

## Enzymes in Relation to Cancer.

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WARBURG'S researches<sup>1</sup> have shown that the question of the character of malignant growths is primarily a metabolic problem. A consideration of the established facts lead to the conclusion that metabolic processes of the cancer cells bear a significant relationship to the total metabolism of the healthy organs closely. Future research should consequently be directed to discover the functional differences between the metabolism of the entire tumour organism, and that of the healthy organism, with a view to elucidate the causes of the pathological behaviour of the cancer cells.

Since the course and intensity of the metabolic activity in the tumour and in the tumour afflicted organism, is intimately bound up with the enzymatic processes, it is obvious that for understanding the character of the malignant growth, it is essential to obtain a clear knowledge of the various types of enzymes and the mechanism of their activations. The results of experiments carried out on various proteolytic enzymes, described here, are intended to act as a guide for further experiments in the same direction.

The intracellular proteolytic enzymes were studied in the tumours—carcinome and sarcome, produced experimentally, and in the organs of cancerous and healthy animals. The pathological-anatomical analysis and the fixation of their proportions in the total substance, served as a basis for the comparison of the growth-changes in the histologically differing elements of the tumour-tissue.\* Of the enzymes examined, cathepsin shows a significant decrease with the ageing of the tumours (increase in the necrotic tissue) (cf. Fig. 1). One can consequently conclude that this enzyme is confined almost exclusively to the parenchymatous tissue. The arginase, on the other hand, behaves differently; the quantity increases considerably as necrosis proceeds.

It appears, that the arginase is to be found principally in the necrotic tissues and only to a small extent in the growing tissues. These facts, which were established by Waldschmidt-Leitz, McDonald and collaborators<sup>2</sup> (1933) led the author to investigate

