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The analgesic effects of anti-inflammatory drugs from the point of view of different pharmacological test methods*

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Abstract

1. The forms of irritation causing inflammation and pain are reviewed, with reference to the significance of histamine, serotonin and bradykinin and in particular to the interrelationship between inflammation and pain. 2. The various types of experimental pain are reviewed and mention is made of the human and animal analgesia test methods derived from them. 3. More detailed descriptions are given of the analgesia test methods used by us, namely: a) Silver nitrate gonarthritis-pain, rat, in which both strong and weak analgesics with an anti-inflammatory action are effective. b) Phenylquinone-induced abdominal pain, mouse, in which all the analgesics and anti inflammatory agents mentioned in this article are effective in a greater or lesser degree. c) Tail-flick and hot-plate tests, mouse, in which the strong analgesics, the weaker analgesics and the anti-inflammatory agents, with the exception of the salicylates, are effective. d) Dental-pain test, guinea pig, which can be used to demonstrate the activity of the various analgesics, including the salicylates and also colchicine, which is not active in any other test. e) Pressure-pain, mouse, in which only the strong analgesics (narcotics) are effective. 4. The action of a large number of analgesics, anti-inflammatory agents and related drugs in the various analgesia-tests and in acute experimental inflammation is presented in tabular form. 5. It is concluded that the use of several pain and inflammation tests is essential for screening both analgesics for special indications (severe, mild pain, pain due to inflammation, etc.) and universal pain-killing drugs.

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THE ANALGESIC EFFECTS OFANTI-INFLAMMATORY DRUGS FROM THE POINT OF VIEW OF DIFFERENT PHARMACOLOGICAL TEST METHODS*

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The connexions between inflammation and pain are manifold. They concern factors inducing both pain and inflammation and in addition both analgesic and anti-inflammatory drugs. These connexions can already be seen from the classical definition of inflammation: *'rubor, calor, tumor, dolor'*, to which is sometimes added *'functio laesa'* of the affected tissue. Here, then pain is mentioned as a symptom of inflammation.

Accordingly it is understandable that suitable drugs may not only remove the sensation of pain by acting centrally or suppress the perception or conduction of pain by the peripheral route; rather is it also possible to achieve an analgesic effect through removal or suppression of pain-inducing factors such as spasm of smooth-muscle organs, ischaemia of some tissue or other, by removing local congestion or a tumour giving rise to pressure, etc.

Vice versa, as you know, pain stimuli can also promote inflammation by reflector routes via the vascular system. In fact it is possible not only to ameliorate the pain with anti-inflammatory drugs, in so far as it is due to inflammation, but also conversely to inhibit certain kinds of inflammaion with analgesics or local anaesthetics. In this sense are also to be interpreted the successes of therapeutic anaesthesia first mentioned by SPIESS[1]. However, the theory which he postulated has not remained undisputed, since it has repeatedly been maintained that experimental inflammation in animals could be induced even after interruption at various points of the path of pain. There have also been various reports saying that certain kinds of inflammation cannot be inhibited by morphine. Secondly, it has been possible to diminish experimental inflammation, e. g. oil of mustard chemosis in the rabbit, by administering potent analgesics such as morphine and cetobemidone (GROSS[2]). These findings were confirmed by TANAKA and MISHIMA[3] with respect to the use of morphine. Moreover, these authors found this analgesic effective also in histamine chemosis and in oil of mustard and cantharidin dermatites in the rabbit. Here it is established, after investiga-

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tions in animals in which adrenalectomy and extirpation of the ciliary ganglion had been carried out, that morphine must act via the sympathetic nervous system by way of an adrenal secretion (after the said operative procedures morphine was no longer effective).

Following these general remarks on the problem of pain and inflammation, I will briefly compare the factors promoting inflammation and pain. The most important stimuli which induce inflammation are, as you know, the following:

1. Mechanical (swellings due to trauma such as contusion, cuts, lesions due to puncture or laceration, pressure due to congestion or tumours), 2. Thermal (tissue lesions due to heat or cold such as burns, erythema caloricum, frost-bite, chilblains), 3. Electrical, nearly always manifested in the form of burns, 4. Ultrasonic (side-effects of ultrasonic therapy), 5. Ultraviolet light (erythema, oedema), 6. Ionizing radiation, and last but not least, 7. Chemical.

