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ON

THE EXPERIMENTAL INQUIRY INTO THE CAUSES OF CANCER.*

BY

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Αιτίην δὲ ἀρρεκέα μὲν ἴσασι μοῦνοι θεοί, ἐοικυῖαν δὲ καὶ ἄνθρωποι.—ARETAEUS.

WITH so much known of the actual manifestations of tumour growths, and with their antecedents so obscure, it is little wonder that speculation regarding the causation of cancer has so long held its sterile and unprofitable way. The gossamer fancies of the armchair philosopher need scarcely a breath of criticism for their destruction; and as for the theories of the greater thinkers, the outcome of much experience carefully interpreted, we may for the present adopt the dialectical strategy of Hegel and say that possibly they all represent partial and different aspects of the truth. Anxious as we should be, in view of the poverty of our knowledge, to avoid bound allegiance to any theory, we cannot wholly dispense with working hypotheses, and the recent experimental investigations have been born of the idea that cancerous growth is the result of some long-continued irritation. That is the oldest theory of them all. The ancient Greek physicians imagined that cancer, as well as many other diseases, was due to the irritating and acrid properties of the black bile. Are there not some to-day who attribute to intestinal stasis, a notion not less nebulous, a similar wide-embracing rôle?

Virchow, the father of modern pathology, contended that tumours were caused by irritation of a chemical or physical nature, not further defining or particularizing, for there had not then accumulated the imposing list of special agents that we now know to be closely associated with the production of cancer. His was a theory that anticipated the evidence. Probably we shall find—our experiments point that way—that few of the substances which we might call tissue irritants are capable of inducing tumour growth, just as out of the myriads of kinds of bacteria there are relatively few which are definitely pathogenic.

These specific irritants, or carcinogenic† agents, as far as we know them, require a prolonged time to work their effects, and they appear to be selective in that certain animal species, certain strains, certain individuals, and certain tissues only are vulnerable to their operation. In the human subject we have the well known instances of the cancer of the scrotum to which chimney-sweeps and labourers in the tar, pitch, and paraffin industries are specially prone; the cancer of the urinary bladder in dye-workers and in the victims of bilharziasis; the epithelioma of the abdomen and thighs in natives of Kashmir; the multiple skin cancers in those who have taken arsenic medicinally over long periods; and the epithelioma of the hands in *x*-ray operators. These and several others seem to show a very intimate relation between particular irritants and tumour formation, but several considerations have long stood in the way of establishing a direct causal connexion between them.

Comparatively few of the subjects exposed to the action of soot, tar, paraffin, aniline dyes, and the rest develop malignant tumours; even those who become affected have been in contact with the noxious substances for many years: more arresting still is the fact that several of these workers have retired from such occupations and yet, years afterwards, have developed the same peculiarly localized cancers. Considering, too, the numerous instances of malignancy supervening on other chronic lesions, and the fact that the so-called irritation cancers are so rare in comparison with the large numbers of tumours arising without the intervention of any known or suspected irritant, we have had to admit that our carcinogenic agents might only be the mediate and not the proximate causal factors of the disease. All that we could claim for them was that they brought about a pathological state of the tissues, on which prepared soil the undetermined cancer germ or virus or influence might then exert its action.

Sometimes, however, the progression of events was so uninterrupted—as, for example, in arsenic cancer, where skin hypertrophy merges into wart formation and warts insensibly into epithelioma—that it was difficult to point to any particular time when one factor could give place to another. But no amount of argument could settle the matter. No one had ever produced cancer experimentally by the use of any of the implicated irritants. Of course, numerous claims to have done so by the injection of this or that parasite have been put forward. Let us not resurrect them. The silent records, too, of our laboratories contain many a failure that we have not liked to parade. But a new era dawned on cancer research when Johannes Fibiger of Copenhagen presented his brilliant experiments on the production of gastric cancer in rats. Then for the first time could it be said that cancer had been produced experimentally beyond all doubt, and explorations into the etiology of cancer became practical problems.

SPIROPTERA CARCINOMA.

While examining the bodies of three rats that had been inoculated with tubercle bacilli Fibiger found in each case a cancer of the fundus of the stomach. Such a thing had never before been seen in the rat, though scores of thousands of these animals had been examined for tumours. Malignant new growths do exist in rats, about once in a thousand cases, but cancer of the stomach had never been observed. Fibiger at once endeavoured to propagate the tumours by inoculation of fragments into other rats, and failed. Fresh rats were fed with other pieces of the tumour; nothing happened. Another batch was put in the cages previously occupied by the infected rats; they remained unaffected. Microscopic investigation of the gastric tumours showed them to be epitheliomata, for the cardiac half of the rat stomach is lined with squamous epithelium, and amongst the epithelial cell masses there were round spaces sometimes containing a peculiar structure that suggested sections of an animal parasite. Tracing

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† From *καρκίνος*, a tumour, simple or malignant, and *γεννάω*, to produce. Such adjectives as cancrigenic, cancrogenic, and cancerigenic, which have been used by others, are hybrids to be avoided.

these through hundreds of serial sections, and reconstructing the pictures, he found he was dealing with a nematode, and subsequent dissection of a preserved portion of the tumour enabled him to obtain an entire worm of a species hithero unknown, to which he afterwards gave the name of *Spiroptera neoplastica*.

