6. Anti-inflammatory drug assessment by the thermographic index

by A.J. **COLLINS**

Royal National Hospital for Rheumatic Diseases, Bath (England)

SUMMARY. Quantitative thermography is an ideal method to assess the response to anti-inflammatory or anti-rheumatic drug therapy in short and in long term drug trials. It is safe, reproductable and acceptable to the patient. It is totally objective. There must be rigid control of factors such as ambient temperature of the examination room, and patient cooling time. For large scale serial measurements, the process requires computer analysis of the thermograms.

Key words: thermography, rheumatoid arthritis, anti-inflammatory drugs, thermographic index.

The introduction of a new drug into clinical medicine requires extensive testing of the product, for efficacy of action and toxicity. Almost all countries have bodies like the British Committee for the Safety of Medicines, or the United States of America's Food and Drug Administration, through which such information must pass. It is most unusual for a new drug to be tested for effect or toxicity at the clinical level, without first being assessed in animal screening tests. To test drugs that are active against the chronic inflammatory diseases, and especially rheumatoid arthritis (RA) is difficult, because no satisfactory model of rheumatoid arthritis exists in animals.

Currently, great emphasis is being laid on finding non steroidal anti-inflammatory drugs active against the whole rheumatic phenomenon, rather than drugs with just anti-inflammatory action, and so drugs which are found to be active against even the best animal models of chronic inflammation may be less effective when used against RA. Often tests of drug efficacy are carried out using animals, with tests differing from those used clinically (Table I). For the clinical assessment of an anti-rheumatic drug a battery of tests are used which measure some aspect of the pathology of joint inflammation; size, some form of articular index, morning stiffness, grip strenght, and perhaps a pain score [6]. It is obvious that not all these criteria used clinically are available for measuring drug action in animals. A subjective analysis of a drugs potency by animal is unavailable, while a parameter such as joint size is more accurately measured in an animal than man. Few of the criteria used clinically are specific indicators of anti-inflammatory activity, for instance, measurements such as an increase in grip strength may be interpreted as a measure of

Tab. I. **Comparison of methods of assessment of anti-inflammatory drugs in clinical practise, and in animal models.**

Human	*Animal*
Joint size measure	yes
Articular index	yes
Morning stiffness	no
Subjective pain	no
Grip strength	no
Infra-red (thermography and radiometry)	yes
Often other complicating therapy	no
Various disease stages	no

analgesic action. An additional complication in the clinical assessment of a drug, especially in the rheumatic diseases, is that the subjects present in all stages of the history and activity of the disease. Animal models of inflammation are invariably used at a uniform stage of the lesion.

Two methods of indirectly measuring a fundamental parameter of inflammation have recently been developed. They are ^{133}Xenon (^{133}Xe) clearance from a joint [5], and measurement of the infra-red emission from a joint, by thermography. Both indirectly measure blood flow which is increased in joints affected by an inflammatory lesion, but of the two, thermography is non invasive and thus repeated studies may be carried out. Furthermore, it provides a valid measure in animals as well as man, and is a function which does not measure pain.

Measurement of inflammation by infra-red emission

Previously, E.F. J. Ring and I showed that in both animals and man, joint temperature did reflect other pathological events of inflammation, and that, in rats, the foot pad temperature of an inflamed limb decreased when the animals were given a non steroidal anti-inflammatory drug (N.S.A.I.D.) [3]. A simple experiment such as that shown in Fig. 1 illustrates this point. To measure the small areas of inflammation created in an animal, temperature measurement using a radiometer is adequate. However, when measuring the much larger areas of human joints a radiometer is not sufficient.

Measurement of joint inflammation by thermography

A thermogram of an inflamed joint measures not only the temperatures of the area, but also displays the distribution of the hyperaemic areas. This added information is most important when considering joint inflammation. Work carried out in Bath has shown that the thermogram of a joint affected by RA accurately shows the distribution of the hyperaemic synovial tissue which can be found when the joint is opened at operation (Fig. 2).

The thermographic index of inflammation

Simple qualitative description of joint inflammation is not sufficient for the measurement of anti-inflammatory drug action. A numerical measure is required, free from subjective error, and which responds to the anti-inflammatory action of drugs. Supra patella temperature, taken by radiometry, has been used to measure the effect of intra-articular anti-inflammatory steroid action in RA[2], but such spot temperature readings, unless taken in great number, and with great effort, do not display the complicated synovitis of a large human joint. Much more information about this state can be seen from a single colour thermogram, with isotherm temperature separation. Such a thermogram usually shows anatomical distribution of the synovitis, and includes all the inflamed areas in the thermogram that can be seen from a single aspect.