MEYER[4] classifies inflammation-producing substances as follows:

1. Substances acting directly on the vessels (vascular poisons) including bacterial toxins, bee and snake venoms and primula poisons, 2. Substances which indirectly damage the cell plasma: vesicants and suppurants (cantharidin, Daphne mezereum from mezereon bark, abrin from the seeds of Abrus precatorius, tuberculin, etc.), 3. Irritants acting indirectly by inducing pain (paprika, pepper and ginger), 4. Substances acting indirectly via the heat receptors: oil of mustard, oil of turpentine, chloroform, ammoniac, camphor, iodine.

This classification has subsequently been modified from time to time and HEUBNER[5] in his subdivision of irritant substances into nerve, capillary and cell poisons came to see that no very specific effects can be established here. It appears that the mode of action of these substances depends largely on their mode of administration with respect to concentration, volume, physicochemical nature, site of administration, etc.

HAAS[6,7] connected the intensity and mode of action of the irritants with the quantity of histamine which they liberate in the tissue. After local application of oil of mustard, cantharidin, capsicum, croton oil, oil of turpentine, colchicine, emetine, caffeine, allyl formiate, ammoniac and sublimate and after ultra-violet irradiation he found an increase in the histamine content of the rat skin. After application of lactic acid, trichloroacetic acid, formic acid, arsenic and acetone, on the other hand, the histamine content of the skin remained normal.

If we consider these substances in the light of their suitability for inducing inflammatory changes in the tissue, we see that in fact, but not exclusively, the histamine-liberating ones are to be regarded as potent inflammation-produc-

ing agents. In addition, naturally, the mediators of inflammatory processes — such as histamine, serotonin and bradykinin, when applied locally can also induce inflammatory symptoms.

Now as far as stimuli especially suitable for pain-production are concerned, these are on the whole the same as those which induce inflammation:

1. Trauma, 2. Unphysiological temperatures, 3. Electrical stimuli, even when they do not cause burns, 4. Ultrasonic waves (HOLLIDAY and DILLIE[8]), 5. Ultraviolet rays (only after a certain latent period), 6. Ionizing rays (only after a certain delay of time), 7. Chemical substances: endogenous, natural substances, synthetic products.

Abundant use has been made of the possibilities arising from those of producing pain experimentally. For instance, a whole series of methods for testing analgesics has been evolved, of which only the most important will be referred to here.

1. Tenderness: in the tail and paw of mice, rats and other animals, in the arm of man, 2. Puncture in the forearm of man, 3. Skin stimulation by means of conducting heat (immersion of rat tail in hot water, hot-plate test in the mouse and rat), 4. Skin-stimulation by means of radiating heat (tail-flick test in mouse and rat), skin-stimulation in man (after HARDY *et al.*[9]), 5. Electrical irritation: in the teeth and skin of man and animal, 6. Ultrasonic stimulation (in the forearm of man), 7. Irritation with chemicals and biological agents. Of these the most important are the following:

Silver nitrate (rat, intra-articularly) Croton oil (guinea pig, subcutaneously) Yeast suspension (injection into the rat paw)	Pain due to inflammation.
Phenylquinone Hydrogen chloride Acetic acid Histamine Serotonin Bradykinin Organic iodine preparations (especially sodium iodomethamate)	Abdominal pain: writhing or stretch test in mice or rats. Inflammatory origin of the pain not explained.

Of particular interest for our investigation are the tests with pain of inflammatory origin. In the case of the writhing test inflammation-producing agents are used, yet one gains the impression that the pain-reaction occurs so rapidly that at this point no inflammatory change in the tissue can have yet set in. With bradykinin, for example, it could be demonstrated that when injected subcutaneously after LISIN and LECLERCQ[10] it leads to the formation of oedema,

while in the writhing test after COLLIER[11] the well-known reaction sets in after only a few seconds. Individually the connexions between the pain-producing and inflammation-producing effects in the preparations inducing writhing or stretch phenomena have not yet been fully explained.

In the test carried out by HESSE *et al.*[12] with the subcutaneous injection of croton oil in the guinea pig, inflammation is undoubtedly provoked. The pain-stimulus being mechanically introduced into the inflamed tissue. Under these conditions pyrazolone, phenylquinoline carboxylic acid and salicylates proved effective in the suppression of the pain-reaction.

