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A MONTHLY JOURNAL OF PRACTICAL MEDICINE & SURGERY
Editor: Dr. P. R. Venkappaya.

VOL. VII

DECEMBER 1938

No. 12

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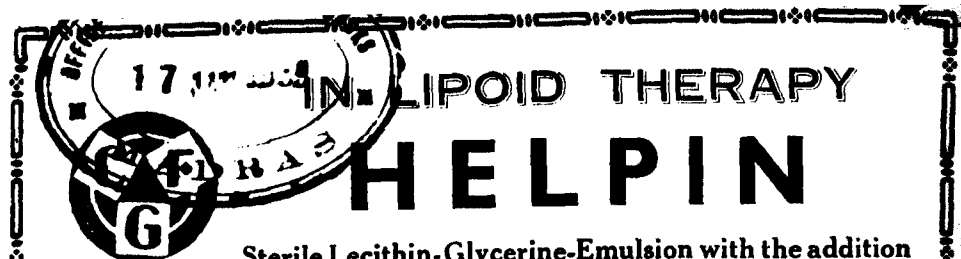
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MADRAS.

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MEDICO-SURGICAL SUGGESTIONS

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Articles.

SURGICAL PATHOLOGY OF TUMORS OF THE BREAST.

R. B. MALCOLM, M. D.

Chicago.

MAMMARY GLAND.

Embryology. The breast is composed of two embryological elements, (a) Glandular tissue derived from the ectoderm by a process of inbudding; (b) Supporting connective tissue derived from the mesoblastic subcutaneous tissue over the fascia of the pectoralis major.

(a) From the deepest stratum of the ectodermal bud arises a number of solid buds, exactly similar to those of the sweat glands. The stalks of these buds from the epithelial lining of the lactiferous ducts. Each bud forms a lobe which subdivides into several lobules, which at first solid become canaliculized, opening by a patent duct through the nipple.

(b) As the glandular buds grow into the subcutaneous mesodermal tissue they become surrounded by perilobular and periductal sheaths. The deep and superficial portions are connected with the anterior sheath of the pectoral muscle and the skin for they are all part of the same subdermal layer.

Lymphatics. During the third fetal month the skin and subcutaneous tissues become invaded by the developing system of lymphatic vessels. The periductal and perilobular lymphatics communicate through the septal or interstitial vessels with the superficial mammary and retromammary lymphatics. The superficial communicate with the subcutaneous and the deep with those of the pectoral sheath. Both of these join in the circummammary lymphatics, and from these pass efferent vessels to the pectoral and central nodes of the axilla; other efferent vessels pass from the circummammary to the anterior intercostal nodes of the upper four spaces.

Histology. The mammary gland is a compound alveolar gland consisting of from 15 to 20 lobes, each of which is subdivided into lobules. An excretory duct passes to each lobe, where it divides into

smaller ducts, which in turn open into alveoli. The alveoli are lined by a single layer of low columnar or cuboidal epithelial cells resting upon a homogeneous basement membrane. Both lobular and lobar ducts are lined by similar epithelium but as the nipple is approached there may be two layers and at the nipple the epithelium becomes of the squamous variety.

Anatomy. The mammary gland rests upon the fascia of the pectoralis major and is held in position by fibrous bands attached to the skin and the pectoral fascia. The major portion of its arterial supply comes from the external mammary artery which is a branch of the lateral thoracic. In addition there are branches from the 2nd, 3rd and 4th perforating branches from the internal mammary and also from the same level lateral branches of the intercostals. The venous return corresponds to the arterial supply.

Lymphatics. The lymphatic return corresponds to the venous return. The major lymphatic drainage passes along the vessels adjacent to the external mammary vein and thus is returned to the pectoral nodes in the axilla, then to the infraclavicular group, and by way of the supraclavicular nodes to the thoracic duct on the left side, and the right lymphatic duct on the right side, thus entering the circulation. In addition the deeper lymphatics go by way of the sternal group to the mediastinal nodes. As the lymphatics of the breast communicate with those of the pectoral fascia there may be drainage along all the fascial planes, viz. those of the pectoralis major and minor, the serratus anterior, the external oblique and even along those of the rectus sheath.

The mammary gland is well encapsulated and is enveloped by pads of fat which gives the breast its round contour.

TUMORS OF THE MAMMARY GLAND.

In the series of 250 cases the largest group is that of carcinomata of which there are 141. The benign cases number 109. There were no malignant tumors of mesoblastic origin.

Benign Tumors. The following varieties composed this group: 92 fibro-adenomata, 11 cystadenomata, 3 papillomata and 3 lipomata.

Fibro-adenoma. The age incidence in decades is as follows: 2nd 10, 3rd 45, 4th 18, 5th 18, 6th 1. The largest group occurred from 20 to 30 years when practically 50 per cent of the total appeared during this period. The clinical history in all cases was essentially the same: During the menstrual period there was complaint of pain in the breast which disappeared on cessation of the flow. The pain called attention to the breast and a tender lump was noticed, which in nearly every case was found in the periphery; there was no discharge from the nipple and the fear of malignancy was the usual cause of medical consultation. The mass was usually single, fairly firm, even nodular, freely movable, not adherent to the skin or fascia, in all cases complete excision of the tumor was done.

Histology. About 50 per cent were intracanalicular, the remainder extra. The amount of fibrous tissue varied greatly, some cases were almost pure fibroma while in others there was a marked predominance of adenomatous tissue.