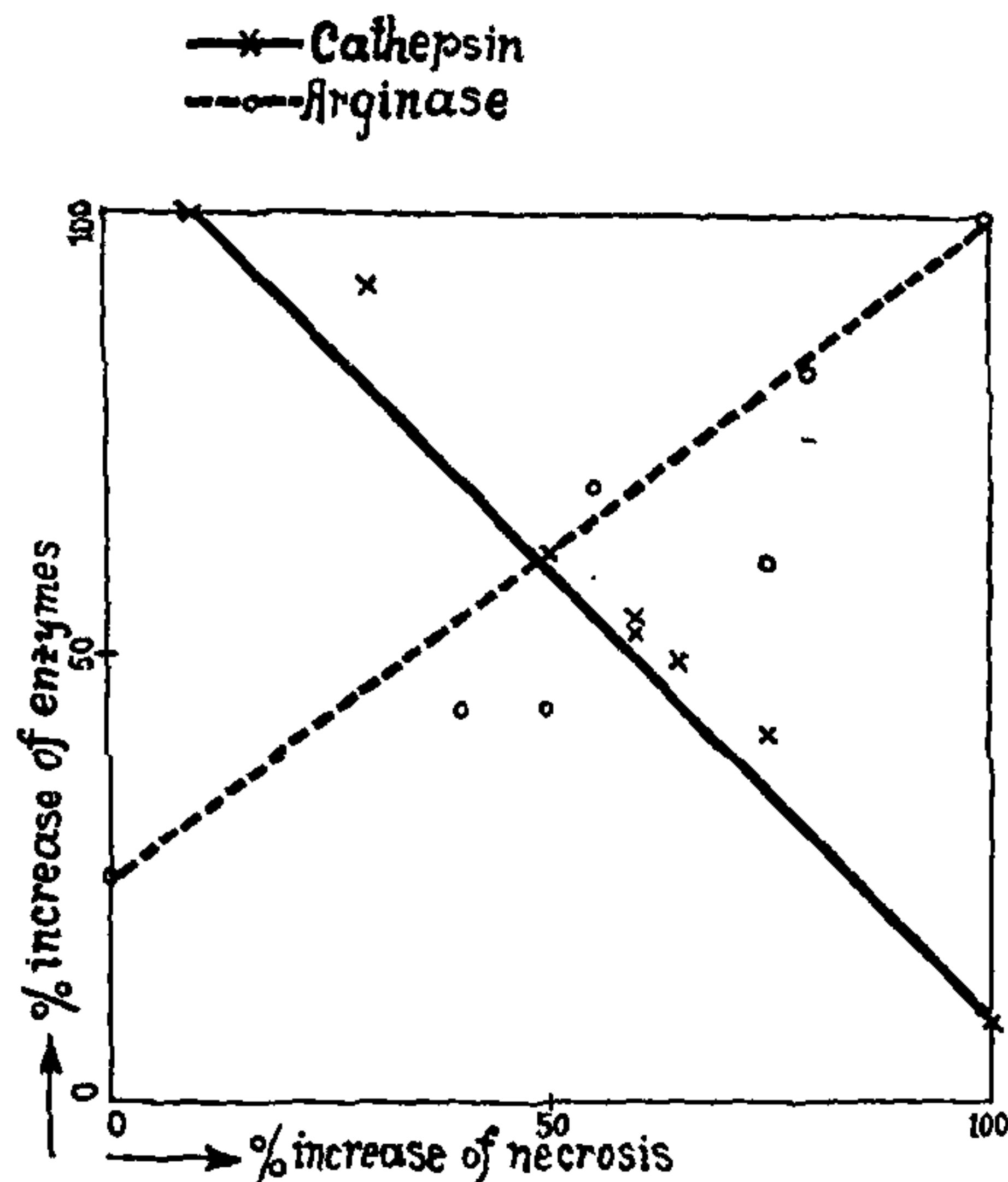


Fig. 1.

further, the general distribution of the enzymic systems in cancerous and healthy animal tissues. In the first instance, attention was directed to the study of the enzymic contents in the organs of healthy, cancerous and cancer-immune animals.

Cathepsin studies with albino rats showed (A. Purr, 1934)<sup>3</sup> that in healthy albino rats (ordinary untreated laboratory rats) the cathepsin content of the liver (measured as full-activity with cysteine as activator) was uniform; the muscle-tissue was found to be practically free from these enzymes. Changes, worthy of note, occur only after these rats have been successfully inoculated

<sup>1</sup> O. Warburg, *On the Metabolism of Tumours*. J. Springer, Berlin, 1926.

\* We distinguish between parenchymatous, fibrous and necrotic proportional parts.

<sup>2</sup> E. Waldschmidt-Leitz, E. McDonald and collaborators, *Z. Physiol. Chem.*, 1933, 219, 115.

<sup>3</sup> A. Purr, *Biochemie J.*, 1934, 28, 1907.

with transplantable rat—sarcoma Philadelphia I; the cathepsin content of the liver increases considerably and the muscle-tissue exhibits appreciable catheptic activity. It should be noted that the increases of the catheptic enzyme concentration in the liver and the muscle-tissue do not run parallel with the decrease of the same in the ageing cancerous tissue as measured by the increase of the necrotic cells); on the contrary all indications point to the fact that there is a disturbance in the enzymatic metabolism. Edelbacher and Merz<sup>4</sup> were able to establish a similar behaviour in arginase, proving that the presence of this enzyme was to be found in the muscle-tissue of animals which had been successfully inoculated with transplantable cancer; they found however no arginase in the muscle-tissue of normal, healthy animals. It may be concluded, therefore, that the increase in the quantity of arginase points to a specific factor of growth, which like the disturbed glycolysis (known through the research work of Warburg<sup>1</sup>) is characteristic of a malignant growth; the increased catheptic activity in the liver and muscle-tissue is also a characteristic sign of a specific growth-factor. A further noteworthy observation may be mentioned in this connection; the albino rats that had successfully resisted the inoculated tumour had from the very beginning more cathepsin in the liver and in the muscle-tissue than the ordinary untreated laboratory rats. Similar experiments on the kidney-phosphatase of cancer-resistant rats led F. Kohler<sup>5</sup> to analogous results. It appears therefore that a higher but well regulated enzymic metabolism is characteristic of cancer-immune organisms. These important observations indicate a successful biochemical method of diagnosing cancer in its incipient stages, a so-called early diagnosis.