Of interest here is the method cited by RANDALL and SELITTO[13] where in the normal rat paw and in the rat paw inflamed by the injection of yeast, a pain threshold is determined by means of a measureable pressure stimulus. In this way it is possible to ascertain in the same animal whether a substance has an anti-inflammatory and/or an analgesic effect.

The procedure is similar in the method after LA BELLE and TISLOW[14] where a pain stimulus is introduced by injection of silver nitrate into the knuckle joint of the rat, while LA BELLE and TORNABEN[15] and others used the same kind of test for investigating the anti-inflammatory effect of drugs. A few weeks ago MARGOLIN[16] reported on the possibility of combining these two tests in one study.

A report is now to be made of our own tests which help to clear up the problem as to which products are primarily analgesic and which produce analgesia by way of an anti-inflammatory effect. Here we have used a method similar to that of LA BELLE and TISLOW[14], on which a brief report has been made (WILHELMI[17]). We injected the irritant, silver nitrate, into one of the knee-joints of the rat, the thickness of the joint in a frontal direction being determined in control animals and in the treated rats, and at the same time a pain-stimulus being introduced by means of passive movements. In order not to have to handle the same animal too much, and in order to be able to select the most favourable times of observation for both parts of the test, however, we went over to a procedure whereby tests were no longer carried out on the same animal. In this case there is no doubt that the pain is caused by inflammation. For instance, the histological examination* of the knee-joint into which silver nitrate has been injected shows the following picture in the acute stage: signs of extremely severe, acute inflammation in the peri-articular tissue with muscle necrosis and inflammatory infiltration. The synovial membrane is likewise partially destroyed by leucocytic infiltrations and necrosis. On the surface is found a film with very fine silver granules, as also on the cartilage of the femur. The cartilage itself is

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intact. In the articular cavity, especially in the recesses, are seen fibrinous flocculi and leucocytes.

Moreover, we used the writhing test in which abdominal irritation after SIEGMUND *et al.*[18] is induced by a phenylquinone solution in the mouse. We modified the method only in so far as we used the irritant substance not as a solution in alcohol but as a 0.02% suspension in gum arabic in quantities of 0.25 ml per animal. This has the advantage that the pain-stimulus lasts somewhat longer. Definite inflammatory symptoms are not induced in the peritoneum by the phenylquinone suspension. At all events we were unable to register any formation of exudate or other macroscopically visible changes. On the other hand, the subcutaneous injection of 0.1 ml of the above-mentioned suspension into the rat paw led to a pronounced formation of oedema. No definite vascular permeability could be established at the points of contact between the peritoneum and the irritant. Histological investigation of the peritoneum was not carried out. The answer to the question of whether inflammation plays any part in producing pain in this method is best sought by trying it out. However, according to BRITTAIN *et al.*[19] phenylquinone liberates serotonin.

Now in order to learn which of the drugs being investigated have a definite anti-inflammatory effect, we have used two models of acute inflammation in the rat.

In *formalin oedema* in the rat paw we injected 0.1 ml of a 0.75% formaldehyde solution subcutaneously into one of the hind paws and determined the degree of oedema by comparing the weight of the hind paw amputated after 2 hours (WILHELMI[20]).

In *formalin peritonitis* in the rat, by intraperitoneal injection of 1 ml of a 1% formaldehyde solution we induced an inflammatory exudate the quantity of which was measured 9 hours after the animals were killed (WILHELMI[20]).

Conversely, to answer the question of whether certain products produce analgesia not only by way of an anti-inflammatory effect but by a central analgesic action, we carried out tests with experimental pain which was definitely not due to inflammation.

1. *Tail-flick test* in the mouse after GROSS[21], in which the root of the tail is subjected to heat rays concentrated by means of a concave mirror, and the time taken for the animal to react is measured.

2. *Hot-plate test* in the mouse after WOOLFE and MCDONALD[22] in which is likewise observed the reaction to a heat stimulus — in this case the animals were placed on a plate kept at a constant temperature of 56 °C.