Cystadenoma. 11 cases. Age incidence in decades, 3rd 2, 4th 4, 5th 3, 7th 3. Usual clinical history similar to that of fibro-adenoma. Tumor was in central portion of breast, rounded but occasionally nodular. Complete excision done.

Histology. All cases showed cystic dilatation of ducts with the presence of adenoma in the wall of cyst. In 3 cases there was a papillomatous growth into the cavity of the cyst.

Papilloma. 3 cases. Two occurred during the 4th decade and one during 5th. Each case gave a history of recurring bloody discharge from the nipple, no tumor noted by either patient or attending surgeon. Exploration of the whole breast was done and in each case a simple mastectomy was performed. Grossly each resected breast showed a centrally located tumor mass which showed a papillomatous growth in a dilated duct, the cavity of which was filled with old blood.

Histology. Marked hyperplasia of duct epithelium which is thrown into folds but with no invasion of the basement membrane. No increase of interstitial elements.

Lipoma 3 cases. Two during the 5th decade and one during the 6th. All were encapsulated fatty tumors within the substance of the breast.

Histology. Simple lipoma.

MALIGNANT TUMORS.

In this series there are 141 malignant tumors, all of epithelial origin as follows: Adeno-carcinoma 117, scirrhus carcinoma 18, squamous cell carcinoma 4 and 2 papillary cyst-adenocarcinomata.

Quadrants of Breast Involved in Carcinoma.

Upper lateral	Lower lateral	Upper medial	Lower medial
70	47	41	35

Involvement of Nipple—7.

Radical Mastectomies—130.

Cases having axillary metastases at operation—72.

Adeno-carcinoma. Age incidence in decades: 3rd 1, 4th 16, 5th 47, 6th 35, 7th 14 and 8th 4. Every phase of this condition was encountered, from one month's apparent duration to a history of a tumor for 4 years. The usual complaint was a painless lump in the breast, the upper lateral quadrant being the one most involved. X-ray examination of the thorax was done in all cases and only negative ones were operated upon. In this group 108 cases were done with resection of the pectoral muscles and complete excision of the axillary lymph nodes, the latter showing carcinomatous

metastases in 58 instances. These metastatic lesions varied in size from that of a small pea to that of a hen's egg. In a few cases it was necessary to dissect away nodes which completely encircled the axillary vein. Several cases showed extensive involvement of the pectoral fascia. The operations were performed by four different surgeons, the most radical procedure being done by the writer who consistently resected, in addition to both pectoral muscles, the fascia of the serratus anterior, the external oblique and the anterior sheath of the rectus down to the level of the umbilicus.

As noted above only nine cases in this group were not subjected to the radical operation. Three simple mastectomies were done on account of the extensive involvement, and in these cases axillary nodes were palpable but not resected and naturally are not included in the metastatic group in that no histological examination was made of these nodes. The remaining six cases were treated by x-ray alone.

Histology. The majority proved to be of the medullary type. There were six cases which were undoubtedly of ductal origin, but to avoid confusion these were left in this group. Several arose from sweat glands. We were unable to prove definitely the exact origin of many others although they were of the adenocarcinomatous variety.

Scirrhus Carcinoma. Of this variety there were 18 cases with the following age incidence: 4th decade 3, 5th 9, 6th 4, and 7th 2. This series gave the longest history of the presence of a tumor in the breast which accounts for the exceedingly high percentage of axillary metastases; 14 out of 18 cases showing axillary involvement and 2 of the remaining presenting clinical evidence. 16 radical mastectomies were done, the other 2 cases were treated by simple mastectomy and x-ray, on account of the extent of the lesions.

Histology. Areas of carcinoma cells surrounded by marked proliferation of fibrous tissue.

Squamous Cell Carcinoma. Four such cases were seen and they all arose in the region of the nipple, with extension centrifugally. No clinical diagnosis of Paget's disease was made. These cases did not show any spread to the axillary lymph nodes. Age incidence: 6th decade 3 and 7th 1.

Histology. All cases showed a typical squamous cell carcinoma arising in the region of the nipple, causing erosion in this area and then spreading peripherally along the lactiferous ducts.

Papillary Cystadenocarcinoma. 2 cases. Age incidence: 6th decade 1 and 7th 1. These were centrally placed and undoubtedly arose from an original benign lesion. No metastases noted.

Histology. Proliferating malignant papillary growth filling a cystic area. In one case there was only a small area of invasion into the surrounding tissues beyond the cystic wall.

Dissemination of Carcinoma of the Breast. Sampson Handley laid down the principles of spread of carcinoma many years ago and with slight change these principles are still accepted, viz. 1. Direct extension, 2. Lymphatic permeation, 3. Lymphatic emboli, 4. Venous emboli.

Direct extension: Under this heading can be included all adjacent invasion other than that through the lymph vessels. This was seen in this series as extensive local growth due to invasion of the surrounding areas. Extension of the tumor by this method is slow compared to the second type.

Lymphatic permeation: In this manner the spread can be rapidly disseminated to even distant parts in a very short period of time. This type means that the carcinoma cells invade a lymph channel, multiply and then obstruct the lumen causing the vessel to rupture and disseminate the tumor to other areas, a retrograde involvement may be set up and Carnett says "retrograde permeation of the trunk lymphatics is a more rapid process than permeation of the small lymphatics of the fascial plexus." As the superficial and deep lymphatics of the breast communicate with those of the pectoral fascia, extension along these planes may be very rapid and thus cause early involvement of the pectoral nodes. Over 50 per cent of the cases in this series showed metastatic lesions in the axillary nodes, only a few of which did not present an almost continuous procession along the course of the external mammary vein and lateral thoracic vein. This phase has convinced the writer that most of our cases showed permeation rather than lymphatic emboli.

