thèse de ses diméthoxy-dérivés. Par ailleurs le second est relativement stable, qui aurait été isolé à l'état cristallisé, et qui, d'après MAZZA et STOLFI, présente la même structure et forme les mêmes diméthoxy-dérivés. Il serait important de savoir, laquelle des ces deux substances est (si c'est le cas) la 2-carboxy-2,3-dihydroindole-5,6-quinone. Avant de pouvoir se former une opinion à cet égard il est absolument nécessaire de réexaminer avec soin les nombreuses preuves chimiques présentées par MAZZA et STOLFI[1] en faveur de la structure de leur «Hallachrome», lesquelles paraissent à première vue très convaincantes[2].

Quoi qu'il en soit, il est utile de rappeler que, même d'après RAPER[3], le «corps rouge» n'est ni l'unique ni le premier produit intermédiaire rouge qui se forme pendant l'oxydation enzymatique de la tyrosine et de la Dopa. Il est précédé par la formation de l'*o*-quinone de la Dopa, qui malgré son extrême instabilité, peut demeurer en concentration suffisante (spécialement pendant l'oxydation de la tyrosine[4]) pour être, seule ou en partie, la cause de la coloration rouge. Une évidence expérimentelle sur ce dernier point sera présentée ailleurs; elle est basée d'une part sur l'examen de l'oxydation de la Dopa par l'oxyde d'argent, suivie de la réduction du produit formé par l'hydrosulfite, et, d'autre part, sur l'étude de l'oxydation enzymatique de la *N*-chloracétyl-tyrosine et de la glycyl-tyrosine.

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Summary

It is generally admitted that the red pigment characteristic of the first phase of melanogenesis, "red body", and Hallachrome are the same substance, viz. 2-carboxy-2,3-dihydroindole-5,6-quinone. However, these two substances possess such widely differing properties that it is almost impossible to regard them as identical. It seems difficult to decide on the basis of the existing evidence which of the two is really 2-carboxy-2,3-dihydroindole-5,6-quinone, if indeed either one of them be.

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Cancer and the Pituitary Gland

The relationship between hormones and cancer is extensively treated in many publications[1]. Lately, sex hormones have been used for the therapy of advanced cancer. Nevertheless, the role of hormones in cancer is not sufficiently clarified.

In 1948, we reported that extracts can be obtained from the pituitary gland of cattle which, when injected into white mice, provoke the appearance of various cancers in the animals treated[2]. Earlier, in 1938, we observed other phenomena which directed our attention toward the pituitary gland as the possible factor causing changes of the general metabolism observed in cancer patients. When studying the so-called FREUND-KAMINER cytolytic reaction in cancer, we found that the characteristic behavior *in vitro* of the serum of cancer patients can be evoked in any normal serum when it is fortified with an acetone extract prepared from the anterior lobe of the pituitary gland[1]. On the other hand, any cancer serum loses its character and behaves like a normal serum when added *in vitro* by an acetone extract prepared from the posterior lobe of that gland. Thus, the positive cytolytic cancer reaction appeared to be due to an excess of lipide secretions of the anterior lobe and present in the serum, while normal human serum contains an excess of the lipide secretions of the posterior lobe of the pituitary.

The role of the pituitary gland in cancer was studied by many authors but with contradicting results. In histological investigations the anterior lobe of the gland revealed an abnormally frequent incidence of adenomas. In addition, SUSMAN[2] found in 21 posterior lobes of 30 pituitaries examined sclerosis of the posterior lobe. SUSMAN assumed that the posterior lobe may produce a growth-checking hormone which acts in a manner opposite to that of the growth-promoting hormone of the anterior lobe of the pituitary, and which is deficient in cancer, but no proof was given for that hypothesis.

We found that the acetone extract prepared by us from the anterior pituitary lobe promotes the growth of young rats, rabbits, plant seedlings, and transplantable mouse cancer while our acetone extract from the posterior lobe of the gland inhibits the growth rate of young rats, rabbits, plant seedlings, and transplantable mouse cancer[3]. Thus, it was established that the pituitary gland contains growth-influencing substances of lipide character, a growth-promoting lipide factor present mainly in the anterior lobe, as well as a growth-inhibiting lipide factor present mainly in the posterior lobe of the gland.

There is not much information in the literature concerning lipide hormones of the pituitary gland.

Thirty years ago, T.B. ROBERTSON and co-workers published investigations conducted on a lipide extract obtained from the anterior lobe of the pituitary. That "tethelin" was prepared from concentrated alcoholic extracts of dried anterior pituitary lobes by precipitation with dry ether[4].

Feeding tethelin to young white mice brought particular results. Tethelin when given to the young subsequently to the 14th day when their eyes are open, caused noticeable acceleration of growth during the 2nd till 5th weeks of their life, followed by a marked retardation of growth despite the fact that the administration of tethelin was discontinued at the end of the 5th week[5]. If the feeding was continued behind the 5th week the retardation of growth was also present. However, from the 20th to 60th weeks after birth, the growth of the pituitary-fed animals was markedly accelerated, so that at about one year of age they came to surpass the controls in weight[6]. In mice which received tethelin the duration of life was extended exceeding the normals by 13 per cent[7].