Observe the conjunction of facts: three rats in one batch, each with cancer of the stomach and in each tumour the same parasites; cancer of the rat's stomach never seen before; a nematode till then unknown. What was the relation between the nematodes and the tumours? A mere accidental coincidence, many would have said, and dismissed it. A probable predisposing cause in these particular cases would have been accepted by the majority. Had Fibiger stopped there he would have made merely an interesting contribution to the literature of our subject, and cancer research might still be the fettered Andromeda of pathology. He killed and examined carefully over a thousand rats, but failed to find either a gastric lesion of any importance or the particular nematode he sought for. Reading the literature of animal parasites, he learned that Galeb had been able to obtain nematodes in the stomach of some rats by feeding them on the common cockroach, *Periplaneta orientalis*, which was infested with another stage in the life cycle of these parasites, and thinking this might be a possible clue he examined rats from a locality in Copenhagen where such cockroaches abounded, but without success. Then he fed fresh laboratory rats on these cockroaches, and again nothing resulted. But finally, when the sustaining hope was almost gone, he heard of a large sugar refinery in the town, where both rats and cockroaches swarmed. The cockroaches here were of a different kind; they were *P. americana*, uncommon in Northern Europe. An examination of the rats revealed many cases of gastric tumours, and in them the long-sought-for nematode was found. A false clue, and a stroke of fortune that was bravely deserved, led him to the great discovery. These cockroaches had come in consignments of sugar from the West Indies; in their muscles were the coiled-up larvae of the nematode, and when the cockroaches were eaten by the rat the larvae were set free and developed in the stomach into the adult nematode. Here, after a time, it produced eggs, which were evacuated with the faeces, eaten by the cockroach, and the larval stage again produced, and so the cycle went on. By feeding other species of cockroaches on the eggs Fibiger succeeded in getting these to serve as intermediary hosts, and thus he obtained his source of supply of spiropterae. By feeding laboratory rats on such artificially infested cockroaches, or on the larvae isolated from their muscles, he induced gastric epithelioma in over 50 per cent. of them.

The freed larva burrows superficially in the gastric epithelium, and there develops to maturity. In some cases no change takes place in the stomach, but in most instances the epithelium begins to proliferate and forms papillomatous projections, and sooner or later the proliferating cells penetrate the muscular coats and reach the peritoneal covering. The nematode may also lodge in the epithelium of the tongue, producing glossitis, leucoplakia, and finally cancer. Strangely enough, though the worms may inhabit the oesophagus they have never been found to induce more than papillary hyperplasia in that situation. In no other portion of the alimentary tract do the parasites lodge or produce neoplasms. Metastases have occurred in several cases in the lungs or lymphatic glands, but from these secondary tumours the parasites were absent. Having once started malignant proliferation, probably by the prolonged toxic action of some excretion, the parasites are no longer essential to the continued growth of the tumour. The parasite may be transferred to wild rats and to other rodents, but in no case has cancer resulted. There are thus species, strains, and particular tissues which are insusceptible to the action of the nematode. Mice are relatively insusceptible, only about 5 per cent. developing gastric tumours; but whilst cancer may be produced in rats in six weeks to three months it takes many months—perhaps over a year—to induce it in mice.

I have given the merest outline of Fibiger's researches—epoch-making, patiently pursued, and brilliantly executed. He was the first to furnish us with a means of producing cancer experimentally at will with a definite agent. He is the pioneer in the experimental inquiry into the etiology of cancer, and I should like, as a humble follower, to pay him my tribute. To my mind, Fibiger's work has been the greatest contribution to experimental medicine in our generation. He has built into the growing structure of truth something outstanding, something immortal, *quod non imber edax possit diruere*.

CYSTICERCUS SARCOMA.

The greatness of Fibiger's achievement stands out in relief when we reflect on the mass of information we had at our disposal regarding another and commoner parasite which is associated with tumour formation, and which, had our eyes been alight, we might have utilized. In examining the bodies of laboratory rats it is no uncommon thing to find cysts of the liver, sometimes single, sometimes in large numbers, filled with clear mucoid fluid and containing a triangular-headed parasite with flattened segmented body—the *Cysticercus fasciolaris*, the larval stage of the *Taenia crassicollis* which affects the cat. Less frequently these cysts may be situated in the omentum, kidneys, or other abdominal organs. Several observers, notably Borrel in 1906, Regaud in 1907, Bridré in 1909, and McCoy in the same year, had described sarcoma of the liver of rats occurring around these parasitic cysts. Bullock and Rohdenburg in America made careful histological studies of several such sarcomata. Histologically the tumours are all of the same nature—spindle-cell sarcomata often highly vascular with a tendency to the formation of large multinucleated cells—and they arise from one or more parts of the compressed connective tissue constituting the wall of the cysts. Borrel and others were able to transplant these sarcomata, and there is no doubt about their true nature.

There are several highly suggestive features about these tumours. Of all the cases of tumours that have been reported in rats, well over a hundred in number, no less than four-fifths have been sarcomata; more than half of these sarcomata have been situated in the liver; and there they have practically always been found around a cysticercus-containing cyst. But it was not until 1917 that any attempt was made to produce sarcoma experimentally by means of the worms. In that year, when reporting a spontaneous case, Hirschfeld, instigated undoubtedly by Fibiger's work, stated that he had instituted feeding experiments on rats with the ova of *Taenia crassicollis*, but as no later communication on the subject came from this author's pen we may assume that his experiments failed. Bullock and Rohdenburg in 1920 were successful. To a very large number of rats they administered by mouth on a single occasion the ova of the adult worm obtained from the faeces of an infested cat. Certain strains of rats, and especially old rats, proved quite insusceptible, but in the majority of young rats the larvae reached the liver and formed cysts, and in about a quarter of the number of such animals sarcoma developed on the cyst wall. Usually only one sarcoma was produced, though there might be dozens of cysts, but in a few cases two independent sarcomata were found. Metastases occurred in about 60 per cent. of the cases. There is a long latent period in the development of these liver sarcomata—eight to fifteen months or more elapse after the ingestion of the ova before the sarcoma starts, but once started it develops with great rapidity. This peculiar feature in the experimental production of sarcoma—the prolonged latent period followed by explosive growth—has struck me in my experiments with paraffin oils and has been noted by Russell in his tar experiments on rats. Possibly we may find it characteristic of sarcoma in general.

