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EXPERIMENTAL HEADACHE WITH ENDOGENEOUS HISTAMINE

*First results obtained by 48/80,
a histamine-liberator drug, in the cephalic and peripheral
circulatory systems of man*

By

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We have already studied experimental headaches induced by histamine, and tried to evaluate the role of vascular changes in the genesis of headache. The use of a peizo-electric sphygmograph (studied and designed by *Bovet & Gatti*), has been a great help to us for its high sensitivity and accuracy. This apparatus allowed us to evaluate the extra-cranial pulse (superficial temporal and occipital arteries), the endo-cranial pulse (ocular pulse, using Sicuteri's technique), and the pulse of cerebrospinal fluid.

Further studies on headache (as considered in its vascular aspects) have been started using the histamine-liberator drugs.

The drug used was 48/80, as prepared by Wellcome¹.

Our present report will be on observations limited to the field of experimental headache induced by 48/80, which, to our knowledge, has not yet been used on men in Italy. Accurate researches using 48/80 have been conducted by *Virno, Gertner & Bovet* on dogs. Lecomte studied the effects on man of another histamine-liberator, 1935 L, similar to 48/80, but less powerful.

¹ We thank prof. Bovet for kindly having offered us the drug.

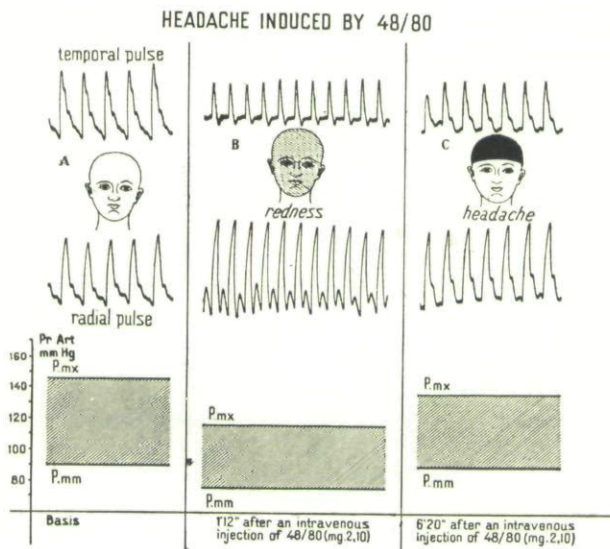


Fig. 1.

A pre-test was made to determine the individual tolerance of the drug. It was observed that the first effects on man are reached with doses of $10 \mu\text{g}$ per kg. Such doses give mainly subjective symptoms of a slight sense of heat, and itch generally localized in the neck and in the upper part of the chest. The doses used in our experiment varied from 20 to 40γ . A micro-dose was first used with each subject, in order to exclude unexpected reactions, since individual responses may vary over a wide range.

With the previously mentioned doses, no striking reaction was observed, except in one subject who showed signs of collapse but who quickly recovered with adrenalin and synthetic anti-histaminics.

In the normal subjects, these doses, 1–3 minutes after intravenous introduction, give a sense of heat in the neck, chest and face, followed by a burning itch; then an intense redness appears in these places, and a few wheals, identical to the wheals of urticaria, appear here and there. After the subjects complain of a sense of tension in the face which corresponds

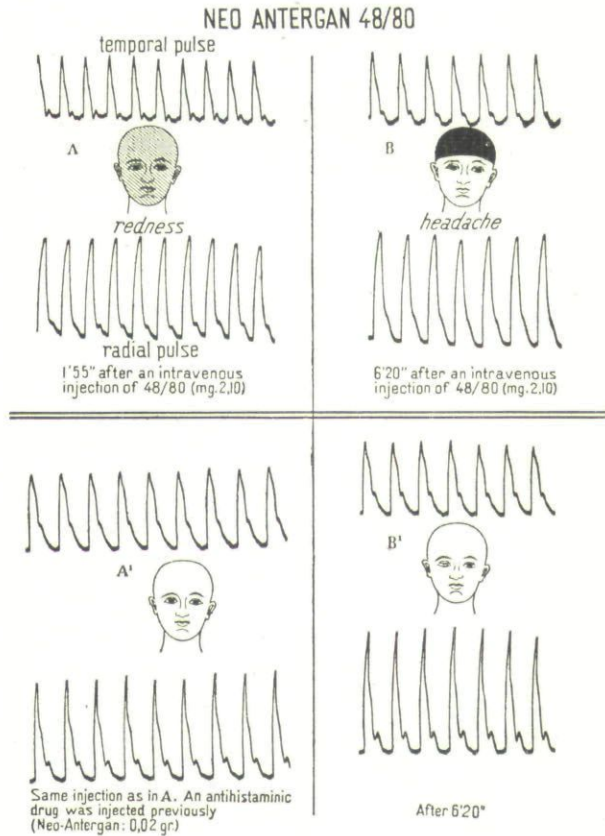


Fig. 2.

to the subcutaneous oedema strikingly similar to Quincke's oedema. At the same time, there is cardiac palpitation, and some pulsation in the neck and temples; the frequency of the pulse and respiration increases, while the systolic and diastolic arterial pressure decrease some 20–50 mm of Hg.

In some subjects, 2–5 minutes after the injection (when the pressure tends to increase) a headache occurs in the frontal and parietal regions, sometimes also in the nuchal area. This headache is at first continuous, then pulsating, and it varies in intensity and duration. The modifications occurring in the temporal and radial arteries after the injection of this drug, are

equal to the modifications that take place after the injection of histamine. Actually, together with the decrease in arterial pressure, a lowering in the incisure may be observed, till the isoelectric line is reached and even further. At times, the incisure rises again with the ascending line of the following wave. The B' wave flattens out, and the systolic wave becomes higher.

Headache may occur when the modifications in arterial pressure get lower, and the curve tends to become normal again (fig. 1). The headaches complained of are quite similar to a histamine headache.

Compression of the temporal arteries does not alter the pain, while this is attenuated by an energetic compression on the carotid at the level of the cricoid.

A group of 5 headache patients, chosen for their sensitivity to histamine (Greppi) were investigated. The threshold of sensitivity was determined using Martinetti's technique. All the subjective and objective modifications previously related were present in the subjects, the only difference between this group and normal subjects was the constancy of headache in the former.

It should be mentioned that it was shown by previous investigations that the vaso-active threshold to histamine, in the radial arteries is more sensitive to histamine than the temporal arteries when both are measured with the peizo-electric sphygmomanometer. On the other hand, in the cases treated with 48/80, no difference between variations in the radial and temporal arteries was found with very small doses. Hypothetically, we believe that 48/80 may liberate other vaso-active substances beside histamine, and the extra-cranial circle may be particularly sensitive to them.

It also has been demonstrated that norepinephrine has no influence on the changes provoked by the histamine-liberator. It is known that norepinephrine causes bradycardia, hypotension, and wheals. When the effect of histamine is over, the norepinephrine effects will appear again.

These observations support other data from the medical

literature of the little or no effect of norepinephrine against histamine and allergic manifestations.

Synthetic anti-histaminics, on the contrary, have an influence on the effects of 84/80. They inhibit or reduce most of the subjective, as well as objective and instrumental variations (fig. 2).

Such data had been observed by others in animals, and our own studies on man (with the aid of a sphygmo-peizograph) are a good support for them also. It is our belief that this antagonism may well be used in therapy. Some cases of headache have been treated with 48/80 under "protection" of a synthetic anti-histaminic with good results. This sort of "protected desensitization" is now under study for other diseases where histamine therapy is required. Great caution is necessary in such experiments, particularly with asthma. We hope to be able to make them known in the near future.

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