Quantitation of thermography

When a colour iso-thermogram of a joint is reduced to a single numerical figure, the result is a comprehensive measure of the total inflammation recorded in the whole picture, irrespective of the position of the synovitis.

A method of quantitation of colour isothermograms has been proposed by Collins et al.[4], and the resultant figure is referred to as the << Thermographic Index >> (TI). The TI is calculated from the expression:

$$\frac{\Sigma(\Delta t \times a)}{A}$$

where: At is the difference in °C from a base-line of 26°C, to each isotherm temperature; *a,* is the area occupied by an indi-

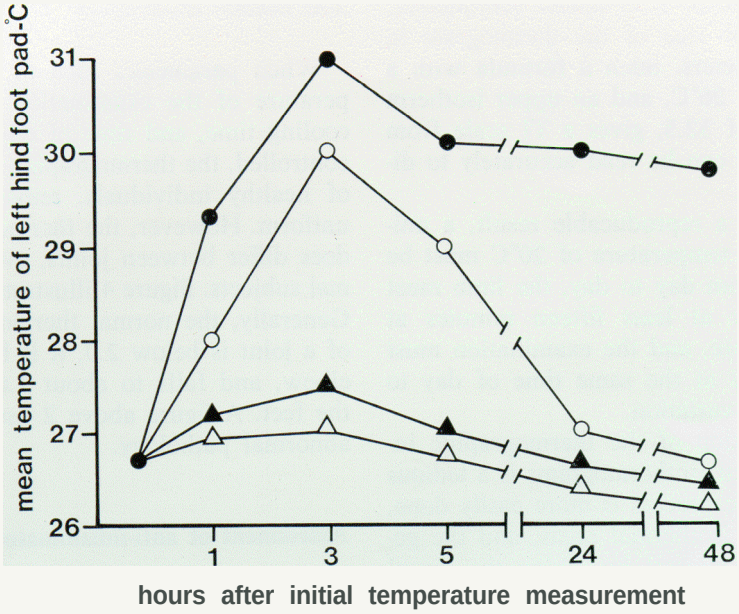

Fig. 1. The dose related anti-inflammatory effect of a non-steroidal anti-inflammatory drug (Azapropazone) measured by radiometry in rats. Inflammation was produced, in the left hind foot pad of Wister rats by the injection of 0.1 ml of a 1% solution of carageenin. The initial temperature of the feet was recorded immediately before the animals were given Azapropazone, orally at 50, O-O, 100, ▲—▲, and 200 mg/kg △—△. ●—● were con t rols