3. *Tenderness test* in the mouse, modified after HAFFNER[23] in which a pressure of 3 kg is applied to the root of the tail by application of a clamp. All normal mice respond to this stimulus with a characteristic pain-reaction. The

animals which do not react are described as having been 'rendered analgesic', those which give a slight response as 'semi-analgesic'.

4. *Dental pain test*, where an electric current is applied to the pulp of the incisors in the guinea pig. This is a modification of the test used by FROMMEL and FLEURY[21] and RADOUCO-THOMAS *et al.*[24a] in the guinea pig (after the test in the rabbit by GORDONOFF[25]) where a hole is bored into the incisors at either side. After a period of at least 14 hours two nail-shaped electrodes held together by spring-pressure are applied there. Stimulation is produced by a transformed alternating current with oneway rectification. The absolute threshold is determined in volts and its alteration after administration of the product given as a percentage.

The intensity of effect in the heat-stimulation and dental pain tests is expressed by the mean prolongation of reaction-time, or the mean rise in the absolute threshold, of 3—4 determinations made during the first hour after administration of the products. In the writhing or stretch test, and in the silver nitrate arthritis and tenderness test the result is given simply as the maximum number of animals without pain-reaction. The results obtained in these tests have now been summarized in several Tables. The products were divided into two groups:

1. Potent analgesic and antipyretic agents or preparations closely related chemically to the antipyretics.

2. Other drugs somehow connected with the problem of inflammation, such as anti-rheumatics, colchicine which is effective in acute gout, uricosurics, anti-histamines and anti-serotonin agents.

DISCUSSION OF THE RESULTS

Table 1 represents the anti-inflammatory effect (i. e counteracting and inhibiting inflammation) of some potent ('narcotic') analgesic and antipyretic agents which were administered in high doses, but not so high as to produce side-effects. Here all the drugs tested, with the exception of phenacetin, showed a more or less pronounced anti-inflammatory effect. This covers also the analgesic effect in pain of the knee-joint which was definitely due to inflammation, and in which phenacetin again is ineffective. Different behaviour is shown by these products in the stretch test, where all the drugs have a distinct — only Tanderil a somewhat weaker — analgesic effect.

Table 2 shows that the tested anti-histamines, the uricosuric agent Anturan, indomethacin and the corticosteroid preparation prednisone all show anti-inflammatory properties — the last-named especially clearly — while the uricosuric agent probenecid, colchicine and the serotonin antagonist methysergide were ineffective.

Table 1 Antiphlogistic and Analgesic Action

Drug	Formalin-edema mg/kg	% decrease	Formalin-peritonitis mg/kg	% decrease	Stretch-test mg/kg	% analg.*	$AgNO_3$-gonarthrit. mg/kg	% analg.*
Morphine	30 i. p.	35	30 s. c.	1.5	2.5 s. c.	100	10 i. p.	92
Meperidine	30 i. p.	37	30 s. c.	16	25 s. c.	100	25 i. p.	90
Aminopyrine	200 i. p.	37	150 s. c.	34	50 p. o.	86	100 p. o.	36
Acetylsalicylic acid	500 p. o.	33	200 p. o.	53	100 p. o.	100	400 p. o.	58
Phenacetin	500 p. o.	23	200 p. o.	15	400 p. o.	90	400 p. o.	12
Cinchophenic acid	500 p. o.	41	200 p. o.	43	400 p. o.	100	400 p. o.	32
Butazolidin®	500 p. o.	34	200 p. o.	64	100 p. o.	80	400 p. o.	53
Tanderil®	250 p. o.	39	200 p. o.	51	200 p. o.	68	200 p. o.	32

* Animals without pain reaction.

Table 2 Antiphlogistic and Analgesic Action

Drug	Formalin-edema mg/kg	% decrease	Formalin-peritonitis mg/kg	% decrease	Stretch-test mg/kg	% analg.*	$AgNO_3$-gonarthrit. mg/kg	% analg.*
Anturan®	250 p. o.	48	200 p. o.	20	200 p. o.	45	200 p. o.	20
Probenecid	500 p. o.	23	500 p. o.	1	500 p. o.	65	400 p. o.	20
Colchicine	2 i. p.	−7	2 s. c.	27	1 s. c.	55	1 i. p.	0
Indomethacin	50 p. o.	−5	20 p. o.	40	50 p. o.	100	10 p. o.	20
Prednisone	2×5 p. o.	48	2×4 p. o.	45	20 p. o.	65	2×10 p. o.	17
Synopen®	30 i. p.	48	25 s. c.	24	30 s. c.	90	30 i. p.	0
Promethazine	30 i. p.	37	25 s. c.	8	30 s. c.	100	30 i. p.	24
Methysergid	1 i. p.	25	1 s. c.	25	1 s. c.	80	1 i. p.	36

* Animals without pain reaction.