Schmidt-Jensen of Copenhagen has failed to produce cysticercus sarcoma in rats, so that there are probably strains of rats that are refractory to this tumour-producing agent. It is presumed that the toxic products of the cysticercus furnish the necessary constant tissue irritant; but however that be, a susceptible tissue is required. The same parasite is commonly found in the liver of mice, but sarcoma of the liver has never been reported in the mouse save in one doubtful case, and neither in that nor in the epithelial tumours of the liver, some thirty in number, could any parasite be discovered.

TAR CANCER.

Workmen constantly exposed to coal-tar and pitch, such as retortmen at gasworks, road sprayers, and briquette makers, are liable to develop skin cancers. This has long been known, and, believing that tar contained some ingredient which directly influenced the tissues to become cancerous, pathologists first used this substance in their endeavours to produce cancer experimentally. Doubtless more numerous attempts were made than the few on record, but they all failed, and the direct relation suspected could not be established. The reasons of those failures are now fairly obvious: either we did not employ suitable animals or our patience was exhausted before results were possible.

Inspired by the success of Fibiger's experiments, two Japanese workers, Yamagiwa and Ichikawa, renewed the attempts. They applied coal tar every other day for several months to the ears of rabbits, and claimed to have produced epitheliomata. While it is probable that many of the epithelial proliferations which they induced would not be recognized as true malignant tumours by the critical, yet the evidence in favour of the malignancy of some, especially the finding of lymphatic gland metastases, must be accepted. I repeated their experiments two years ago on twenty rabbits, applying the tar to the skin between the shoulders, and though in all cases I obtained multiple horny papillomata, commencing in about ten weeks and reaching in some cases the size of acorns, they never became malignant; indeed, the surprising thing was that the tumours tended to diminish in size in spite of the continuance of the tar applications, and in one or two instances entirely disappeared. Possibly Yamagiwa employed a more susceptible strain of rabbits, but more probably the tar he used was more potent. Deelman, Moeller, and Teutschländer have also failed to produce tar cancer in rabbits.* Tsutsui, a pupil of Yamagiwa, discovered that the mouse was the animal of choice; amongst 67 mice which had survived the tar applications for over a hundred days, he found that 35 developed tumours, 16 of which were epithelioma and 1 sarcoma; two of the epitheliomata metastasized to the lungs.

When, after the war, these results became known to us in Europe, it was evident that we were provided with a means not only of producing tumours *de novo*, but also of studying the phenomena of their onset and development. Fibiger and Bang were the first to publish corroborative experiments, soon to be followed by the various other members of our international society—the Leeuwenhoek Vereeniging. In the short space of time that has elapsed, scarcely more than two years, since our Danish colleagues presented their preliminary observations, very many experiments have been done with this one irritant. If tar be applied repeatedly, say thrice weekly, to the skin of mice the hair is lost, at first temporarily, but in the course of time permanently, the skin becomes rough and scaly, and after the lapse of three to six months or more tiny warts, single or multiple, make their appearance, and, increasing gradually in size, form excessively cornified upstanding papillomata with branching vascularized stalks of connective tissue. By and by the epithelium commences to grow downwards into the dermis, the cells become more atypical, the panniculus carnosus is penetrated, and metastatic deposits may be found in the lymphatic glands or in the lungs. The malignant stage is not generally apparent before six months at the earliest. Sometimes the malignant epithelioma is not preceded by preliminary simple wart formation: a minute superficial ulcer may mark the commencement of the epithelial downgrowth, and subcutaneous induration may be the first sign apparent of a neoplastic reaction. In the case of mice almost all develop tumours in response to the tar applications, and in practically all of these one of the papillomata, seldom more, becomes an epithelioma sooner or later. Very few of those that live more than eight months escape without tumour formation. But there are considerable differences as regards the length of time that may elapse before tumours are evident and great variations in the rate of progress of the tumours. The first papilloma to appear is not necessarily the earliest to become malignant.

Given the fact that repeated applications of tar to mice result in the production of epitheliomata in a large proportion, we first addressed ourselves to the consideration of the specificity of the irritant. Did it merely induce a chronic inflammation, a non-specific lesion, on which a malignant process, attributable to some mysterious added cause, was prone to develop? The question is not yet answered. Employing exactly the same technique as in the case of mice, I tried the effects of the tar on several series of rats for periods of more than a year. The rat's skin is more sensitive than that of the mouse, and it does not tolerate the applications so well; the area painted shows the same changes that we find in mice, but I have never succeeded in producing in rats any papillomatous or epitheliomatous formation. The same failure has attended the experiments of others. On the other hand, Russell, by injecting tar in lanoline subcutaneously into rats, has produced sarcoma in two or three cases; it is the fibrous connective tissue and not the epithelium of the surface that responds to the action of tar in this animal. I have similarly applied tar to the skin of a batch of guinea-pigs for two years now, but in no instance have I produced any epithelial proliferation whatever. The experiments with rabbits have already been mentioned. We are thus impelled to the conclusion that, just as in the case of pathogenic bacteria, only certain animal species are responsive to the action of the pathogenic agent, and probably only certain tissues. But this is, after all, only an indirect and partial reply to the question.

The next point that interested us was, given this active agent and a responsive species, what part does age play in the onset of cancer? It is usually said, and generally believed, that cancer is essentially a disease of old age, or of ageing tissues, but anyone who has had much to do with cancer in the human subject knows that it by no means infrequently occurs in quite young people. I therefore made two parallel series of experiments, using in one set adult mice and in the other mice all under six weeks old. Neither in yield of tumours nor in rate of tumour growth was there any appreciable difference between the two. This has been confirmed by subsequent experience so often that the fact is beyond doubt. The conclusion is that age by itself is not an important factor. It is merely a question of the length of time the causal agent has been in operation. We may argue that if we exposed a child of 10 and an adult of 40 to one and the same carcinogenic agent, and the latent period necessary was ten years, the cancer would declare itself when the former was 20 and the latter 50.