For a proper understanding of the change of the enzymatic metabolic processes in the tumour cells in relation to the organisms which are resistant against inoculation, the study of the activation phenomena for the individual enzymes is important, not only as regards their characterisation but also as regards their collective and individual disturbance within the organism as a whole. Such studies should prove particularly valuable for purposes of early diagnosis.

The study of these activation changes, carried out on the intercellular proteolytic enzymes cathepsin and papain, required a number of preliminary tests,<sup>6</sup> to which special attention should be drawn since they led to the standardisation of a method for the determination of physiologically active substances in the blood,<sup>7</sup> the application of which rendered possible a comparison between the intracellular metabolism of healthy and cancerous organs. As a measure of the concentration of such active principles, the activation of papain brought about by SH-groups has been adopted (cf. Fig. 2).

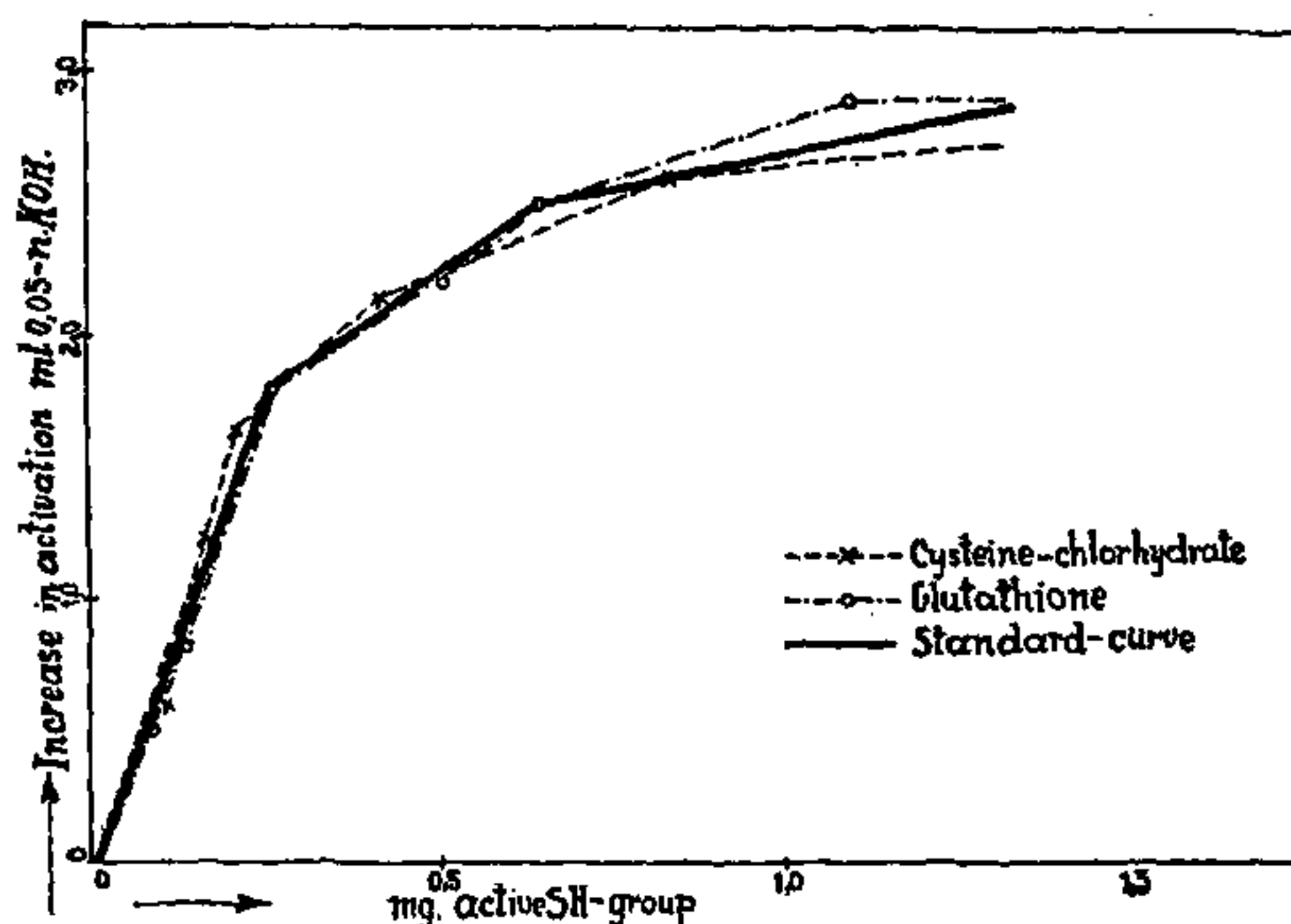


Fig. 2.

The progress of the activation of papain through cysteine hydrochloride or possibly glutathione has proved useful in estimating the latter substance on the basis of the SH-group (cf. Fig. 3). The employment