Permeation of the lymphatics is undoubtedly the method by which there can be extensive spread to the pectoral fascia, the axillary and mediastinal nodes, the diaphragm, the thoracic and abdominal viscera, the lumbar nodes, the spine, the pelvis and even to the brain. Every one of these types of metastases has been in evidence in the follow-up of this series. Carnett again says "retrograde involvement of the lymphatics along the posterior wall of the abdomen extends into the pelvis long before subcutaneous permeation nodules reach the upper abdomen." In this manner there can be extensive distant involvement and yet very little can be noted near the primary focus.

Ewing, quoting Gross from 423 autopsies, placed the organs in the frequency of involvement in the order: pleura 50.9 per cent; lungs 49.9; liver 48.6; bones 20.5; brain 9.4; ovary 8; opposite breast 7.8; dura mater 5.9; kidneys, retro-peritoneal nodes and uterus 5.7 to 5.2 and other organs less than 5 per cent.

Lymphatic emboli. Undoubtedly a certain number of these cases showed this method of spread but once the emboli reach the axillary nodes the picture remains the same as the foregoing type.

Venous emboli. This type is much less common than one would imagine as early metastases to the lungs are not frequently encountered.

Summary. 250 cases of tumors of the female breast have been studied clinically and pathologically. In this series there are 141 carcinomata. (56 per cent of total.)

130 radical mastectomies were performed. 72 of this group showed axillary metastases on histological examination of nodes. (55.3 per cent of cases operated upon radically.)

The 11 remaining cases all showed clinical axillary metastases, thus making 83 cases showing histological and clinical metastases. (58.8 per cent of all carcinomata.)

In only 2 cases is there a certainty that malignancy arose in an original benign lesion.

(Illinois Medical Journal, Jan. 1938.)

X-RAY THERAPY IN CANCER OF THE BREAST.

JAMES T. CASE, M.D.
Chicago.

The literature presents conflicting statements and statistics concerning the employment of radiation therapy in connection with operation for carcinoma of the breast; and in the mind of the average surgeon there still exists considerable skepticism as to the value of radiation as well as a notable lack of understanding of the principles underlying proper technic and dosage. In every breast cancer case the clinical and gross pathological factors must be evaluated and a plan of irradiation mapped out with respect to the operative procedure, so that one knows pretty well in advance what frequency of application, what intensity and dosage, of each individual seance, what total dosage, what filter, focus-skin distance and portals are appropriate; and this course when embarked upon should be followed without interruption and only with such minor modification as reactions may indicate. Such a plan requires just as much technical knowledge, training and judgment born of experience as does the surgical procedure. Few surgeons have found it possible to spend time to acquire this training and experience in radiological applications, yet I have more than once had the disturbing experience of having a patient only a half or a third through the planned treatment series inform me that the attending surgeon had said no more treatments would be required, or that the seances might be suspended for a few weeks and then possibly resumed, or that it would be better to space out the treatments at longer intervals; or of having the surgeon call me on the telephone and blandly informing me that he thought the patient had had enough x-ray therapy! X-ray

management of breast cancer requires a thoughtfully and scientifically planned course of treatments, accurately executed.

Statistics may render great aid in the evaluation of certain methods, yet they may lead to erroneous conclusions. One must consider the source of the calculations, the material involved, the probable value of the work done. It is therefore necessary to set aside a great mass of figures offered and accept for judgment only those which come from large clinics with an abundance of controlled biopsy material, where the facilities for follow-up are satisfactory, and where the criteria for radiotherapeutic technic are strictly up to modern standards. One well known clinic recently published statistics which seemed to show that the addition of x-ray applications to surgical treatment actually shortened the life expectancy of breast carcinoma patients operated on; yet a little inquiry would have revealed that the radiological technic would be considered by most of us as grossly inadequate and that a manifest unfairness was evident in the statistical computations. For instance, it is unfair and illogical to include in the surgical statistics only those cases considered operable and to embrace in the x-ray column all cases receiving therapy, even those for early or late post operative recurrences and metastases, or those whose disease was considered too far advanced for any surgery and were sent for radiotherapy rather than have nothing at all done.

The statistics which seem most reliable originate in such institutions as the famous tumor clinics in Stockholm, Lund, Paris, London, Zurich, the Memorial Hospital of New York City and similar large institutions maintaining thoroughly efficient departments for following up end-results. The statistics from such institutions show beyond question that the five-year survivals after combined operation and radiotherapy adequately administered are nearly double the figures obtained after surgery alone. One must consider these statistical observations very seriously, for they can hardly be subject to question. The Swedish figures are particularly valuable inasmuch as the government pays the travelling expenses of patients to and from the tumor centers, for treatment and for follow-up.

Furthermore, the statistics on cases treated eight or ten years ago are hardly comparable with the results which may be reasonably expected from the treatment now being given, because of the improvements of technic and apparatus which have come about within the last decade, and yet the five-year results now available constitute facts which are not easily explained away. They leave the surgeon practically under bond to subject all his cases of mammary carcinoma to radiotherapeutic supplementary management in connection with his surgical attack.

What cases of breast carcinoma should have x-ray treatment?