In view of the fact that countless and careful investigations of human growths have almost invariably failed to reveal the presence of any irritant, and knowing from previous experiments that tumours reaching the stage of malignancy continued to grow after tar applications had been stopped, it became of importance to determine whether the bias towards malignancy was given to the cells at a more remotely antecedent period. I therefore stopped the tar paintings as soon as minute warts made their appearance. Nevertheless, these small warts continued to grow and became epitheliomata just as speedily as if the irritant had been continued. Going still further back, I found that if I stopped the irritant before there was any sign whatever of neoplasia, in due course warts appeared and the phenomena of malignancy were unfolded just as before. Though, in mice, the usual course is first papilloma and then epithelioma, we have occasionally found that the epitheliomatous formation was not preceded by simple tumour. Bang has had similar results. We have grounds, therefore, for believing that in the case of human cancer, the antecedents of which are for the present hid from us, some irritant may have been in action and have disappeared, leaving no other evidence of its presence, long before the cancer declared itself.

My colleague, Dr. E. L. Kennaway, has been endeavouring to find the particular ingredient in tar which has this tumour-producing property. So far he has not isolated the substance, though it seems to be in greatest abundance in the higher boiling fractions. We know that pitch, for example, the solid part of tar left after the lower boiling fractions have been extracted, is associated with epitheliomatous ulceration in briquette makers, and he has been able to induce tumours in mice by using pitch dissolved in benzol or in lanoline. How does the pitch dust, a rather

* Immediately after this paper was read, Menetrier and Surmont reported a single success. Dr. J. A. Murray informs me that he has recently succeeded in two cases with an ether fraction of tar

insoluble substance, produce its harmful effects on the exposed skin? By dissolving pitch in human sebaceous fat I have produced malignant tumours in mice in less than three months. On the other hand, I have applied Scottish blast-furnace tar, which is produced at a comparatively low temperature, to mice for eight months without obtaining any sign of tumour formation. Tars are found to vary considerably. Thus we applied a direct ethereal extract of a tar to 500 mice, with the result that at the end of five weeks, so toxic was the extract, only 26 remained alive. As it was useless to continue we stopped the applications, but in one case a tumour appeared in the record time of thirty-seven days. It and several others which subsequently appeared became malignant. Using the same extract of another tar from the same gasworks we found no such toxic action, and the earliest tumour took nearly three months of repeated applications to declare itself. Kennaway's experiments are of practical importance because means may be found in the industries concerned to obviate the necessity of exposing men to dangerous distillation products of tar, and thus to prevent a certain number of cases of cancer.

Deelman of Amsterdam has discovered that if the tar applications are preceded four or five times by light scarification of the skin tumours result in the second month. Apart from this demonstration that the superficial layers of the epithelium act as fairly efficient barriers against the irritant, it seems to me that his experiments open up suggestive paths for the investigation of the relation between the processes of wound repair and malignant proliferation.

Murray has recently made a contribution which may have far-reaching results. He found that if he extirpated a tar epithelioma and then resumed the tar applications he could not induce any subsequent tumour formation in that animal. Further, if he removed a spontaneous tumour from a mouse and subjected that mouse afterwards to tar paintings it did not show any neoplastic response to the tar. In view of the fact that two different cancers are of very rare occurrence in the same individual, and, judging from statistics, much rarer than the laws of chance would indicate, he argues that the occurrence of one form of cancer in an individual protects the body in some way against the occurrence of another. The practical application of this must be obvious. There is, however, room for some difference of interpretation of the facts, and more extensive experiments may modify the conclusions that one is tempted to draw from these important observations.

I cannot here touch on numerous other observations by ourselves and other workers—the analyses of precancerous states, the reactions of defence, or the questions of immunity and susceptibility. Though of interest from the theoretical point of view, their practical bearing is not yet of general interest.

CHIMNEY-SWEEPS' CANCER.

It is now nearly 150 years since Percivall Pott called attention to the chimney-sweeps' cancer of the scrotum. Not only was this the first time that any tumour formation was attributed to a definitely ascertained irritant, but, still more important, it was the earliest recognition of the purely local origin of a cancer; as Pott said, it was not a "disease of the habit." Since his time numerous English authors have written on the disease without adding much to the classic description. Frequently they have remarked on the increasing rarity of this form of cancer, attributing the decrease to the wider recognition of the value of cleanliness amongst sweeps. In point of fact, it is probably as common to-day as it was then. The English mortality returns give a yearly average of five or six cases. There are two features about this cancer that merit attention: (1) its geographical distribution, and (2) its exclusive localization to the scrotum.

It is practically unknown on the Continent. By the courtesy of the Registrars-General of Ireland and of Scotland I gather that it is relatively common in the former country, and so rare in the latter that several years may elapse between cases. In their recent paper Southam and Wilson state that of 141 cases of cancer of the scrotum admitted to the Manchester Royal Infirmary during the last twenty years only one was a chimney-sweep. Thirty years ago Butlin dealt fairly exhaustively with the question why the disease was so common in England and so rare on the Continent, concluding that the greater protection in the matter of clothing in the case of the foreign sweeps and the different methods adopted abroad in the use of domestic coal accounted for the contrast. But no such explanation can account for the unequal distribution of the disease through the British Isles. It is well appreciated in industrial concerns that coals from different localities have their well marked characteristics; even in the same pit and the same seam coals of different composition exist. The tars obtained by the destructive distillation of different coals vary very much, and this holds good with regard to the pitches. Chimney-sweeps, whom I have questioned on the matter, claim to be able to identify the particular kind of soot which is most dangerous, though they do not agree in their description of its physical appearances. I suggest that the soot which contains the tumour-producing substances is derived from the more bituminous coals coming from the Midlands of England.