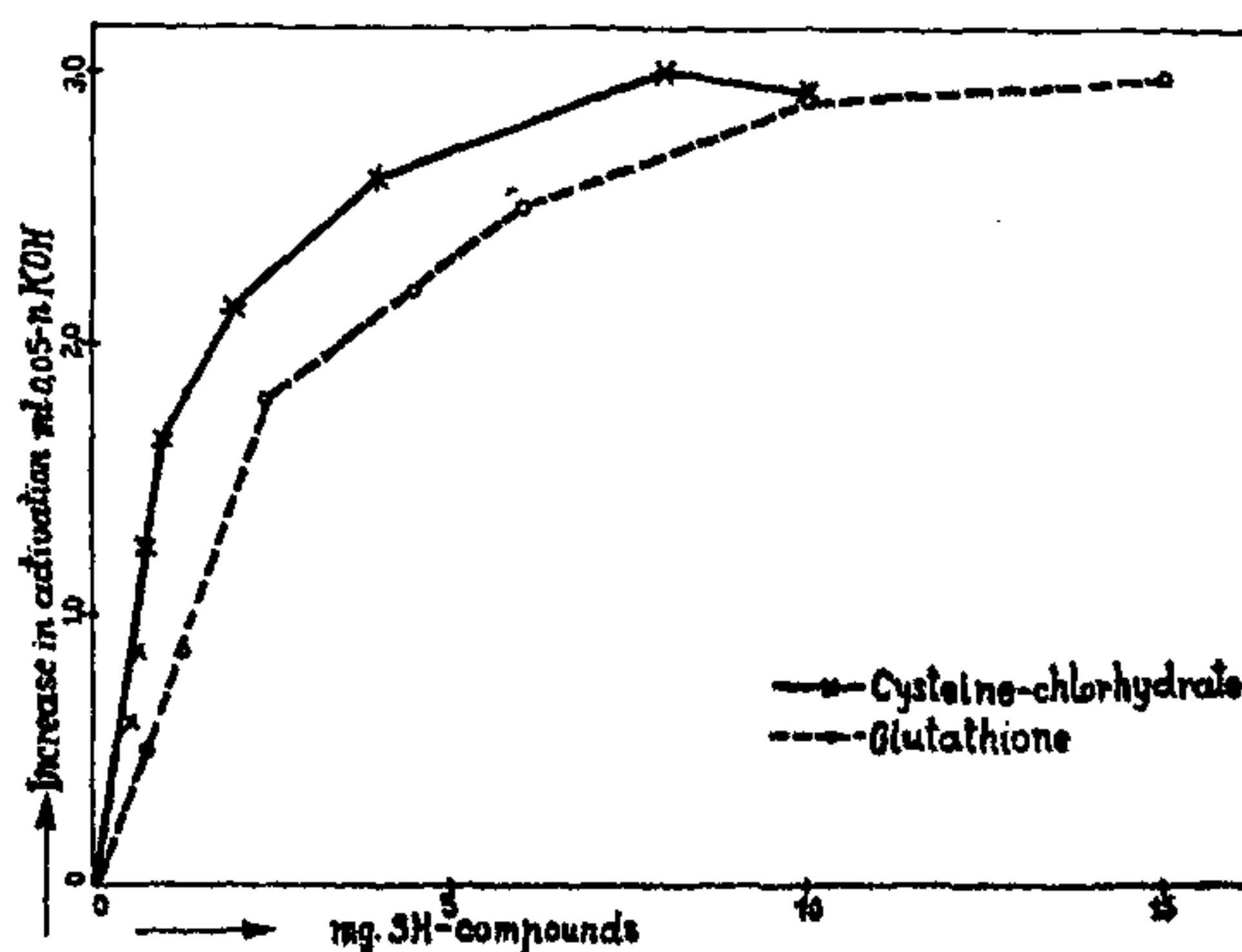


Fig. 3.

<sup>4</sup> Edelbacher and Merz, *Z. Physiol. Chem.*, 1927, 171, 252.

<sup>5</sup> F. Kohler, *Z. Physiol. Chem.*, 1934, 223, 38.

<sup>6</sup> A. Purr, *Biochem. J.*, 1935, 29, 5-20.

<sup>7</sup> A. Purr, *Z. Physiol. Chem.*, 1934, 228, 198.



of this procedure for comparing the activating effects produced on the papain by blood from healthy and from cancerous organisms, showed that the blood from the latter possessed a lower activating capacity than the blood from healthy organisms (cf. Fig. 4).