1. There has been no dissension over the proposition that in those cases unsuited for surgery x-ray therapy is clearly indicated. This group includes not only cases where an otherwise operable tumor is not submitted to surgery because the patient refuses operation or because other co-existing disease renders operation out of the question, but also cases with fixation of the breast tumor itself to the chest wall, supraclavicular glandular involvement, definite involvement of the opposite axillary nodes, diffuse subcutaneous nodules, diffuse inflammatory carcinoma involving a considerable skin area, pleural or mediastinal metastases or more remote metastases. Life expectancy is usually materially prolonged where proper irradiation is given in such cases. In a few instances little benefit is seen, and some patients may be damaged by over-treatment so that life is shortened and suffering increased. On the other hand the great majority are benefited and live from one to five years longer than would be possible without radiation, with partial or complete relief from suffering over a considerable period. I have seen metastatic bone involvement, even so severe as to render the patient a helpless bedridden wreck, restored to normal and the patient enabled to resume her usual activities for as long as five years. Such palliation is infinitely worth while even though obtainable in a minority of cases. Adair reported 37 patients treated by irradiation alone with 36 per cent alive over five years. Even metastases to the lungs and pleura do not contraindicate palliative efforts by radiotherapy.

2. Cases operated on but showing signs of inoperable recurrence offer no favourable field for radiotherapy and yet all authorities join in agreement that the application of x-rays or radium or both is the only recourse. A small non-adherent skin lesion or a small movable nodule may be looked upon as operable if no other evidence of disease is found, and it is justifiable to remove such a recurrent nodule, giving irradiation before and after the excision. Wide dissemination of the recurrence must be assumed if several such lesions are present and in such cases attempts at operative relief are surely futile. If very advanced breast recurrences are present, one may only hope for such relief of suffering as may be obtained by adequate doses of pain-relieving drugs and frequent dressings of any foul ulcers to satisfy the patient that treatment is still in progress. Of those cases of recurrence in which, with reason, something favorable might be anticipated from palliative radiotherapeutic efforts, about 25 per cent will be alive and in comfort three or four years later. These patients must be kept under constant observation and general health upbuilding measures. Some of my cases have maintained their normal home and social activities for more than five years after the discovery of the first osseous metastases. Particularly striking improvement has been observed in several cases

of disabling metastatic involvement of the lumbosacral spine, where complete recalcification has taken place with restoration of normal function. In a few cases collapsed vertebral bodies have recalcified in their compressed form and have become symptomless.

3. In the primary operable group an increasingly large proportion of surgeons have recognized the value of radiotherapy as an adjunct to surgical attack on breast carcinoma. Many believe that if properly administered x-ray therapy is useful after operation to prevent or discourage recurrence, those very arguments for post-operative prophylactic treatment indicate the value of pre-operative radiotherapy.

Statistics concerning postoperative radiation following breast operation are difficult to analyze, for the results depend upon a number of factors: (a) whether operation was radical or only resection of the breast itself; (b) whether the tumor was non-adherent without palpable lymph nodes; (c) whether the tumor was non-adherent, but palpable lymph nodes were present which on section showed carcinomatous invasion; (d) whether the tumor was adherent and lymph nodes involved; (e) whether there was a large adherent tumor with enlarged supraclavicular nodes and skin ulceration.

In the group of simple tumor without adenopathy, which comprises only five or ten per cent of cases coming to our clinics, results are excellent by surgery alone or combined with radiation. The difficulty of being sure not to over-look small but involved axillary lymph nodes is so great that one cannot depend on palpation, even at operation, to exclude them. In spite of good results in this favorable group from surgery alone, it is our opinion that associated radiotherapy should not be omitted. Anschütz found nearly 30 per cent of ten year cures in this group by routinely combining post-operative x-ray radiation with surgery. In the other groups no one denies the indications for postoperative irradiation.

The value of pre operative radiation therapy.—The case for pre-operative irradiation is growing stronger as statistics accumulate. In the Radiumhemmet at Stockholm since 1921 preoperative therapy has been employed in many cases, as well as the postoperative treatment; and the tendency to preoperative treatment is steadily increasing. In one section all breast cancers have for several years been receiving preoperative treatment. The aim is to act upon the neoplastic tissue, its surroundings and possible metastases. The hope is to establish a diminution of the perinodular infiltration thus facilitating radical operation; to cause attenuation of the neoplastic virulence thus reducing the danger of operative dissemination of tumor particles; and to initiate by irradiation a certain resistance in the body against latent metastases in an early stage of development. This latter hope has some good foundation

in clinical observations. The plan of treatment is such that the least possible damage will result to surrounding and underlying tissues, and to cause a minimum of systemic upset. Tangential radiation is utilized where possible. The tumor often disappears entirely, and in the majority of cases it diminishes considerably. Our tendency has been to increase the intensity of our dosage, but to extend it over a longer period of time.

Under this mode of adequate intensive prolonged pre-operative therapy, some apparently inoperable cases become operable. In a case where surgery is planned I never consent to give the pre-operative series without having the patient's promise to go on with the surgery as planned by the surgeon who refers me the case; and plans are made for possible further irradiation after recovery. I believe a radical operation should always follow such an irradiation series, no matter how completely the lesion may seem to clear up. A lapse of time is needed after terminating the pre-operative irradiation before proceeding to the surgery. This period has been gradually lengthened year by year. The best time for the operation is forty to sixty days after the termination of the x-ray treatment, to allow time for the return of the skin to normal and to permit full development of the perinodular fibrosis and other biological changes upon which the favorable results depend.