But even more mysterious is the fact that soot cancer in chimney-sweeps is confined to the scrotum. That one or two cases of epithelioma arising in other situations have been reported in workmen engaged in the handling of soot does not affect the general statement. Other parts of the body in sweeps are as much exposed as the scrotum, probably more exposed, to the action of the soot, and though occasionally soot warts may be found on the skin at other places, the scrotum is the seat of election of the epithelioma. The same thing holds to a lesser extent in the cases of pitch and paraffin cancer. Why should this be so? The laxity of the scrotal skin, enabling the soot to lodge in its folds, as suggested originally by Pott, seems to offer only a partial explanation. One peculiarity has hitherto escaped attention. The scrotum in the human subject contains unusually large sebaceous crypts, which are not infrequently rendered prominent by the retention of inspissated secretion. I imagine that the soot may lodge there, and that the carcinogenic principle it contains is abstracted and dissolved in the sebaceous fat.

For years experimenters have endeavoured to produce cancer in animals by means of soot, but without success. I have rubbed soot into the scrotum of rabbits (in which animals, be it noted, the scrotal skin is lax and rugose) thrice weekly for two years; I applied it to the scrotum of rats for a year; and I had batches of male mice living in boxes of soot for several months; but in no case did I succeed in producing any perceptible lesion of the epithelium. It may be that I was unfortunate in not having the right kind of soot, but I am more inclined to the belief that the natural solvent necessary is absent from the scrotum of these animals. Passey induced epithelioma in mice by painting on their backs an ethereal extract of soot. His experiments are valuable in demonstrating that soot does contain a tumour-producing fraction to which mice at least are susceptible, but it is obvious that in the animal body we have no such powerful solvent at work. To supply the natural solvent which I fancy is present in the human scrotum and absent or deficient in the scrotum of laboratory animals, I have had recourse to the sebaceous fat from ovarian dermoid cysts. I have to thank numerous gynaecologist friends for supplies of ovarian dermoids. Different samples of this fat vary a little, but they are all liquid at about body temperature, and they dissolve some fraction of soot, the melting point of the solution being lower than that of pure fat. The experiments with this solution have not proceeded far enough to forecast the result. I have already mentioned that with this sebaceous fat as a solvent for the active ingredients of pitch I have readily produced malignant tumours in mice.

PARAFFIN CANCER.

It has been known for fifty years that workmen exposed to the action of the crude products obtained by distillation of the oil-bearing shales of Scotland and of the brown coal (lignite) of Germany are prone to develop chronic skin affections, papillomata and epitheliomata, especially on the arms and not infrequently on the scrotum. The most

authoritative account of these occupational lesions, the result of several years of intimate observation, has recently been given by Dr. Alexander Scott of Broxburn, from whose pen we hope soon to see a more detailed study. My own experiments with paraffin-containing oils have not long been published and I need not recount them. It will suffice to recall the fact that the repeated application of these oils to mice brought about the formation of tumours. Simple papillomata, frequently multiple, resulted in many cases, commencing three months after the beginning of treatment. Some of the animals, however, even after nine months, showed no neoplastic reactions. Two cases developed carcinoma in seven and seven and a half months, and two developed sarcoma in six and ten months respectively. The sarcomata arose underneath simple papillomata, probably owing to the paraffin oils obtaining access to the underlying connective tissue through fissures in the warts. These sarcomata were slow to begin, but the subsequent growth was extremely rapid. Here is an instance of two very different kinds of malignant tumour being caused by the same agent. Rats and guinea-pigs did not tolerate well the applications of paraffin oils: the irritation of their skin was severe and few lived more than nine months. None of them showed tumour growth. The experiments with rabbits have gone on now for eleven months without yielding any sign of new formation. One of the oils used which induced epithelioma in the mice was an unfinished lubricating oil, the possible dangerous properties of which no one had previously suspected. We were surprised, therefore, to have our experiments confirmed quite independently by the clinical observations of Southam and Wilson. They called attention to the occurrence of cancer of the scrotum in mule spinners, attributing it to the action of lubricating oils. I have reason to believe that cancer of the scrotum amongst mule spinners is much commoner than even their paper suggests, and we shall await with interest the results of their promised experiments with the particular lubricating oils used in the mills of Lancashire. Most of the lubricating oils in commerce are obtained from crude petroleum, and though not more than three or four cases of petroleum cancer are recorded in literature, it is probable that unrefined petroleum is just as dangerous as shale oil. It may be that the results of our experiments with petroleums, which are in contemplation, may be useful in preventing the risks, at present unappreciated, to man. Since my paper was published I have frequently been asked if the habitual use of liquid paraffin as a laxative may not cause intestinal cancer. I do not know of any clinical observations pointing that way, and, until we obtain strong experimental evidence (which we have not yet elicited) to support it, it may be wiser to stifle any uneasy suspicion.

Arsenic Cancer.

Kennaway and I in a recent communication dealt with the late Sir Jonathan Hutchinson's theory that the prolonged use of arsenic medicinally may produce cutaneous epithelioma. Nearly all the reported cases were patients suffering from psoriasis, and though most dermatologists agree with Hutchinson, there are still some who dispute the relationship, believing that even in the absence of arsenic epithelioma may supervene on psoriasis. I have seen a workman in an arsenic factory who showed pigmentation, palmar keratoses, multiple papillomata, and multiple epitheliomata coexisting together, and I learned from him that several of his fellow workmen had suffered in the same way. Probably it is commoner than we had suspected. We reported that we had succeeded in producing a metastasizing epithelioma in a mouse by repeated applications of a weak solution of potassium arsenite. Feeding experiments on rats were negative. We have repeated the experiments on several series of mice, but have failed to produce another positive result. The difficulty, which is still unsurmounted, is to keep the animals alive for the necessary length of time while applying the arsenic solution in a concentration likely to be effective. Our single success, though a matter of good fortune, yielded us the necessary experimental proof of the carcinogenic power of arsenic.

