

## INDIAN SUMMER, THE AUTUMN CROCUS AND COLCHICINE

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"The great and the small and everything is part of the whole. Men, wanting and valuing only a single thing, rushing into one-sidedness—in order to find satisfaction—make themselves unhappy."—A. STIFTER

### I. THE ALKALOID

During the last ten years a star of the first magnitude has risen in the night-sky of researches into the nature of substance: the alkaloid colchicine. Attempts have been made from various angles to explore the effective mechanism of this substance. Botany, pharmacology, clinical medicine, and cytology have accumulated a considerable amount of material, and yet until now the "living idea" is missing which tries to link all these single observations into a harmonious whole.

Dustin recognized colchicine as a mitotic poison in 1934, and since then his researches have been greatly enlarged and confirmed. LETTRE in particular has published some fundamental facts and has shown, besides other things, that in the course of cell-division it is the spindle in particular which is affected by colchicine. The substance is therefore also described as a spindle-poison, and MARQUARDT (1) gives an exact description of its effects; he says: "The symptoms are:

- (1) Failure to develop a true spindle, so that both the arrangement of the chromosomes in the equatorial plate, and an anaphasic movement with the regular formation of daughter-nuclei are impossible.
- (2) The extreme contraction and thickening of the chromosomes during longitudinal division which proceeds very slowly from the chromosome ends towards the spindle attachment.
- (3) The separation of the daughter chromosomes which finally hang together only at the spindle attachment.

They usually remain lying at little distance from each other.

- (4) The formation of a single resting nucleus instead of two daughter nuclei on conclusion of the disturbed mitosis, which has only a pro-phase, and no clearly defined meta-, ana-, and telo-phases. This 'restitution nucleus' contains twice the number of chromosomes."

LETTRE (2) also believes that it is the spindle-apparatus which is affected by colchicine, and most other investigators agree with this. SCHERER and BERGMANN (3) were able to show that the mitochondria themselves are not affected by colchicine.

In plant-growing experiments very definite and well-defined malformations were produced with colchicine (HERGER and POETHKE (4), BOAS (5), and others).

That such results induced cancer research to take possession of colchicine is very understandable. As early as 1939, BRUCKE and HUEBER (6) reported on the combined colchicine and radiation therapy of skin metastases in a case of cancer of the stomach. Since then a great number of such findings and attempts have been published. So far no final results are available, however, and the problem is as yet open and unsolved.

Important for the effective application of colchicine are the new attempts at a therapy of leukaemia which go back to investigations made as early as 1908 by DIXON and MALDEN (7). They observed that the subcutaneous use of colchicine on rabbits causes at first a leukopenia and about six hours later a strong leukocytosis.

WIDMANN (8) has been able to show that a leukocytosis may arise without there having been a previous leukopenia, and that the latter only occurs if the amount of colchicine given has acute toxic effects. At any rate, the bone marrow is a very sensitive barometer for the effect of colchicine and can react to the alkaloid with a decrease or increase in the production of granulocytes. Further research led WIDMANN (9) to believe that the points of attack for colchicine in the bone marrow are not identical with its effect as a cytostatic substance.

The investigations made by KEIBL and LOTSCH (10) which are based on many earlier observations point in the same direc-

tion. They found that if colchicine is used in cases of myeloid leukemia the number of leukocytes is lowered for a short time. They found aggregates of chromatin in the nuclei of the mature cells and in the nuclei of the myelocytes. The results of their investigations they give in the following sentences: "Although colchicine does not provide a therapeutic agent to influence the white blood picture, it is able by means of a specifically selective action, to make the young cells of leukemia more sensitive to X-rays."

All these researches constantly emphasize that neither the lymphocytes nor the red elements of the blood can be influenced by the administration of colchicine. It is rather the whole system of granulocyte-formation and decomposition in particular which seems to be affected by this substance.

SELYE (11), on the other hand, has shown that colchicine and other mitotic poisons lead to a disintegration of the thymolymphocytes in those cases where the activity of the adrenal cortex is maintained. The hyper-function the adrenal gland has altogether shown itself to be causally connected with lymphopenia (VALENTINE, GRADDOCK and LAWRENCE (12); I mention this here because during recent years the similarity between the effects of colchicine and ACTH has often been pointed out.

HELLMANN (13), for instance, showed that ACTH is capable of inducing as well as stopping the acute attack of gout. ACTH produced a decrease of chloride and sodium and at the same time an increase of uric acid in the urine. MARGOLIS and CAPLAN (14) reported remarkable therapeutic successes in cases of acute gout, with the use of ACTH followed by colchicine.