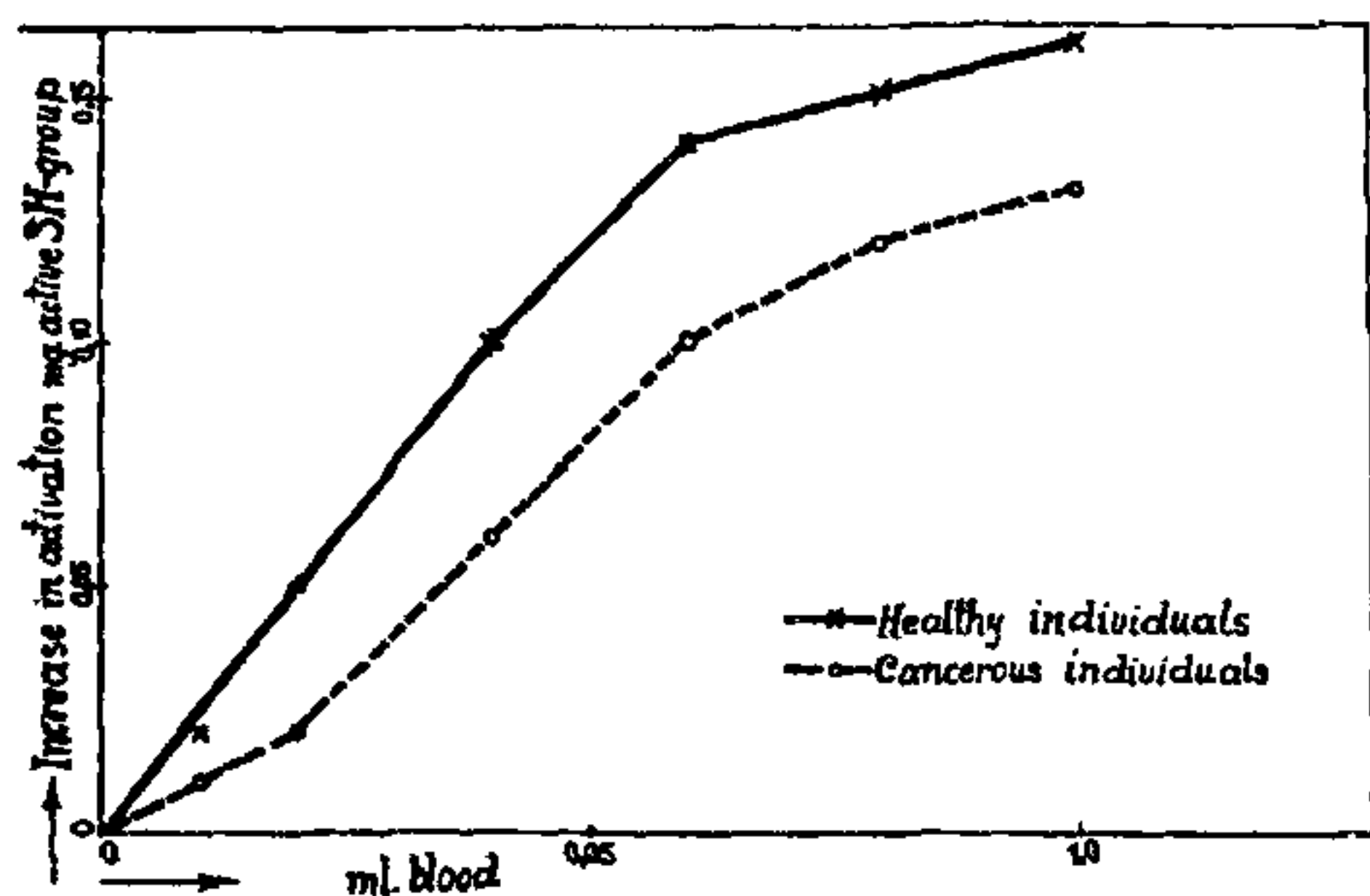


Fig. 4.

A most striking point in the result of this experiment and one worthy of particular note is that the glutathione present in the blood can only participate to a slight extent in the total capacity of activation of papain; for, the activating effect does not correspond quantitatively to the amount of glutathione found in the blood. Consequently the greater part of the activation must have been produced by auxiliary activating systems present in the blood, a circumstance which facilitates the recognition of such physiologically active systems in the blood.

It is proposed to carry out the experiments on a more extensive scale and the results obtained so far lead to the belief that an early diagnosis of cancer is possible by the study of activation phenomenon.

The differences in the behaviours of the cathepsin and arginase referred to at the commencement of this article, were pointed out by Waldschmidt-Leitz, McDonald and collaborators<sup>2</sup> and was later confirmed by the author<sup>3</sup> working with histologically uniform structural elements of the tumour-tissue. It appears that a young, vigorously proliferating cancer-tissue, free from necrosis, is characterised by a high cathepsin and a low arginase concentration. This is especially true in the case of melanomes in horses (also included in the series of experiments<sup>8</sup>) and on account of its striking behaviour, this material is worthy of further tests.

These findings possessing profound physiological significance lead to the conclusion that in the cancerous cells, the synthesis of the albuminous covering, in which process, cathepsin participates, is delayed. There is no ground for the supposition that in the ageing cancerous tissue the autolytic cell-destruction is related to the catheptic activity; it is much more probable that the arginase is connected with these autolytic processes.