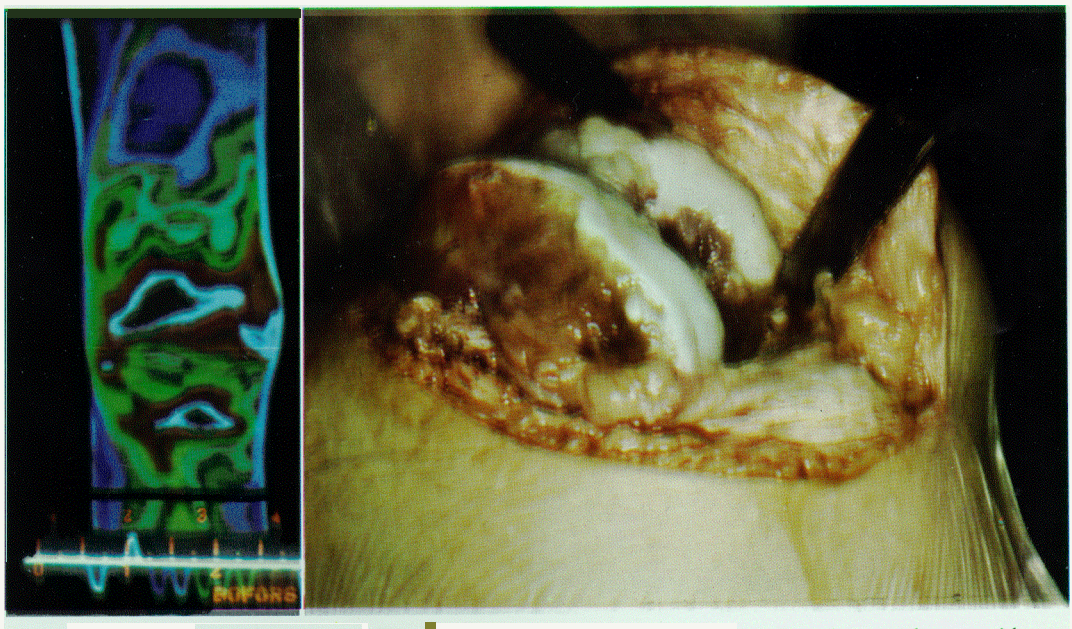

Fig 2. The thermograms of the right knee of a patient with synovitis due to rheumatoid arthritis. The operative findings showed a hyperaemic synovium encroaching into the femoral condyles. The leg is in flexor extension.

vidual isotherm area, in square centimeters; *A*, is the total area of the thermogram in square centimeters. Such a formula with a a base line of 26°C, and an upper isotherm temperature of 32.5, gives a TI scale from 1 to 6, which can be read accurately to divisions of 0.1.

To achieve a reproducable result, a uniform ambient temperature of 20°C must be maintained from day to day, the limb must be cooled for at least fifteen minutes at this temperature, and the examination must be carried out at the same time of day to avoid/ diurnal variation.

The generation of the thermographic index from colour isothermograms is a tedious procedure. The process is more easily done, by computing isothermal areas, and the general area of interest by taking the signal from the infra-red scanner, and processing the signal with a computer which re-synthesizes the picture on a colour television screen. Any region of interest of the thermogram may be chosen, by this method, and the areas of individual isotherms, and the total thermographic index calculated immediately. We use such a system, which utilizes a PDP8e computer, interfaced to the Bofors infra-red scanner (Fig. 3).

The normal thermographic index

When parameters such as, ambient temperature of the examination room, patient cooling time, and time of day are carefully controlled, the thermographic index of joints of healthy individuals, remain remarkably uniform. However, the thermographic index does differ between joints, even in the normal subjects. Figure 4 illustrates this finding. Generally, the normal thermographic index of a joint is below 2.0, it is highest for the elbow, and falls to about 1.0 for areas of the feet. A figure above 2 usually indicates abnormal pathology.

Assessment of anti-inflammatory drugs

1. Non steroidal anti-inflammatory compounds

There are a great many non steroidal ('aspirin-like') anti-infiammatory drugs used in the treatment of the rheumatic diseases. As well as possessing anti-inflammatory activity, these compounds usually have analgesic action, which confuses the results of many clinical tests used to detect their anti-inflammatory activity. A thermographic de-

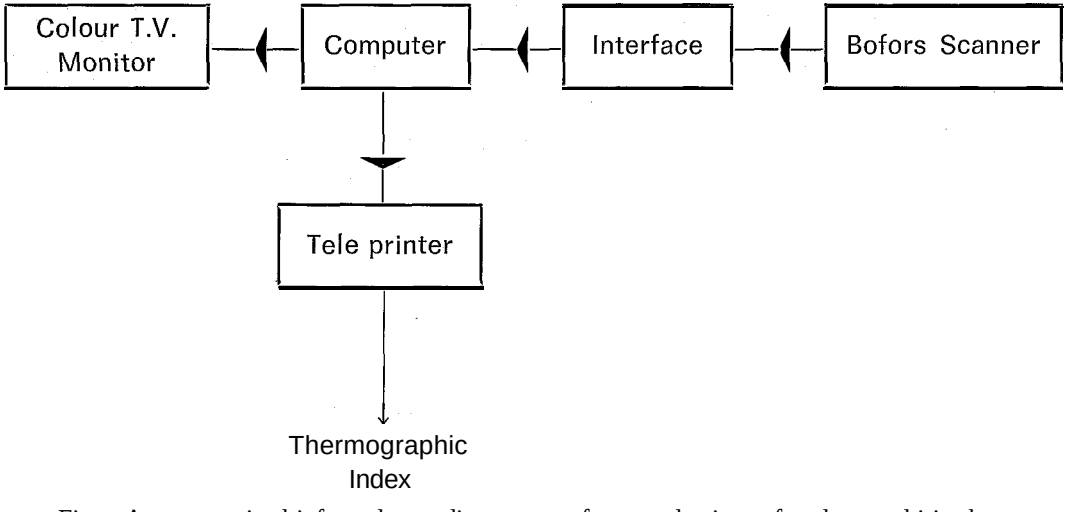

Fig. 3. A computerized infra-red recording system, for production of colour multi-isothermograms and the thermographic index.

