THE INFLUENCE OF COPPER UPON THE GROWTH OF MOUSE CARCINOMA.

By A. J. GELARIE, M.D.

(From the Cancer Research Laboratory, University of Liverpool.)

DURING the last decade the surgical treatment of cancer has been supplemented by attempts to influence the growth of tumours by procedures directed towards causing immunity, as well as by physical methods—for example, x-raying, exposure to radio-active substances, fulguration, the action of chemical substances, such as arsenic and selenium in various combinations—with the object of causing retrogression of the tumour.

The substances which tend to produce immunity to carcinoma are not at all well defined chemically. Attention has, however, also been paid to the action upon carcinoma of compounds of relatively simple chemical composition.

The idea of studying the effect of copper upon carcinoma occurred to me while carrying out an investigation directed to exhibit the influence of metallic salts upon various staining methods in common use. To this end the present experiments were undertaken. These fall into two series—in the first a solution of a cuprammonium sulphate was injected subcutaneously into tumour mice; in the second colloidal copper was employed.

Subcutaneous Injection of Cuprammonium Sulphate into Tumour Mice.

Cuprammonium sulphate ($\text{CuSO}_4 \cdot 4\text{NH}_3 \cdot \text{H}_2\text{O}$) was obtained by adding to a saturated solution of CuSO_4 strong ammonia and then boiling; the blue crystals of the cuprammonium salt, which separated out upon cooling, were dissolved in 0.85 per cent. NaCl solution and used for injection, the concentration of the solution employed ranging from 0.62 per cent. to 0.70 per cent. of metallic copper.

The lethal dose of this salt was found to be represented by about 0.05 gram of copper per kilogram of body weight. The injections were made subcutaneously at a distance from the tumour. Only mice with small tumours were employed for experiment, and it may be observed, in reference to the experimental results, that spontaneous retrogression of mouse tumour has been in our experience an excessively rare event.

The results of experiments made with cuprammonium sulphate are summarized in Table I, the number of injections

TABLE I.—*Subcutaneous Injection of Solution of Cuprammonium Sulphate into Tumour Mice.*

Condition of Tumour at End of Experiment.	Number of Animals.	Percentage Results.
Completely disappeared ...	3	25.0
Nearly disappeared	1	8.2
Diminished in size	1	8.2
Stationary	5	42.0
Increased in size	2	16.6
Total	12	

tions varying from two to five. The injections, which frequently caused inflammatory swelling, sometimes leading to necrosis of the skin at the site of injection, were always made as far as possible from the tumour so as to avoid any direct effect upon the growth.

In three cases complete disappearance of the tumour occurred, and in two other cases great diminution in size took place. In five experiments the tumour remained stationary for periods varying from five to ten days, and in the remaining two experiments an increase in size of the tumour attended with softening took place.

* The tumours used for experiment originate from Ehrlich's Stamm XI, which has been cultivated in this laboratory for the last seven years, and ordinarily gives 75 per cent. to 100 per cent. positive results of implantation.

Subcutaneous Injection of Colloidal Copper into Tumour Mice.

With a view of avoiding the local inflammatory reaction which occurs when cuprammonium sulphate is used, it was determined to employ colloidal copper for subcutaneous injection. This was observed to be slowly absorbed without producing a marked irritating effect.

Colloidal copper was prepared after Bredig's method, a galvanic current of 10 ampères being allowed to pass between two thick copper electrodes immersed in a beaker containing distilled water, free from CO_2 , placed in a larger vessel filled with ice. In this way a colloidal solution of copper was obtained containing 0.04 to 0.3 per cent. of copper. It was found that the colloidal solution could be boiled without precipitation occurring, and when air was excluded no change in the aspect of the liquid occurred in the course of several days. In all the experiments made, however, the colloidal solution of copper was freshly prepared. The addition of stains such as methylene blue, eosin, and basic fuchsin, in small quantity, was found not to precipitate copper from solution.

A solution of colloidal copper is incompatible with saline solutions. A very small quantity of sodium chloride solution, for example, causes precipitation almost immediately. It was, therefore, used in a non-isotonic solution, the injections being slowly made into the subcutaneous fascia in amounts of about 1 c.cm., in several areas removed as far as possible from the tumour in order to avoid a direct effect of the copper; in some cases intraperitoneal injections were employed (1 c.cm.), or both methods of injection were used. The minimal lethal dose of colloidal copper was not determined.