Further observations are necessary for elucidating the mechanism of growth of malignant swellings and the influence which such swellings exert on the organism. The relations existing between the effects of the intracellular enzymic systems arginase and cathepsin, and the typical respiration ferments, such as the aerobic dehydrases, of which the xanthine dehydrase<sup>6</sup> may be specially mentioned, deserve careful investigation.

<sup>8</sup> A. Purr, *Z. f. Krebsf.*, 1935, **41**, 483.

### The Elephanta Caves.

THE rock-cut sculptures at Elephanta, like others in the different parts of the country, are decaying under the influence of weather and moisture, apart from the mantle of vegetation. The decomposing effects of the latter due to the exudation of organic acids have been undermining these mural decorations for generations, and several attempts have been made to arrest the process of disintegration, and preserve their architectural beauty. The Government of India, recognising the supreme importance of protecting these historical works of art from

the ravages of the elements, have appointed a strong Committee to investigate the causes of deterioration and to suggest remedial measures. The Committee is composed of Mr. J. F. Blackiston, Director-General of Archaeology, Dr. S. S. Bhatnagar, Professor of Chemistry, the Punjab University, Mr. A. Croad, Superintending Engineer, Central Public Works Department, and Mr. S. N. Gupta, Principal, Mayo School of Arts. The Committee will commence their investigations in November.