X-ray Cancer and Radium Cancer.

The epithelioma to which, in the past, radiographers and others working with Roentgen rays have been so liable is probably the clearest example we have in man of an irritation cancer. Not much more than a quarter of a century has elapsed since *x* rays came into use, and, in the earlier days at any rate, a comparatively small number of men were subjected frequently to their action. Yet the number of cases of epithelioma of the hands of these workers has been inordinately high. Of seven radiologists of long experience with whom I have been acquainted, no fewer than four developed local cancer. Now that the dangers have been realized and adequate precautions adopted, its incidence is fast diminishing and we may never see it again. The lesions, expressing themselves as severe radiodermatitis followed by irregular hyperplasia of the skin, fissuring, simple ulcerations, and wart formations, intractable ulcers, and finally true epithelioma, often multiple, occurred on the back of the hands and fingers because these were the sites directly exposed to the rays when the operator was holding the fluorescent screen. So gradual was the progression from the slightest to the most serious manifestation that we could think of no moment when a new determining factor could intervene. Whether a single *x*-ray burn of sufficient magnitude is all that is necessary, or several burns, or numerous repeated exposures to lesser doses are essential has never been satisfactorily determined, but certainly the exposure lasted for several years in the cases with which I am familiar.

No one has yet succeeded in producing epithelioma in animals by the application of *x* rays. Marie, Clunet, and Raulot-Lapointe in 1911 reported that they had subjected a series of rats to frequent but very feeble irradiations without inducing any neoplastic lesion, but in another series where they used more destructive rays a sarcoma occurred on a site which had been treated nine times during five months, the tumour developing eleven months after the last séance. This observation excited slight interest at the time. It was dismissed by the critics as a chance occurrence, the spontaneous development of a tumour unconnected with the skin lesions induced by the *x* rays, a sarcoma to which rats are prone, and not the squamous-cell carcinoma such as is found in the human subject. Moreover, it did not arise for nearly a year after the exposures had been discontinued, and only one animal was affected. I have already stated that in spite of numerous experiments I have failed to produce epithelioma of the rat's skin by means of tar applications, whilst Russell has succeeded in producing sarcoma by the subcutaneous injections of tar, and in one of his rats the sarcoma started nearly a year after the injections were discontinued. It would seem as if the rat's connective tissue was much more responsive to the action of a carcinogenic substance than its skin. Though in the human subject the malignant tumour is almost always a frank epithelioma, yet I have examined a nodule removed from a radiologist, a supposed recurrence, which I would not hesitate to call a sarcoma, and in two of the cases reported by Porter sarcoma was a favoured diagnosis. Again, the long delay after removal of the irritating agent fits in with my experiments, already quoted, on the delayed action of tar. If the experiments of Marie, Clunet, and Raulot-Lapointe could be repeated on a larger scale and gave the same result we should have to give the credit to these authors of being the first to produce cancer experimentally. Caulfeild and I failed to produce tumours by single exposures in the case of guinea-pigs, nor have we yet succeeded with thrice-weekly exposures over many months in the case of mice.

Probably the lessons that were learned of the harmful effects of unscreened Roentgen rays prevented similar accidents amongst those who have had to handle radium. At any rate, no such casualties have been reported. I have, however, seen two cases of radium warts on the forefinger and thumb, and I have heard of three cases of epithelioma in radium workers occurring on the Continent. Though I applied 6 mg. of unscreened radium bromide for ten minutes daily for several months to the backs of a batch of rats, I never succeeded in producing any perceptible skin lesion.

Tobacco Cancer.

That tobacco-smoking is one of the chief factors in setting up cancer of the oral cavity, and especially of the tongue, is an idea that has been widely held. Some have said that the lesions produced are due to the heat conveyed to the lips through the stem of the pipe or to the tongue by the smoke,

whilst others have maintained that they are due to the products of combustion of the tobacco. Still others have supposed that the noxious principles exist as such in the unsmoked tobacco and are not produced during combustion. In favour of this last idea are cited instances of malignant growths of the oral mucous membrane in tobacco-chewers, and much attention has been directed to the cancers of the cheek observed in natives of Southern India and the Philippines who chew "betel." Here, however, it must be noted that the betel preparation is a crude mixture of areca leaves, lime, and probably other substances as well as tobacco, and the effect of these accessories cannot be discounted. That betel-chewing is indulged in by millions—men, women, and children—and that the number of cases of cancer of the cheek actually observed by any one medical man seem to be surprisingly few, are points that should make us cautious in accepting this as an instance of cancer due to tobacco, or even as an example of an irritation cancer at all. Again, not a few surgeons of great experience in lingual cancer have stated that tobacco-smoking is of quite subsidiary importance in producing the lesions which, in their opinion, are the sequelae if not the result of local tertiary syphilitic infections.