This behaviour of the above-mentioned products is in no way connected with the effect in silver nitrate arthritis, where especially the tested serotonin-antagonist and the similarly active antihistamine promethazine proved effective. In the stretch test, on the other hand, all the products named here show a more or less pronounced analgesic effect.

According to Table 3, all analgesics and antipyretic agents tested — the pyrazole preparation Tanderil less so than the others — show an effect in one of the kinds of pain definitely not due to inflammation.

From Table 4 it is seen that a certain analgesic effect is to be found in individual tests with the gout agents tested, with indomethacin and with the phenothiazine preparation promethazine.

On the whole (cf. Table 5) it can be maintained that the selected models of acute formalin-inflammation are most intensively inhibited by the corticosteroid preparation prednisone and by cinchophen, but also by other antipyretic agents

Table 3 Analgesic Action

Drug	Tail-flick mg/kg	% change[1]	Hot-plate mg/kg	% change[1]	Pressure pain mg/kg	% analg.[2]	Tooth pain mg/kg	% change[3]
Morphine	5 i. p.	+124	10 i. p.	+58	10 i. p.	59	15 i. p.	+64
Meperidine	50 i. p.	+ 99	25 i. p.	+57	50 i. p.	62	50 i. p.	+38
Aminopyrine	400 p. o.	+120	400 p. o.	+70	400 p. o.	0	400 p. o.	+42
Acetylsalicylic acid	500 p. o.	+ 17	400 p. o.	+13	400 p. o.	0	400 p. o.	+41
Phenacetin	800 p. o.	+ 10	800 p. o.	+24	800 p. o.	28	600 p. o.	+25
Cinchophenic acid	400 p. o.	+ 10	400 p. o.	+51	400 p. o.	3	400 p. o.	+14
Butazolidin®	150 i. p.	+ 23	150 i. p	+57	150 i. p.	8	100 i. p.	+41
Tanderil®	200 p. o.	+ 33	200 p. o.	+14	400 p. o.	0	200 p. o.	+ 3

1) Change in reaction time, 2) animals without pain reaction, 3) change in threshold.

Table 4 Analgesic Action

Drug	Tail-flick mg/kg	% change[1]	Hot-plate mg/kg	% change[1]	Pressure pain mg/kg	% analg.[2]	Tooth pain mg/kg	% change[3]
Anturan®	200 p. o.	+24	200 p. o.	+ 3	200 p. o.	13	400 p. o.	+ 8
Probenecid	500 p. o.	+23	500 p. o.	+41	400 p. o.	0	400 p. o.	+ 8
Colchicine	1 i. p.	− 2	1 i. p.	−10	1 i. p.	3	0.5 i. p.	+43
Indomethacin	50 p. o.	+16	50 p. o.	+14	50 p. o.	3	50 p. o.	+27
Prednisone	20 p. o.	+ 2	20 p. o.	+12	20 p. o.	0	20 p. o.	+12
Synopen®	30 i. p.	− 6	30 i. p.	− 9	30 i. p.	8	30 i. p.	+ 6
Promethazine	30 i. p.	+27	30 i. p.	+ 6	30 i. p.	23	30 i. p.	+ 9
Methysergid	1 i. p.	+ 8	1 i. p.	+18	1 i. p.	3	1 i. p.	+ 8

1) Change in reaction time, 2) animals without pain reaction, 3) change in threshold.

such as acetylsalicylic acid, the pyrazoles, Butazolidin and Tanderil and somewhat less intensively by aminopyrine. On the other hand, phenacetin, probenecid, colchicine and the serotonin-antagonist methysergide were practically ineffective against these forms of acute inflammation. The remaining products showed an anti-inflammatory effect in only one of the above-mentioned kinds of inflammation. The antipyretic agents mentioned, which inhibit both forms of formalin-inflammation, have an analgesic effect also in both kinds of pain in the genesis of which inflammation plays a part. But this is not the case with prednisone, mentioned in the same connexion, since it inhibits to a slight extent only abdominal pain.