Just before he died Bloodgood was unceasing in his efforts to advocate pre-operative irradiation of breast cancer. He urged that there is no danger whatever in giving pre-operative irradiation to clinically operable breast cancers, and no danger in delaying the complete operation from two to three months devoted to a thorough course of irradiation. The majority of surgeons are willing to give irradiation a trial in hopeless and inoperable cases but there is an increasing number of surgeons who feel that the moment pre-operative intensive irradiation begins, the danger of delay is averted, so there is ample time for a carefully planned course of treatment with x-ray and an appropriate further delay of eight to ten weeks before the surgery is done. There is good ground for believing that if there is no existing internal metastases there is very little danger of its occurring or of further axillary gland involvement after properly performed pre-operative irradiation.

Bloodgood in 1935 stated: "At present, throughout the entire world, the modern and efficiently trained operator fears and wishes to avoid any delay the moment the diagnosis of cancer of the breast has been made, clinically or at biopsy. Apparently we have evidence to conclude that this is based upon fear and not on facts; and on the most careful study of my cases up to date, my entire evidence confirms the statement that there is no danger from further delay if the time is taken for proper pre-operative irradiation." "Of course, all the clinically malignant cases

are now irradiated first, no matter what the degree of malignancy may be."

All clinically benign or doubtful tumors should be excised and sent to the laboratory. Unless they are distinctly benign, irradiation should be commenced at once while waiting for the decision of the several pathologists to whom sections are submitted. When cancer is diagnosed the irradiation is completed before the radical operation is performed. When the sections show a benign lesion irradiation should be stopped, of course and no harm has been done.

Bloodgood further stated: "I am convinced that we have sufficient evidence to demonstrate that closure of the wound after the excision of a tumor of the breast and thorough pre-operative irradiation promise the patient more, even when the axillary glands are involved, than the immediate complete operation without irradiation. There is sufficient difference of opinion, however, and both procedures will be followed in various proportions by the different operators of the civilized world. Those who give pre-operative irradiation, with and without preliminary biopsy, are at present in the minority, but their number is gradually increasing, and those who are proceeding with immediate operation, because of the evidence of a distinctly malignant tumor, although still in a majority, are diminishing in numbers."

It must be admitted that a third of a century of breast surgery leaves us without great hope that the present percentage of five- and ten-year cures will be appreciably raised by any modification of the present highly developed surgical technic. On the other hand there has been a steady increase in percentage of five- and ten-year survivals when to the radical surgery is added the steady improvement in radiotherapeutic technic. Dosage measurements are now precise, whereas a decade ago we had no accurate means. Marked advances have been made in our knowledge of the effects of radiation and in the technical application of x-rays and radium. Both have their field of usefulness. The radium is especially valuable in the treatment of local nodules, the x-rays for a well-distributed homogeneous radiation effect.

The use of radiation therapy either before or after operation for breast cancer, by all our modern concepts means a prolonged therapy which is also more costly than the relatively simple and short treatment courses of twenty-five years ago. In the early days we could use any diagnostic x-ray apparatus with a filter of aluminum and we soon had given enough x-ray to tan the skin. Any definite skin reaction approaching vesiculation was feared. Dosage measurements were rather unsatisfactory and empirical methods of dosage estimation made all of us over cautious. Today we realize that a good result requires the delivery into the disease-bearing tissues and

into the potential avenues of cancer dissemination of a dose several times that required to kill epithelial cells. To accomplish this requires high voltage of at least 200 peak kilovolts; high filtration with copper or silver or equivalent; longer focus-skin distance; very carefully chosen treatment portals with protection of surrounding parts; and a consequent enormous increase of the intensity of the radiation. The result is a great multiplication of the expense and prolongation of the time which the physician radiologist must personally devote to each case. The period of treatment, taking our hint from Regaud and Coutarc's success in head and neck tumors, is usually spread out over twenty-five to thirty or more sances, given daily or as nearly so as the patient can tolerate. There are great individual differences in susceptibility to radiation, to which the plan of radiotherapy must be adapted. I now routinely employ a combination of the saturation dose method of Pfahler and the fractionated dose method (Coutard) in all my pre and post-operative breast irradiation.

Pre-operative irradiation, by this plan, really requires a rather definite diagnosis of cancer. Though I have not seen any harm result from pre-operative intensive x ray therapy given in a case where later surgery showed the lesion to be benign, one feels considerable chagrin over the unnecessary effort and expense. Ewing, Adair, and others at the Memorial Hospital have devised an aspiration biopsy method which they consider satisfactory.

There are some distressing complications, such as pneumonitis with fibrosis and in some cases anemia, but fortunately they are not frequent, and in the majority of cases recovery takes place spontaneously. It is well to watch carefully for them and to take such prophylactic precautionary measures as may be indicated.

Ample statistics from reliable sources now show that at the end of five years with no treatment 12 per cent of breast cancers will be alive; surgery alone promises 35 per cent cures and surgery with irradiation 55 per cent cures. Is it not then proved that every surgeon is dutybound to associate radiotherapy with his surgical attack on this serious disease?

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SERUM, ANTITOXIN AND DRUGS IN THE TREATMENT OF MENINGOCOCCUS MENINGITIS.

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HISTORICAL DATA.

Serum therapy in meningococcus meningitis had its beginning with Jochmann in 1906. He immunized horses and treated 30 human cases of meningitis with their serum. Results were so encouraging that he expressed the belief that serum might prove a useful means of combating the disease.