I need not discuss the arguments at length, for the discussion would be as fruitless as the arguments are interminable. Can experiment help us to settle the question? I must leave aside, as too difficult of approach at present, the test of heat, syphilitic infection, and other general irritations, merely remarking that Fibiger succeeded in producing leucoplakia and epithelioma in the tongue of the rat by an animal parasite (*S. neoplastica*), and record the results with tobacco. We set up an artificial pipe where the tobacco was smoked by suction from a water pump and collected the fluid products of combustion, such as are found in the stem of an ordinary pipe. These products consisted of a brown tarry material easily soluble in chloroform or ether, and a light-coloured watery fluid which darkened through time or by oxidation. The latter fraction, tested on mice for over a year, was without toxic properties and produced no pathological effects whatever. The chloroform-soluble fraction, with the solvent driven off, had, on the other hand, both toxic and pathogenic properties. A minute trace of it applied to the mucous membrane of the tongue or of the vagina, or even to the skin, of rats and mice brought about death by clonic convulsions, usually within a minute. This poisonous effect is probably due to nicotine. By diluting the tarry fraction with acetone to 5 per cent. and afterwards gradually increasing the concentration we found that we could accustom the mice finally to the undiluted stuff. Again, we boiled the tobacco in water first of all in order to deprive it of nicotine and obtained a non-toxic product by smoking. We applied these fractions to two series of mice for many months. They produced epilation of the areas to which they were applied, and they induced chronic ulcerations, but in no single case did any neoplastic reaction result. We have thus no evidence in support of the contention that tobacco smoke contains a cancer-producing property, though we may not therefore conclusively reject the idea that there is something connected with tobacco-smoking which may be operative on the oral mucous membrane of human beings. But what is of more theoretical and practical interest is the fact that here we had a substance with a very marked irritative effect on the skin in that it produced chronic lesions and yet no tumour formation supervened. We might say that it is not a specific irritant of the tumour-producing class.

Aniline Cancer.

In the German literature much has been made of the occurrence of tumours of the urinary bladder in workmen engaged in the manufacture of aniline dyes. Though we have insufficient data to allow us to say that the incidence of bladder cancer amongst them is much greater than in the general population, the reports of its absolute frequency lead us to regard it as a particular form of cancer to which dye workers are liable—an irritation cancer of a different kind from what we have been considering. No cases have been known to occur in English dyeworks. There is no general agreement amongst the authors as to the particular chemical substance responsible for the condition, and an analysis of the reported cases with reference to the process in which the men were employed fails to reveal any definite clue. In one factory the greater number of cases may occur in the aniline department, in another the fuchsin workers would seem to suffer most, and so on. To complicate matters still further, cases have been noted in clerks and others who do not come directly into contact with any of the processes. This has led to the belief that it is something in the atmosphere. Miss Alice Hamilton, the American authority on industrial diseases, has suggested that the particular noxious substance is hydrogen arsenide, but the German experts strenuously deny that this is present in their workshops, and, as far as I know, no case of so-called aniline bladder cancer has exhibited the usual skin changes that are found in arsenic workers. Aniline, benzidine, and fuchsin are the main products that have come under suspicion. Inhaled, or absorbed through the skin, they undergo probably very complex changes in the economy, and are excreted in different combinations in the urine. It is imagined that the long-continued action of low concentrations of these end-products, whatever they may be, on the epithelium of the bladder induces villous papilloma and finally epithelioma. No other tissue of the body responds in this way to the aniline derivative: it is definitely selective in its action; indeed, the kidneys and ureters, equally exposed to it, do not show tumour formations.

If we could produce cancer of the urinary bladder in animals by applying some aniline product to the skin we would succeed in carrying our experimental inquiry to a more important stage than it has yet reached; it would enable us to demonstrate clearly the selectivity of a carcinogenic agent. So far we have given a prolonged trial to aniline, benzidine, and fuchsin, applied to the skin of mice, but in no case have we produced any neoplastic response either in the bladder or elsewhere. We have also kept series of mice for a long time on xylene and benzene, the precursors of most of the aniline substances, but here also we have failed to induce tumours. Everybody knows the irritating effect of xylol on the skin. In the case of mice its long-continued application produces epilation and that chronic scurfy dermatitis which we generally find with all the tumour-producing agents we have hitherto employed. In several cases, after the lapse of several months, we obtained what we thought were flat warts of a non-progressive character. The histological examination of these, however, showed us that there was no epithelial proliferation but merely a peculiar vitreous degeneration of the tissues of the dermis. Though the experiments, therefore, are negative as far as tumour production is concerned, and leave the question of aniline cancer as undecided as before, those with xylol especially are of value in indicating once more that all tissue irritants have not the property of setting up, or paving the way to, cancer.

Other Substances.

In addition to those I have mentioned we have tried a large number of substances which might be supposed to have an irritant action on the tissues, but they have proved altogether incapable of producing tumour formation. Thus we may tentatively claim that there are only certain specific agents which have the property of eliciting neoplastic reactions. We hope in the course of time to discover more. It will not escape notice that in all the cases in which we have succeeded in producing tumours experimentally, these tumours, epithelioma or sarcoma, are of the same structure whatever substance we employed to produce them. No one examining the final lesion could say what particular agent we used. And it might be maintained as strongly as before that some single common cause must be postulated. It does not follow. Similar acute or chronic inflammations may be caused by very different bacteria.

I must leave to some future occasion the argumentation regarding these disputed points, but even supposing our contentions that some of the substances above mentioned are direct causes of cancer be admitted, it might yet rightly be urged that they are all external irritants, that they are responsible only for a very small number of cases of cancer in the human subject, and that we have thrown no light whatever on the processes that occur within the cells to pervert them to the anarchic and progressive proliferation that we call cancer. We may reply that the demonstration that

has already been given tempts us to hope that some day we shall be able to isolate endogenous carcinogenic substances, local malproducts of metabolism it may be, which have similar effects on tissues long subjected to their action. It is true that we know nothing regarding the intimate cell processes that are set up by the irritants, but the investigation is not beyond practical methods of inquiry.