If one considers all the pain tests used, the following products are seen to be fairly universal, i. e. effective in at least 4 pain tests: morphine, meperidine, aminopyrine, phenacetin, Butazolidin and also the phenothiazine derivative promethazine. In all 6 pain tests only morphine and meperidine showed a

Table 5 Antiphlogistic and Analgesic Action (Synopsis)

Test / Drug	Formalin-edema	Formalin-periton.	Stretch	$AgNO_3$-arthrit.	Tail-flick	Hot-plate	Pressure pain	Tooth pain
Morphine	+	0	++	++	++	++	++	++
Meperidine	+	0	++	++	++	++	++	+
Aminopyrine	+	+	++	+	++	++	0	+
Acetylsalicylic acid	+	++	++	++	0	0	0	+
Phenacetin	0	0	++	0	0	+	+	+
Cinchophenic acid	++	++	++	+	0	++	0	0
Butazolidin®	+	++	++	++	+	++	0	++
Tanderil®	+	++	+	+	+	0	0	0
Anturan®	++	0	+	0	+	0	0	0
Probenecid	0	0	+	0	+	+	0	0
Colchicine	0	0	+	0	0	0	0	++
Indomethacin	0	++	++	0	0	0	0	+
Prednisone	++	++	+	0	0	0	0	0
Synopen®	++	0	++	0	0	0	0	0
Promethazine	+	0	++	+	+	0	+	0
Methysergid	0	0	++	+	0	0	0	0

reliable activity. For the rest, the range of action of the individual products, which are all effective in one or other of the pain tests, varies considerably. It is not clear why this is so. Probably it just depends on the varying nature of the species used (mouse, rat, guinea pig), where perhaps the individual products do not undergo the same kind of metabolism. Possibly differences in absorbability, distribution, breakdown or elimination of the various products play a role.

One should also take into consideration how the pain-reaction takes place in the individual kinds of experimental pain. Various parts of the peripheral and central nervous systems may be involved. Higher centres are in any case involved in tests where complicated defence, fright or flight movements are to be observed. This is so especially in the tenderness test and the arthritic pain test, where the cry is the most important criterion for the onset of the reaction. In the tail-flick test and the stretch test one can imagine that the pain reflex occurs only in the lower segments of the spinal cord, while in the hot-plate test and the dental pain test again a somewhat more complicated reaction takes place, in the first case usually only the front-paw being raised, but also a licking movement being made, and in the second case a chewing movement with opisthotonus being induced. Accordingly the point of attack in the nervous system might be different with the individual analgesics, about which meanwhile very little is known.

With respect to the *tenderness test* we may assume that very intense pain, such as that induced in the mouse tail with 3 kg pressure, can be successfully treated only with the above-mentioned ('narcotic') analgesics whose central mode of action is known. Apart from these, only phenacetin in extremely high doses and also promethazine had a certain effect. This test accordingly serves as a criterion for the intensity of analgesic effect of newly investigated products. Here the anti-inflammatory agents are ineffective.

In the *arthritis of the knee test* in the rat the situation is different. Here, as in all the tests described in this paper, the potent analgesics can be effective, while secondly — since the pain concerned is caused by inflammation — an anti-inflammatory component of action can also be of advantage. This seems to be the case especially when acetylsalicylic acid and Butazolidin are used. Drugs which are only anti-inflammatory in effect and whose analgesic properties are negligible, such as prednisone and indomethacin, are also ineffective against pain in the knee joint.

The pain induced by heat (*tail-flick test* and *hot-plate test*) can be favourably influenced chiefly by the potent analgesics but also by the pyrazoles, aminopyrine and Butazolidin. Strangely enough, in this test acetylsalicylic acid and other well-known salicylates, even when used in very high doses, are absolutely ineffective, and phenacetin brings about slight analgesia only in the hot-plate test. The analgesic effect obtained in the two heat tests may be modified to a certain degree by the antipyretic effect of the drugs tested (especially aminopyrine and Butazolidin). Our investigations into the influence of anti-inflammatory and analgesic agents on the normal skin-temperature, however, have not yet been concluded.