I do not at this point want to touch the hypotheses connected with these effects, but let the phenomena speak for themselves. SPIES and STONE (15) are convinced that ACTH, in a way similar to that of colchicine, has a specific effect on the acute attack of gout.

MUGLER (16) then tried to describe the parallel modes of action of colchicine and ACTH in more detail, and he comes to the conclusion that both substances are anti-allergic and antiphlogistic. This explains the clinical experience that both

substances show their instantaneous action only in acute attacks of gout, and HARKAVY (17) has recently again been very definite about the allergic component of gout.\*

MUGLER then tries to trace the "biological" efficacy of colchicine and ACTH. Both substances he describes as blood-pressure-raising agents at the same time they effect an involution of the thymus and the other lymphatic organs; they cause a relative leukopenia and a decrease in eosinophils. All these symptoms can be interpreted as originating from the adrenal gland.

This gives a first picture of the three main fields of action of colchicine.

(1) Colchicine is a cytostatic substance (HEILMEYER) and has a particular influence on the spindle formation in mitosis.

In this respect it belongs to one group together with arsenic (cacodylates), urethane and other substances.

(2) Like other cytostatic substances, colchicine has a particularly sensitive relationship to the bone marrow and especially to the granulocyte-system.

(3) In its action colchicine is remarkably similar to ACTH. It is antiallergic and antiphlogistic, and thus shows a close relationship to the whole adaptation-syndrome as described by SELYE.

It is difficult even today to say whether all these effects come from a single source, or whether colchicine has several points of attack in the organism. All the same, an attempt should be made to try and bring these various results together in such a way that a picture arises which takes us closer to an understanding of the whole colchicine problem.

From ancient times, Colchicum and colchicine have been with mankind as a medicament as well as a poison, and only now, during the last few years, are we given a new insight into its action.

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\* F. HOFF (18) also mentions the allergic component of gout and refers to GUDZENT, SCHITTENHELM, HANHART, and others. However that may be, the assumption of an allergic factor does not resolve the great problem of gout itself.

Why does colchicine act the way it does? Why does it interfere with the processes of cell-division as a spindle-poison and act so much like ACTH? A purely quantitative investigation will hardly be able to reach a true image; a qualitative one, however, aiming at the pure phenomenon, might lead a good step further. We shall therefore describe the living medium in which the substance colchicine is constantly created, and start by observing the plant *Colchicum Autumnale* itself.

## 2. THE PLANT

This flower which is usually called the autumn crocus is common and well known in the central parts of Europe. It grows all over Germany and France, spreads down to Spain and Italy, follows the Danube into Hungary and also into the Balkans, and surrounds the western and northern shores of the Black Sea. The latter seems to be its native place, and its name comes from Colchis. "Botanists today know that in those and neighbouring regions of the Caucasus, and altogether on the shores of the Pontus, the autumn crocus appears in several large-flowered varieties" (USTERI (19)). It is believed that *Colchicum* has gradually spread across the remaining parts of Europe from those regions.

There is a legend that Medea the Colchican sorceress knew how to prepare the poison of this plant. In Rome and Athens the plant was called *Hermodactylos*; this did not refer to the fingers of the messenger of the gods, but to those of the great magician and initiate Hermes Trismegistos, the legendary founder of Egyptian culture. He knew how to prepare the poison and taught his pupils how to use it as a love or death potion. The ancients took it as an aphrodisiac, but they could also use it for public or secret death-sentences. Procreation and death, whose common origin is so often hidden from the outer eye of man, are both rooted in this plant.

In Germany the plant is called "Herbstzeitlose" which is the Germanized version of the Italian words *cittola* (maid) and *osa* (naked). Its original name therefore was "naked maiden", and in some rural districts the peasants use the even more can-

did term "naked whore". More religious souls call it the Michaelmas flower, and here indeed nomen is omen. For it blooms in the autumn when the meadows have been mown and the brown earth begins to shine through. Then the pale lilac flowers come up from the soil in hundreds, similar to the spring crocus; they really do look naked for there is no leaf around them, and the whitish neck of the flower arises unprotected from earth. After a few days it has ceased flowering and looks miserably pale and ragged.