In 1913 Flexner reported the treatment of 1,300 cases with serum with a mortality less than half as great as that prevalent during that period. The importance of the serum being polyvalent was stressed by Dopter and by Wollstein who had found that meningococci were not all alike serologically.

The importance of polyvalency was emphasized further by the intensive work done during the World War when meningococcus meningitis was so prevalent in the army camps of France, England, and the United States. Out of this work grew classifications of meningococci into two broad, main groups. The French (Nicolle, Debains Jouan) referred to these as A and B; the British as I and II (Griffith; Scott). Then Gordon and Murray subdivided these two groups, by absorption of agglutinins, into I, II, III, and IV. The Gordon-Murray classification has come into use in practically all Englishspeaking countries, while the French A and B classification is more commonly used on the Continent of Europe. No confusion need arise if it be remembered that the French A represents the Gordon-Murray I and III, and that B represents II. Too little is known of IV to be sure of its relationship, although it is apparently quite distinct in this Country.

It was during the World War period that the value of antitoxic as well as antibacterial properties in serum was emphasized by Gordon.

From 1918 to 1928 there was relatively little meningitis, and the cases were mostly sporadic. There was a general feeling that serum therapy was on a satisfactory basis.

In 1928, a severe wave of meningococcus meningitis appeared on the West Coast of the United States and moved slowly eastward. Evidence indicated that this wave had its origin in China and that it reached the United States by way of the Philippine Islands. In these outbreaks, serum proved very disappointing. Mortality remained high. Many physicians felt that serum did no good at all

TESTS OF THE EFFICACY OF SERUMS.

To what could this apparent failure of a method of therapy which had once seemed so promising be attributed? In order to find an answer to this question it seemed imperative to find a more satisfactory way of evaluation, serum before it was released for distribution. "What constitutes a good serum?" is a question that can be answered only when a good serum can be recognized as such before the therapeutic test is made.

Efforts to determine the value of serum had been made from the very beginning of its use. Jochmann protected small laboratory animals before he gave serum to patients. Flexner and Jobling did likewise. A general impression developed among workers in this field that laboratory animals, other than the monkey, were not susceptible to infection with meningococci, that death among them was due to endotoxins which gave irregular results, and that, in consequence, a protection test for standardizing serum was not feasible. Bacteriological knowledge has developed rapidly within the last few years, and modern aids to technical skill have made many things easy that were formerly difficult. We know now that very virulent meningococci may often lose their virulence within a few days after isolation, and that stock cultures kept in laboratories may lose specificity and antigenicity as well. These factors were all involved in complicating the problem of satisfactory standardization of antimeningococcic serum upon a protection basis. It was largely due to this situation that the mouse-protection test, worked out by Hitchens and Robinson in 1916, was not more successful in other hands.

Thus test-tube methods came into use. The agglutination test became generally adopted. Such a standard is arbitrary, but it has served a two-fold purpose: (1) It indicates that the horses responded to injection by producing some kind of antibodies, and (2) it shows polyvalency. Evidently there are other factors involved and such a test does not tell enough.

During the last decade it has been shown (Branham and Lillie; Zdrodowski and Voronine; Zdrodowski and Golinowitch) that meningococcus infection can be produced in several types of small laboratory animals if cultures of sufficient virulence are used. Intracisternal injection of rabbits and guinea-pigs with relatively small doses of very virulent meningococci is followed by a typical acute meningitis. It has been impossible to protect these animals (Branham and Pabst) because horse serum is very toxic for them when it is given by the intracisternal route, and it has thus far proved ineffective by other routes. With mice, however, intraperitoneal injection is followed by a generalized infection (Miller; Branham; Rake; Mishulow and Melman; Cohen) and they can be protected against such infections by immune serum. Different lots

of serum vary widely in protective action, although the agglutinin content of all may be high.

Virulence in meningococci is transient, and therefore frequent changes in cultures used in such protection studies have been necessary. Recently, Miller has found that suspending meningococci in a solution of mucin emphasizes any virulence which such a culture may possess, so that with very virulent strains as few as 2 to 10 meningococci may produce a fatal infection. This technic makes it possible to use a given culture over a long period of time and increases the possibility of standardizing such a method sufficiently for its use in evaluating sera. Such a small minimal lethal dose makes a more accurate titration of serum possible. With so many variable factors, i.e., mice, virulence of culture, lot of mucin, and variation in serum, reliable standardization of such a protection test is not easy, but until that is done it is impossible for a comparison of results obtained in different laboratories to be accurate. Nevertheless, the fact that many sera protect mice so well, whereas others do not, may be considered as valuable information, although the relation between mouse protection and human protection is not yet established. Steps toward working out a standardized mouse-protection test have been made. Mishulow, Cohen, and Rake have published preliminary reports in this field.

ANTITOXIN.

Within the last few years an antitoxin for the treatment of meningococcic infection has been developed by Ferry, by immunizing horses with toxic filtrates of broth cultures of meningococci. Some excellent results have been reported to have followed its use (Hoyne, Banks). Various lots of antitoxin undoubtedly vary in efficacy, as do the various lots of the usual antibacterial serum, and this will result in conflicting reports of its value until such time as its standardization becomes more satisfactory. Toxin-antitoxin neutralization has not been demonstrated successfully in laboratory animals, nor do the antitoxins contain sufficient demonstrable antibodies to allow the use of arbitrary test-tube methods. On the other hand, many lots of antitoxin protect mice well against meningococcus infection. Thus far the only method of standardizing the antitoxin is by the partial neutralization of skin tests in human beings. The ideal serum should perhaps be both antibacterial and antitoxic.