The findings of ROBERTSON were not confirmed by other investigators who used an "improved" method of extraction of the gland, and no further investigations were reported in that matter.

When studying the carcinogenic activity of extracts from the pituitary gland we found that the appearance

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of cancer after the injection of carcinogenic extracts from the posterior lobe was much delayed when compared with the time of the appearance of cancer after the injection of carcinogenic extracts prepared from the anterior lobe of the pituitary gland. The average time necessary for the development of tumor was 9·3 months for anterior lobe extracts, and 14 months for posterior lobe extracts.

This difference in time could be caused by some growth-accelerating factor present in the extracts from the anterior lobe. But some of our extracts, although prepared in the regular way, had only a feeble carcinogenic activity or were inactive. Thus, it was probable that these extracts included an unknown factor which renders the carcinogenic component partially or totally ineffective, and under normal conditions in the body, prevents the carcinogenic activity of the gland.

The presence of such factor could be determined only in experiments on cancer-bearing individuals. The experimental mouse cancer was not the proper subject for these experiments because there are basic differences in the biological and clinical behavior between the human disease and the mouse cancer. The investigations were conducted on human cancer patients in terminal conditions.

The acetone extract from fresh posterior lobes of pituitary of cattle was diluted with water and extracted with ethyl ether. The brownish mass obtained after freeing the mixture from the solvent was separated in fractions by chromatography with activated calcium carbonate. The particular fractions were eluted with ethyl ether, dissolved in oil, and injected subcutaneously or intramuscularly 1–3 times weekly in doses of 10–25 mg.

Of these fractions those eluted from the middle part of the chromatographic column, when administered to cancer patients, caused marked improvement of the patients condition.

The injection of the "Cancer Checking Lipide" (CCL) first is not followed by any reaction. In toxicity tests mice, rats, rabbits, and dogs tolerated perfectly relatively enormous doses of CCL. The effects on the cancer patient usually are observed from after about 10 injections on.

The effects of CCL injections are twofold:

The CCL acts upon the size of the tumor, and it influences the general condition of the patient.

After about ten injections a marked decrease of the size of the tumor is observed which may continue after subsequent injections. If the tumor finally disappears entirely the disappearance of the tumor is followed by a perfect restitution of normal tissue. Some tumors disappeared after 30 injections, other need more than 100 injections to disappear. The histological structure of the tumor treated does not influence the effect. Carcinomas and sarcomas respond equally to this treatment.

Simultaneously a decisive improvement of the general condition of the patient is observed. Pain and paralysis of nerves, if present, disappear. The urge to eat returns as well as the ability to enjoy sleep.

The symptoms of cancer cachexia gradually improve. The atrophic muscles regain their prior volume. The morale of the patient improves to a degree which cannot be ascribed to suggesting influences. Finally the "lost" patient may regain "normal" health and return to his usual occupation even if the tumors are present in the body.

The two effects of the CCL injections: the tumor effect, and the general condition effect, are not caused by the same factors.

Preliminary chemical investigations revealed that the CCL fraction is composed of at least 20 different chemical compounds some of them containing P, N, or S. In experiments with separated groups of these compounds we obtained groups which acted on the tumor but did not influence the general condition of the patient. On the other hand, other groups did not influence the size of the tumor but improved decisively the health of the patient. Thus, the two activities of the CCL fraction depend on different factors.

The medical aspects of our investigations will be presented in medical papers.

Here we like to stress that our experiments indicate that the pituitary gland contains not only carcinogenic but also cancer-checking factors. The cancer-checking factors when supplied to the cancerous organism counteract cancer. In consequence it must be assumed that the human cancer disease is intricately connected with an insufficience of the hormonal activity of the pituitary gland.

This deprives the cancer problem of its mystery, and reduces it to the investigation which normal activities of the pituitary gland are deficient in cancer, and how they may be checked. It has also to be investigated how far the other glands of internal secretion are simultaneously involved in cancer, and how far they are influenced by the cancer-checking lipide extract of the posterior pituitary. Our work is directed toward clarification of these questions.

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Fordham University, New York 58, July 13, 1950.

Zusammenfassung

Ein Extrakt aus Hypophysenhinterlappen wurde gewonnen, der an Krebskranken weitgehende Verkleinerung der Tumoren und Besserung des Allgemeinzustandes erzeugt. Die beiden Wirkungen sind voneinander unabhängig und durch verschiedene Faktoren hervorgerufen. Die Hypophyse enthält nicht nur krebserzeugende, sondern auch krebshemmende Prinzipien. Die Krebskrankheit dürfte mit einer Störung der hormonalen Hypophysenfunktion zusammenhängen.