Underneath the earth, the neck leads to a brown corm from which it arises on a short stem. The corm is not, as commonly believed, a bulb, but a stem node, so that *Colchicum* in fact is a plant which grows and flowers underground. The corm is an internode from which the flower arises first of all, in the autumn. Self- or cross-pollination occurs above ground, and the pollen tubes grow down through the extraordinarily long style, which often reaches a length of 15-20 cm., until they meet the ovary below ground. This takes many months, through the whole of autumn and winter. For only in May do the pollen-tubes combine with the ovules for fertilization.

In the meantime, three leaves have developed on the corm below ground, which come up from the earth in March or April, together with the syncarpy. The fruits need until July to develop; then they are ripe, fall from the seed-capsule and are distributed by grazing cattle, adhering to their hooves.

That is more or less the life-history of a *Colchicum* corm. The plant itself has a subterranean rhizome which forms new internodes every year. Two things are significant and remarkable in this: the plant, flowering and sprouting below ground, has, like Demeter's unhappy child Persephone, taken refuge in the darkness of the earth. But *Colchicum* does not, like Persephone, rise up in the spring, but in the autumn. It begins to flower at a time when other plants are dying. Its flowers are bereft of leaves for those only appear during the next period of vegetation, in the following spring. The fruit ripens slowly during the summer. It takes almost nine months from fertilization to ripeness, for a plant a disproportionately long time.

Everything here is, as it were, out of place; the flower rushes ahead before the leaves can unfold and, instead of in the spring, breaks through in the preceding autumn. The leaves follow at their convenience and at the right time. The fruit, however, is particularly late and out of time. This distortion of the periodicity becomes even more obvious when the plant is seen against the back-ground of its family the *Liliaceae*; these belong to the very earliest plants to flower in the course of the year; they appear in March and April, and are not naked, like their strange sister, but clothed in leaves, joyful, and gay.

The autumn crocus does not only grow underground, it also develops against the periodicity common to its family. In my opinion such behaviour should not be disregarded; for this is the language in which *Colchicum* tries to express itself. Within the sphere of this distorted rhythm colchicine is constantly being formed, and to want to see the one without the other would mean an arbitrary separation within a biological whole. *Colchicum* and colchicine are a unity and should only be regarded as such.

If *Colchicum* belonged to the late flowering plants, like asters and chrysanthemums, its behaviour would not be so obvious; for in that case it would be part of an annual environment which is always there at the same time: the early autumn, or Indian summer. That is a period when for a very short time a kind of second blossoming occurs in temperate regions. If it is especially warm even the lilac and chestnut flower again, and a kind of second spring wafts over the land.

The great Austrian poet Adalbert Stifter says in one of his novels about this time of the year: "In the spring, the most frivolous birds become serious, they are busy without pause in feeding their offspring, educating and teaching them, so that they will be capable of the great task of the big journey before them. Towards autumn, again a time comes when they are more free. Then they have so to speak, an Indian summer and play for a while before they go away."

Not only the birds but also the insects and many plants have this Indian summer period when they can still "play for

a while". And although it has not yet been described in detail, this time does exist, and many poets have spoken and sung of it most beautifully. Into this time of Indian summer the Colchicum has sneaked. It takes part in it and uses it for pollination and thus for its perpetuation. But because it misuses an environment which does not belong to it, it turns into a plant which produces poison. For poison arises only where otherwise disease would develop.

A natural process arising at the wrong site and at the wrong time is poison in the plant; in the animal and in man, however, it can be poison as well as disease. Both are synonyms of the created world. Only for this reason can a poison cure a disease as well as cause it. This becomes truly manifest in the autumn crocus. It lives unnaturally in the cycle of the seasons, and therefore produces the alkaloid which acts as a poison. Pollinated during a period when otherwise nature is dying, it bears within itself death as well as procreation; the ancients knew of this.

But we have gone one step further and come to know the exact spot where these forces act; there where growth originates and creates anew, in the formation of new cells, this poison strikes. It takes its revenge at the very place where it is not allowed to appear. The spring forces of sprouting cell-growth are struck by the deadly breath of the plant which flowers in the autumn. The spindle formation comes to a standstill and instead of forming daughter cells the mother cells remain distorted.

This same deathly autumnal breath appears in Colchicum where it acts as an anti-allergic and antiphlogistic agent. For inflammation is a heightened defensive force of the organism; it is an enhanced life force, either concentrated on a certain region of the body, or displayed over the whole of the organism. This defensive power is dampened by colchicine and often extinguished altogether.

Thus a first understanding can arise of these effects. But colchicine has not only been investigated experimentally, it has also been tried in its clinical effects, and the symptoms appearing in the patient and in drug provings will now be taken into consideration.

(To be Continued)

—The British Homœo. Journal, April '58