METHODS OF ADMINISTERING SERUM

After a good serum has been prepared and standardized, how should it be given? There has been much discussion on this question and it is difficult to observe any rules, since any case may seem to be a law unto itself. This probably accounts for the fact that the person who is most successful in treating meningitis is usually the person who has had to handle a great deal of it. All are agreed that much

depends on its being given as early as possible. Intraspinal therapy has long been most common. Its chief advantage has been that it enables the serum to come into direct contact with the meninges. If, as is commonly thought, the serum acts directly on the meningococci, this would indeed seem to be the most rational mode of administration. Some physicians feel that the serum does not always reach the infection, and that with a purulent and viscid spinal fluid the serum remains in the spinal canal where it was injected and is drawn out again when the next spinal tap is made.

A factor often overlooked is the toxicity of horse serum for the meninges. Acute and fatal meningitis is produced in guinea-pigs and rabbits by intracisternal injection of very small amounts of many normal horse sera. There are instances on record of "aseptic meningitis" following intraspinal injection in human beings. A really excellent serum may apparently do so much good that the irritation that it causes may be a minor consideration, but if such serum therapy is carried on too long the continued irritation may delay the patient's recovery. According to some very excellent clinicians it is almost as important to know when to stop giving serum as to know when to start it.

Intravenous serum therapy, both in combination with intraspinal therapy and alone, is being used more and more often. Since meningococcus meningitis usually begins as a septicemia and usually with evidence of a severe toxemia, intravenous administration of serum would seem to have a rational basis. The usual procedure is to dilute the serum greatly with physiological saline or glucose solution before injecting it intravenously, and some physicians make it a rule to add adrenalin also. Since meningitis patients often become very dehydrated this large amount of fluid serves an additional purpose. Caution is exercised in administering serum by this route until it has been determined that the patient is not hypersensitive to horse serum.

Since it is not entirely certain how much of the serum that is given intravenously reaches the meninges, a combination of intravenous with intraspinal therapy is most often employed. But some clinicians are warm advocates of the intravenous method alone. They believe that by avoiding the irritating effect of serum on the meninges lumbar puncture to relieve increased pressure does not have to be done so frequently.

VALUE OF SULFANILAMIDE

Since sulfanilamide and its related compounds have been shown to be so useful in streptococcus infections, its effects upon other microorganisms have been investigated. Buttle, Gray and Stephenson Proom, and Rosenthal, Bauer and Branham have found sulfanilamide to exert a marked curative action in mice infected with meningococci. Disulfanilamide prepared by Bauer has been

found to be more effective than sulfanilamide, and less toxic although less soluble.

A comparison of the curative action in mice of sulfanilamide with that of polyvalent antimeningococcic serum has indicated a marked difference in individual strains of meningococci. With some strains the drug was more effective; with others the serum was more effective; and with still others the drug and the serum were equally effective. This led us (Branham and Rosenthal) to investigate the combined action of the drug and serum. It was found that with all strains of meningococci that were tested in mice the combination was far more effective than either alone. The curative action was more than could be accounted for by the sum of the effect of the two agents—there seemed to be some kind of synergistic action. These observations have been confirmed by Brown.

Several reports of the successful use of the drug alone in clinical cases of meningitis have appeared in recent journals. No reports of cases treated with both drug and serum have yet been published, but such treatment is being used in several places. I have seen at least 15 cases and have been told of others in which this combined therapy has been employed, and the results have been very promising. Among these 15 cases there was 1 death. This patient was 50 year old man with heart complications who was admitted to the hospital in coma from which he never aroused. Before allowing ourselves to become too enthusiastic about the clinical use of this combined drug and serum therapy we must remember that this is not an epidemic period and that relatively mild cases are to be expected; and that, with the exception of the 1 fatal case, the patients receiving this treatment were in a decidedly favorable age group, i.e., 12 to 25 years old.

CONCLUSIONS

It is becoming more and more evident that it is necessary to use cultures of meningococci which are good antigens in order to make good serum. The best antigens may not necessarily be the most recent or the most virulent strains. Just how such strains are to be chosen is a subject of much study at the present time.

Some better way of standardizing serum than the commonly used agglutination test is important. Good sera do seem to have a high agglutinin content, but not all good agglutinating sera have an equally useful effect therapeutically.

At the present time a mouse-protection test seems promising. There are so many variable factors involved in such a test that standardization of the technic is difficult but will be necessary if such tests are to be compared with each other.

The relation between the protective action of any given serum for mice and for man can be known only through the help of the clinician. Every lot-number of serum is different. Each represents

a pool of serum in different proportions from several different horses. Each has passed the standardized agglutination test required by the United States Government for its release for distribution. But all do not help the patient equally. Sometimes one will be more helpful in one case, and another in other cases. Occasionally, one will seem particularly good with all patients. What constitutes this difference? These serums are now all being subjected to intensive laboratory study. If the clinician can require the lot number of every serum used to be recorded on his patient's chart as a matter of record, much useful information about the clinical value of the serums may be obtained, and compared with the laboratory findings. Through such a collaboration we may perhaps some day find out just what constitutes a good antimeningococcus serum and how to make it.

At the present time it seems likely that certain drugs may prove to be useful adjuncts to serum in treating meningococcus infections.

(*Medical Annals of the Dist of Columbia, Jan 1938*).