termination of anti-inflammatory activity overcomes this problem. Adoption of a standard regime for open-blind study using thermography enables a comparison to be made of similar non-steroidal anti-inflammatory agents over a given time span. Patients with advanced rheumatoid arthritis are almost always taking some form of anti-inflamma-

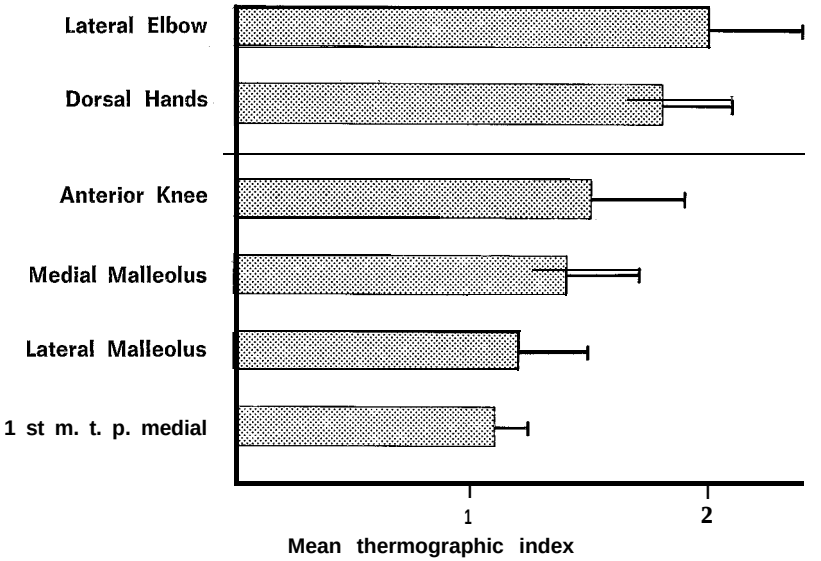

Fig. 4. The mean thermographic index of normal joints. Bars indicate the standard error of the mean:

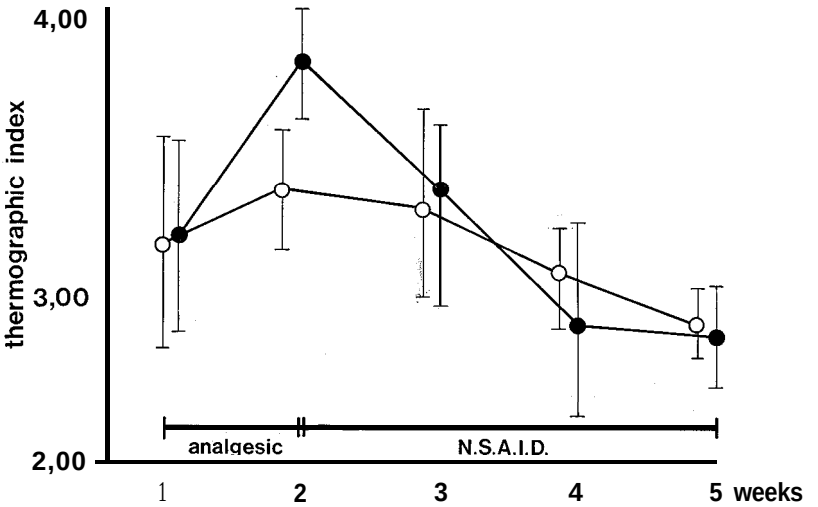

Fig. 5. The thermographic indices of the hands and knees of seven patients, with RA, measured over four weeks. During paracetamol therapy the index increased, the following three weeks of therapy on a non steroidal anti-inflammatory drug produced a fall in the index. The index for hands (•-•) deteriorated faster than the knees (O-O), during paracetamol therapy, and recovered faster during anti-inflammatory therapy. Bars indicate standard deviation.

tory drug. Thus, in this hospital we routinely give a seven days 'wash out' period on a pure analgesic agent, such as paracetamol. We then measure the fall brought about by a N.S.A.I.D. using the compound TI from up to four selected joints. The rate of fall in the TI caused by the test drug, and the extent of improvement of the inflammation can then be measured. The typical deterioration in the inflammatory state after paracetamol and improvement after an aspirin-like drug is shown (Fig. 5).