In the *dental-pain test* in the guinea pig and also in the stretch test in the mouse, however, the most varied analgesics can have an effect. These tests are of significance because with them can be demonstrated the effect of salicylates and of phenacetin. There is no explanation of why colchicine, which elsewhere is practically without effect, brings about such distinct analgesia just in dental pain.

The least specific seem to us to be the results attainable with the *phenylquinone stretch test*, and this apparently corresponds to the findings with the HCl-writhing-test of WEAVER and ABREU[26], since here, as stated above, all the drugs mentioned in this study prove effective. According to these results we can make no statement as to whether in the writhing symptom, as one might think from the test results of ECKHARDT *et al.*[27] and of BRITTAIN *et al.*[19], decisive significance can be attached to the liberation of serotonin, which is effective in the same sense and which, by the way, can potentiate after SCHAUMANN[28] e. g. the analgesic effect of morphine. The fact is, however, that the two serotonin-

antagonists tested prevent reaction in a high percentage of mice (free from pain). The same applies to the question of a phenylquinone-induced liberation of histamine. Here, too, it is well known that histamine can induce the writhing symptom (ECKHARDT *et al.*[27]), and again the antihistamines tested have an outstandingly potent effect here. However, since in this test far too many different products prove to have an analgesic action, the question of what role serotonin and histamine play in the production of the writhing or stretch phenomenon must remain without any definitive answer.

It is seen clearly from the studies of YAMASAKI *et al.*[29-31] and from the article by SANUKI[32] that with a wide variety of drugs which are capable of bringing about a release of histamine in the tissue an analgesic effect can be achieved, and that the effect of morphine and other analgesics can be potentiated by histamine-liberating measures.

In this connexion I may mention only that some antihistamines can have an analgesic effect, as seen from the findings of HEWER and KEELE[33] with respect to pain induced by ischaemia in man (method described in detail by HEWER *et al.*[34]) and from the animal tests carried out by BURN[35] and by JACOB *et al.*[36] We, too, have found such effects in earlier investigations in the rabbit. However, it should be pointed out that the onset of analgesia could also be due in part to the sedative properties of some of these products (especially promethazine).

From these statements it can be taken that the assessment of an analgesic is scarcely possible after a single test. Rather would it seem appropriate to test in various forms of experimental pain just those products — on which is focussed great interest today — which have both analgesic and anti-inflammatory properties. Corresponding to the varying origin of the pain coming under clinical observation, it is not always possible to use a universally effective analgesic clinically since the well-known side-effects of the "narcotic" pain-killing drugs prohibit the frequent use of morphine, etc.

Nevertheless, the aim must naturally be towards analgesics which are to some extent polyvalent in effect whilst having few side-effects. The way to this goal would seem to be via various test methods in animal experiments. This is why I have given a report here on a number of tests, including those which more or less concern pain of inflammatory origin, in which we have gained personal experience.

SUMMARY

1. The forms of irritation causing inflammation and pain are reviewed, with reference to the significance of histamine, serotonin and bradykinin and in particular to the interrelationship between inflammation and pain.

2. The various types of experimental pain are reviewed and mention is made of the human and animal analgesia test methods derived from them.

3. More detailed descriptions are given of the analgesia test methods used by us, namely:

a) Silver nitrate gonarthritis-pain, rat, in which both strong and weak analgesics with an anti-inflammatory action are effective. b) Phenylquinone-induced abdominal pain, mouse, in which all the analgesics and anti-inflammatory agents mentioned in this article are effective in a greater or lesser degree. c) Tail-flick and hot-plate tests, mouse, in which the strong analgesics, the weaker analgesics and the anti-inflammatory agents, with the exception of the salicylates, are effective. d) Dental-pain test, guinea pig, which can be used to demonstrate the activity of the various analgesics, including the salicylates and also colchicine, which is not active in any other test. e) Pressure-pain, mouse, in which only the strong analgesics (narcotics) are effective.

4. The action of a large number of analgesics, anti-inflammatory agents and related drugs in the various analgesia-tests and in acute experimental inflammation is presented in tabular form.

5. It is concluded that the use of several pain and inflammation tests is essential for screening both analgesics for special indications (severe, mild pain, pain due to inflammation, etc.) and universal pain-killing drugs.

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