The results of subcutaneous injection are summarized in Table II. In all thirty-two experiments were made,

TABLE II.—*Subcutaneous Injection of Colloidal Copper into Tumour Mice.*

Condition of Tumour at End of Experiment.	Number of Animals.	Percentage Results.
Completely disappeared ...	2	6.3
Diminished in size	4	12.5
Stationary	16	50.0
Increased in size	10	31.2
Total	32	

the number of injections into individual mice ranging from two to seven. In these experiments it was found possible to keep the animals alive a much longer time than was the case when cuprammonium sulphate was employed. Nevertheless, the number of cases in which complete disappearance of the tumour was obtained was relatively less than in the preceding experiments. In the greater number of experiments in which an effect upon the tumour was observed this was manifested by the tumour becoming stationary in size. On reference to Table II it will be noticed that the effect upon the implanted tumour of injection of colloidal copper was much less pronounced than when cuprammonium sulphate was used. Some of the stationary tumours were kept under observation for a very much longer period of time than in the preceding experiments; in one case the tumour remained stationary for as long as three months.

In four experiments, not recorded in Table II, repeated intravenous injections of colloidal copper were employed. The amount of fluid injected always exceeded 1 c.cm., and in one case reached as much as 2 c.cm.† After the latter injection the mouse became collapsed with rapid and deep respiration, subsequently recovering and surviving for forty-two days. With this exception no ill effect followed upon injection. After intravenous injection the implanted tumours increased slightly in size during the next few days, and then became soft, subsequently remaining

† I have found the following method best for intravenous injection: The tail of the mouse was placed for a few minutes in water at 45° to 50° C. The veins soon swelled up, and no difficulty was experienced in passing a fine needle into the vein. The injection was made with great slowness. White mice were found to be most suitable for experiment, the vein being easily recognized in such animals. During injection the fluid could be seen passing along the vein.

stationary. On sectioning these tumours very marked degeneration was observed. The results obtained in this and the preceding section show that by means of injection of copper-containing fluids implanted tumours in a certain proportion of cases pass into a stationary condition or undergo regression, and suggest that a similar result might be obtained in cases of spontaneous carcinoma.*

In those cases in which the tumour was unaffected a possible explanation is that the amount of copper absorbed into the circulation was too small to produce an appreciable effect. In the case of ammoniated copper sulphate difficulty was experienced owing to the irritating character of the liquid employed; in the case of colloidal copper difficulty was experienced owing to the large amount of fluid which it was found necessary to inject.

Reference may here be made to a series of nine experiments in which colloidal copper, to which basic fuchsin had been added, was employed for injection. In these experiments an unexpected result, which is difficult to interpret, was obtained—namely, that the growth of the tumour was in all cases unaffected by the injection.

Before concluding this paper I have much pleasure in expressing my great indebtedness to the director of this laboratory, Dr. J. O. Wakelin Barratt, for his kind attention and constant assistance.

EIGHTY-FIRST ANNUAL MEETING

OF THE

British Medical Association.

Held in Brighton on July 23rd, 24th, and 25th.

PROCEEDINGS OF SECTIONS.

SECTION OF MEDICAL SOCIOLOGY.

REGINALD JOHN RYLE, M.D., M.A., President.

PRESIDENT'S INTRODUCTORY ADDRESS.

My first duty is to welcome those members of the Association who are kindly helping us with their presence, their papers, or their speeches; and my second duty is to welcome those who are not members of the Association, but who have done us the honour of accepting the invitation which we have the power to extend in the case of this particular Section to non-members. Most of the Sections now meeting in this building are dealing with particular branches of medicine and surgery from the points of view of physicians and surgeons who are discussing medical and surgical problems with their professional brethren. There are, however, a large number of topics of great importance which interest both the public at large as well as the doctor in the course of his work. These may be profitably dealt with, from either point of view, in language not always technical, and it is with the object of introducing such a consideration that this Section has been brought into being. The definition of Sociology appearing on our syllabus is:

The scientific study of society and of all the phenomena it exhibits, including the various forces and processes at work within and upon it.

