cervical Cancer was given by Prof. EMIL NOVAK (U.S.A.).

Last year, said Professor Novak, 18,000 women in the U.S.A. died from cancer of the uterus. It would appear that as regards the development of malignant disease there are three classes of people: (1) those whose inherent predisposition is so strong that they are predestined to suffer cancer irrespective of any other circumstances; (2) those in whom the predisposition is less prominent and in whom an exciting factor is required for development of the growth (the factors possibly exciting the uterus being injury, infection, and œstrogenic hormones); and (3) those who have no predisposition and who will never develop cancer even when exposed to those activating factors which determine the onset of the disease in class 2.

The relationship of œstrogens and carcinoma is difficult to define. Judging by the well-known effects of these hormones, they might reasonably be supposed to cause cancer in susceptible women; but this action could operate only in respect of the breast, uterus, vagina, and vulva. Experimentally cancer of the breast has been produced with œstrogens only in mice. Cervical changes in animals after the administration of œstrogens can be prevented by giving progesterone, which seems to have some protective effect against the carcinogenic action of œstrogen. Though agreeing that there might be hesitation in employing œstrogen therapy in the presence of a precancerous lesion, or in a woman with a strong family taint of malignant disease, Professor Novak said that he did not know of a single case in which œstrogens had been shown to have caused cancer in women.

Turning to pathological features, he observed that leucoplakia of the cervix is now generally held not to predispose to malignant change. The most important lesion is intra-epidermal carcinoma, alternatively known as Bowen's disease or carcinoma in situ. In this the cells of the epidermis take on malignant features, but the disorder may remain localised for many years, ultimately breaking through the basement membrane to assume typical malignant characters. When this condition is found in one part of the cervix, fully established carcinoma is commonly found in another part when a thorough search is made. Nevertheless, with routine and careful examination of cervices it should be possible to find and treat this lesion while it is localised. Amputation of the cervix is probably sufficient, though in Professor Novak's clinic total hysterectomy is usually carried out—partly for the purpose of having all the material for study and research. Another change in the cervix which may be significant is unusual activity of the basal cells of the epidermis. This may be a reaction to a hormonal stimulus. Such a change, and even pseudomalignant features, are to be seen in the cervix sometimes during pregnancy; they are reversible and may well be associated with the profound hormonal changes of pregnancy.

In the early diagnosis of malignant and premalignant states the Schiller test with iodine has little application, since it indicates merely the site of pathological change and not its nature. Vaginal-smear studies are in vogue but are extremely difficult to interpret; even the few experts with adequate experience admit a comparatively high percentage of errors in diagnosis. Cervical biopsy still remains one of the most reliable methods, particularly when the modification known as "surface biopsy" is adopted. By this method large areas of the superficial layers of the epithelium are removed by scraping with a curette or sharp spoon. This is a most satisfactory way of revealing intra-epidermal carcinoma.

New Inventions

A MONOCHROMATIC HALOMETER

THE halometric determination of red-cell diameters is capable of considerable precision provided the diffraction halo is reduced to its simplest form and a sound method of measurement is adopted. The halo appears as a central bright disc surrounded by a bright ring—the fainter outlying rings can be ignored. The problem is to measure the angular diameter of the bright ring. The ring fades off indefinitely inwards and outwards, and when, as is usual, an ordinary lamp is used, it ranges through the spectrum from blue on its inner side to red on its outer side. It is impossible to define at all simply what one means by the diameter of such a ring. If, however, a monochromatic light is used the ring will appear of a uniform colour fading off inwards and outwards from a brightest central zone. One is thereby provided with a perfectly definite diameter—that of the brightest zone.

The most popular method of measurement is to use two lights and thus produce two halos. By adjusting the distance between the lights one attempts to bring the two rings into contact, when the angular distance between the lights will equal the angular diameter of either ring. If the rings were thin circles of light this method would be ideal, but that is not so with diffuse rings. Even with monochromatic halos it is extremely difficult to estimate when the brightest zones coincide, owing to overlapping of the edges; but with coloured halos the overlapping colours reduce the procedure to mere guesswork.

Early last century Thomas Young measured halos by a most effective method which seems to have been forgotten. He introduced between the blood film and the light a screen containing a central aperture surrounded by a ring of pinholes, so that the pinholes appeared superimposed upon the halo. By adjusting the distance of the screen, he placed the pinholes on the brightest part of the coloured ring. The distance between the eye and the screen was then proportional to the diameter of the red cells. If a monochromatic light is substituted for the white light, one can place the pinholes on the brightest zone of the monochromatic ring with much greater precision.

An instrument incorporating a monochromatic light and Young's perforated screen has been in use in my laboratory for twelve years, and its theoretical advantages have been fully borne out in practice. The design has recently been modified and the completed instrument has been built for me by Kaylene Ltd., of Cricklewood. A mercury lamp with choke is enclosed in the apparatus and can be plugged direct into the alternating-current mains. Part of the beam passes through a filter to produce a green or yellow monochromatic halo; another part remains unfiltered and illuminates the pinholes which thus appear as whitish points standing out sharply against the green or yellow halo. To obtain the highest accuracy the brightness of the halo is con-