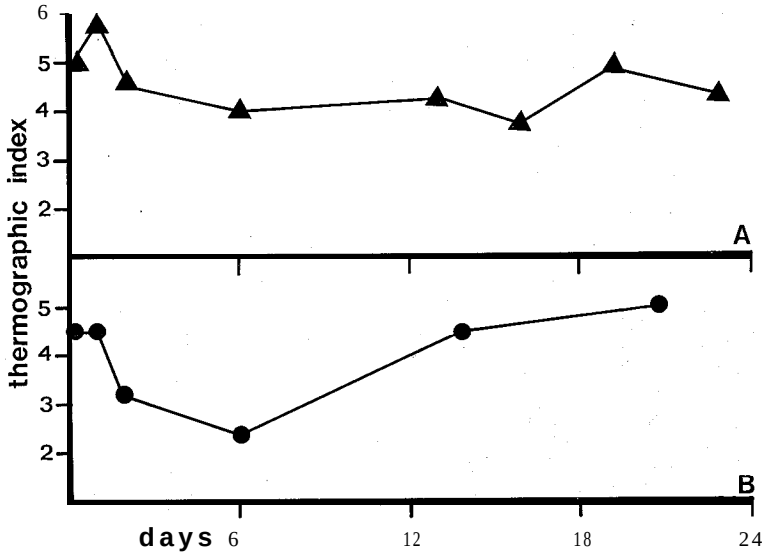

Fig. 6. The fall in the thermographic index, after a single intra-articular injection into two inflamed knees, of prednisolone tributyl acetate (Codelcortone) of 50 mg (A) and 100 mg (B).

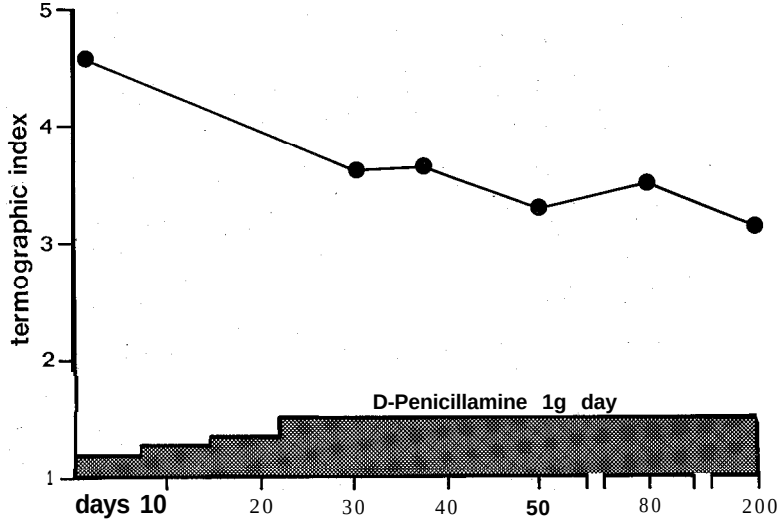

Fig. 7. The mean thermographic index of the hands and knees of a patient with RA, given increasing doses of D-penicillamine followed over 200 days. There was a slow improvement, shown by the steady, but unspectacular fall in the thermographic index, typical of this drug.

2. Intra-articular steroid injection

The anti-inflammatory response to intra-articular steroid injection has been well documented, and is useful as a demonstration of the TI response to this type of therapy [4,7]. Figure 6 shows the fall in the TI achieved by the intra-articular injection of prednisolone into the knee, at two doses.

A single injection of an anti-inflammatory steroid into an inflamed joint produces a fall in the TI, maximal within two to seven days. The duration of the improvement varies between subjects, but the joints usually revert to near the initial state by three weeks. The technique has been used to distinguish between chemical analogues of the same steroid used as an anti-inflammatory therapy for acute synovitis in RA.

3. Assessment of long-term anti rheumatic therapy

When the conditions for thermography are rigidly controlled, change in TI may be used to follow the patients response to long term treatment with drug such as penicillamine or cytotoxic agents. A study which compares two doses of penicillamine has been made in this hospital, covering a time span of up to one and a half years[1]. The relatively rapid response to high dose penicillamine suggests that this drug may have direct anti-inflammatory effect, in some situations (Fig. 7). The long term changes in the TI often occour before other changes in the clinical state of the patient are observed, both when the patient improves and deteriorates.

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