May I recall some old experiments that I did several years ago? I had a transplantable mouse carcinoma which had passed into a depressed phase: the percentage of successful inoculations was very low; when tumours did result they were very slow in their growth. I ground up some of the tumour material in fine sand in a mortar and shook this up with saline solution. A batch of mice were injected with this extract and subsequently they were inoculated subcutaneously with living tumour tissue at the same time as another untreated series of mice. The contrast between the two sets was striking: in the untreated series the proportion of successful inoculations was small and the tumours were slow in developing; in those previously treated with the extract the percentage of successful inoculations rose from 30 to 80 and the rate of growth was rapid. We had supplied something—a "growth aggressin"—which was not supplied to the controls, and we had obtained it from the same tumour tissue. Such a substance, whatever its nature may prove to be, may be produced in small amounts in ordinary wound repair: it may be produced in excessive amounts in the neoplastic reaction.*

Looking back on the great discoveries of the past, we may wonder why they were so long delayed. The essential data for a conclusion, the materials with which to build, the terrain for the advance, all were already prepared, available for everybody, and sufficiently obvious, we should imagine, to the ordinary mind. It is all so simple to us now, for we fail to appreciate the difficulties of the pioneer. A future generation, knowing surely the causes of cancer, will have no patience with our flounderings, our guesses, and our contending arguments. Had we not all the facts before us, they will say, staring us in the face, clamouring for recognition? Probably we have, but we are like children gazing at a starry sky—the stars that are so bright to us may be very small worlds and those that we barely see may be infinitely great. When we can place our facts in their order of importance, and make order out of seeming disorder, the answer will be easy. At present do we stand in respect of our subject as our predecessors stood fifty years ago at the dawn of bacteriology, and will our discoveries be as great, as rapid, and as epoch-making as theirs? I wonder.

SURGERY OF THE HEPATIC AND COMMON BILE DUCTS.†

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THE great bile duct as a whole, from the point where the hepatic duct emerges from the liver to the duodenal papilla, is discussed because the pathologic processes with which the surgeon is concerned in this special field must be treated as a whole.

In the period from December 31st, 1890, to December 31st, 1922, there were 16,980 operations performed on the biliary tract for all conditions — acute, chronic, and malignant—by the eleven surgeons on the general staff of the Mayo Clinic, with an average mortality of 2.6 per cent. Of these operations 1,920 were on the hepatic and common ducts, with an average mortality of 7.8 per cent. In the ten years from 1910 to 1920 the average mortality for operations on the great bile duct was 6.8 per cent. In 1921 the mortality for operations on the common and hepatic ducts was 5.6 per cent., in 1922 it had dropped to 3.8 per cent., while in 1922, for 942 cholecystectomies, it was 1.6 per cent.

All patients dying in the hospital following operation, without regard to the length of time thereafter or the immediate cause of death, were classified as having died from the operation. It may seem somewhat severe to classify patients as having died from operation who, when operated on, had chronic nephritis, hepatic insufficiency from biliary cirrhosis, and secondary cardio-renal disturbance, the result of months of cholaemia and duct infection, and patients who died in the hospital some weeks after operation from causes not connected with the operation. However, without an arbitrary standard of classification it is difficult to secure comparable statistics from different hospitals. Perhaps, too, there is a certain stimulation in holding to a high standard of responsibility.

A satisfactory improvement, so far as mortality is concerned, is manifest by these data. Improvement has been greater than would be apparent from a study of mortality alone, because of constantly increasing knowledge and improvement in technique. Because of a better understanding of the conditions more and more severe cases have been undertaken, and operations carried out successfully which, in earlier days, were not attempted.

Certain fundamental principles which greatly affect the welfare of surgical patients must be evaluated. They concern (1) mortality from the operation, (2) benefit from the operation, and (3) disability following the operation.

The pride of the operator and his statistical skill in honestly juggling percentages make most astonishing apparent differences in statistics which are nearly identical. For instance, the early transference of the dangerously ill patient to the medical side of the hospital because of a medical complication, from the standpoint of surgical statistics, is helpful. If operations rather than cases are counted, and a number of operations are performed on the same patient, a small series of cases may make a large series of operations. Mortality estimated by cases is high; estimated by the number of operations it is low, although the number of deaths would be the same. Again, a slight operation which does not cure will be the test in a bad case. If the patient does not react well, the curative procedure with the major operative risk, for many reasons, may not be undertaken; consequently the patient is not given the chance for cure which a primary radical operation would have given.

We study surgical tragedies and endeavour in every way to hold operative mortality at the lowest point, but the mere fact that a patient recovers from an operation is not in itself sufficient. If he does not receive sufficient benefit to warrant the risk of life, the pain and suffering from the operation itself, the expense, and the loss of time, he has just cause for dissatisfaction. On the other hand, if a more radical operation would have resulted in correspondingly greater benefit, an increase of primary risk might be justified.

The question of post-operative disability is important. A surgical procedure should be planned so that the patient, with the least possible risk and loss of time, will receive the greatest possible benefit. To-day industry is on a full-time basis, and every unnecessary day that the patient is disabled is an economic loss. To perform several operations when one would suffice, and thus deduce an apparent but not a true reduction in mortality, to use a type of incision not strictly indicated for the work at hand, or to use unnecessary drainage which will confine the patient to bed longer, or leave him with a greater hernia liability, is unjust. This economic loss is illustrated by a comparison, at ten-year intervals, of the hospital morbidity following operations on the biliary tract. The methods in use to-day, as compared with methods used ten years ago, save for each patient operated on in the clinic ten days of hospital time, or thirty-six years of the lifetime of one person each year.

The incision used in the majority of operations on the biliary passages has been the incision introduced by Bevan in 1898, slightly modified. The method of McArthur, in leaving undivided the posterior aponeurosis, the peritoneum, and the nerves in the lower third of the incision, is followed because the posterior aponeurosis, peritoneum, and nerves are sufficiently mobile to be drawn down readily by a retractor.

Secondary operations on the common duct for the removal

*Important experiments in tissue culture which are being carried out by A. H. Drew of the Imperial Cancer Research Fund may have an important bearing on these points.

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