I do not wish to enlarge upon that definition, but merely to hold it out as a kind of thread on which we may hang the consideration of the problems as they arise. Medical sociology means a similar study, having reference to the work of the medical profession. Such work is very much wider than it was even half a century ago. No one who has read any one of the reports issued by Royal Commissions on housing, education, inebriety, feeble-mindedness, destitution, can fail to know that there is involved in every one of them a larger or smaller social problem with which the profession of medicine is concerned, so

* Since commencing these experiments my attention has been called to the work of Loeb, McClug, and Sweek, in which human cancer has been treated by intravenous injection of colloidal copper (*Interstate Med. Journ.*, 1912). The authors are of opinion that definite judgement on the outcome must still be suspended at present, but state that the treatment is capable of causing gradual retrogression of the growth.

that I hope every year this Section will be more and more useful.

We have endeavoured to select subjects which will cover a large area of ground and be of interest both to medical and non-medical minds, and which may be said to have a mutual connexion between them. At the beginning we have taken the subject which goes by the name of eugenics. Let me remind you that eugenics is a very old conception. Far back in the days of the ancient Greeks the poets and philosophers fully realized that if you are to get the best men and women you must pay attention to the best stock and the best race. That consideration has never been absent from the minds of diligent students from that day. The matter, however, has been revived and very largely set on a new footing by the work begun by Darwin and Wallace, carried on by Mendel, and carried further by the late Francis Galton. Therefore I hope we may keep in view Galton's revival of the word with some of the signification he attached to it. Remember that eugenics have primarily to do with racial qualities, which are being studied by two methods—the biological and the statistical or mathematical.

DISCUSSION ON "EUGENICS."

OPENING PAPERS.

I.—EDGAR SCHUSTER, M.A., D.Sc.,

First Galton Research Fellow.

THE SCOPE OF THE SCIENCE OF EUGENICS.

THAT there is a sort of antagonism between the arts of medicine and eugenics has been recognized for some 2,400 years. Its nature is clearly indicated by Plato in the *Republic* in the passage in which Socrates is represented as making a comparison between the older school of medicine and the school which was active in his own day. The former, which he personifies under the name of Asclepius, he regards as working on eugenic lines, whereas the very successes of the latter were, in his opinion, dysgenic in their effects.

If Asclepius did not instruct his descendants in valetudinarian arts, the omission arose not from ignorance or inexperience of such a branch of medicine, but because he knew that in all well-ordered States every individual has an occupation to which he must attend, and has therefore no leisure to spend in continually being ill. . . . And therefore our politic Asclepius may be supposed to have exhibited the power of his art only to persons who, being generally of healthy constitution and habits of life, had a definite ailment; such as these he cured by purges and operations, and bade them live as usual, herein consulting the interests of the State; but bodies which disease had penetrated through and through he would not have attempted to cure by gradual processes of evacuation and infusion; he did not want to lengthen out good-for-nothing lives, or to have weak fathers begetting weaker sons.

Now medicine to-day, as in Plato's day, endeavours to lengthen out lives of all sorts, and does not presume to judge what are good for nothing and what are not, and it enables weak fathers and mothers to have children; and in this respect it may be accused with some justice of being dysgenic. Eugerists are sometimes represented as being a savagely tyrannical clique who regard the lethal chamber as a more valuable institution than the hospital, and castration the greatest good to be got out of the surgeon. Perhaps what I have just said may appear to give some support to this view, so I take the opportunity of stating most emphatically that eugenists are not antagonistic to medical science, even if it does lead to the prolongation of good-for-nothing lives. But the fact that the work of doctors on behalf of humanity may by its very success lead to results which eugenists deplore, imposes a sort of obligation on the medical profession to make what contributions it can to the science of eugenics. Eugenics in some of its aspects may indeed be regarded as a branch of preventive medicine, and the proverb that prevention is better than cure is in this field more true than most proverbs, at any rate from the point of view of the lay public.

It is for these reasons that I shall endeavour in the present paper to give a brief analysis of some of the principal problems in eugenics as they appear to me, with the object of arousing discussion on the nature of the contributions to the science of eugenics which might fairly be expected from medical men.