OBSERVATIONS ON ANESTHESIA IN EUROPE IN 1938.

BY J. S. LUNDY, M.D.

Section on Anesthesia.

During the voyage on the Rex I had the opportunity of making a tour of inspection with the ship surgeon, Dr. Gullini and learned that he uses only ether or spinal anesthesia for operation. I was informed that the intravenous injection of 1 mg. of atropine gives almost instantaneous relief of seasickness.

I went to Rome where I visited the Policlinic of the University of Rome as the guest of Dr. Frugoni who is the editor of *Il Policlinico*. He investigates the condition of his patients on a scientific basis from the aspect of physics and chemistry, and all the other known aids. I visited the clinic of Dr. Alessandri and saw him remove a gallbladder under spinal anesthesia. The spinal anesthetic consisted of 40 mg. of tutocain and 0.25 mg. of adrenalin. Five minutes before the intraspinal injection 50 mg. of ephedrine had been given intramuscularly. If untoward reaction should develop during operation, 100 mg. of caffeine or 1 c.c. of cardiazol would be administered. Sometimes as much as 3 c.c. of cardiazol is given intravenously. I was told that they have 2 per cent failures in spinal anesthesia and when failure occurs, ether is given by the open drop method. The only untoward effect subsequent to spinal

anesthesia was headache which occurred in about 25 per cent of cases. They treat headache by further lumbar puncture. In 1 per cent of the patients who have headache the headache is severe. Neither pantocain nor nupercain is used because of unsatisfactory results. For intravenous anesthesia which is used for minor operations only they give 10 per cent eunarcon, never using more than 15 to 20 c.c. They do not use the soda lime absorption technic and find cyclopropane expensive; no doubt for that reason they prefer ether administered by the open drop method. The surgeons give transfusions of blood by the direct method, using from 250 to 800 c.c. but the larger amounts are seldom used. The smaller amounts of blood are frequently used in the postoperative period. Intravenous solutions of saline, dextrose, and so forth, are prepared in the hospital pharmacy, and are administered either by gravity or positive pressure method. In dentistry block anesthesia is used, and in obstetrics anesthesia is employed in the operative cases but not in normal labor. The smell of wood alcohol is very noticeable throughout the operating rooms. They have in the operating rooms a German device for heating ether vapor, but they prefer the cone and drop method. The airway most frequently used is a wire one.

Dr. Puddu took me through University City and the new public health building. I saw a fine new microscope that projects the field on a screen and can be used for photomicrographs with any kind of colored light or adjustment. In Dr. Frugoni's clinic one of his assistants, Dr. Corelli, has been investigating other substances than sodium citrate as anticoagulants, and recommends the use of his new preparation, the results of which he will publish soon. Refrigerated blood is kept at 4° C. and it can be used for twelve days. It is given slowly by the syringe method. They think that the physical, chemical and biologic properties are preserved by their particular anticoagulant with less dilution than with citrate, and they believe there are fewer untoward reactions with this than with citrated blood. In the new museum of the newest chest hospital in Italy one of many babies and fetuses exhibited showed an ectopic heart which had been studied by Dr. Puddu with the electrocardiograph. He thought it the first time this had been done with the human heart. The baby lived three days. Dr. Ascoli, the hospital surgeon, is about to introduce intratracheal positive pressure gas anesthesia in intrathoracic operations.

Dr. Bastianelli operated on a middle-aged heavy man for a tumor of the left vocal cord while I was there. Preliminary medication was pantopon 1 c.c. and scopolamine 1 c.c. (Sometimes 2 mg. of dilaudid is used instead of pantopon for preliminary medication.) Anesthesia was induced by infiltration of 1 per cent solution of procaine. The patient slept part of the time. After the wound was closed, the patient sat up for dressing and saluted the doctor. After

the operation he told me that he had used intravenous ether anesthesia thirty years ago when Dr. W. J. Mayo visited him.

In Florence I visited the Ospedale di Careggi and met Dr. Torrigiani who showed me his electrically lighted microscope for use at operations. He is enthusiastic over the minute structures he can visualize and operate on with the magnification available through this instrument as compared to ordinary vision. It is especially valuable, he says, in operations on the mastoid. He uses pentobarbital sodium and also dilaudid for preliminary medication, and ether as a general anesthetic in some cases. He uses local anesthesia in a great many of the cases, and wherever possible preliminary medication is given also.

In Milan I called on Dr. Donati at the Princes Yolandi Hospital. In this hospital was the first four-gas machine that I had seen in Italy. It is made by Brambilla and is similar to the Foregger machine. It has no soda lime absorber. Blood transfusion is done by using a German receptacle made of Athrombit. This transparent container has a double wall which holds warm or hot water, keeping the blood warm. The inside surface which contacts the blood is perfectly smooth and blood does not coagulate for twenty minutes. I visited the University of Milan Policlinic and met Dr. Pagliano, and was taken around by Dr. Radici of the surgical clinic. They have two new gas machines, one for four gases and one for two, both made by Brambilla.

I had a visit with Dr. Dogliotti from Modena, Sicily, who had come to Milan to perform a therapeutic alcohol injection. He informed me that one of the younger men will attend the meeting of anesthetists in New York in October, 1938, and will speak on the use of heated ether vapor, and also on the use of mixtures of anesthetics which some of the Italian clinics are trying.

In Venice I met Dr. Protti, who was president of the local medical society. He gave me a letter of introduction to the city hospital which I visited.

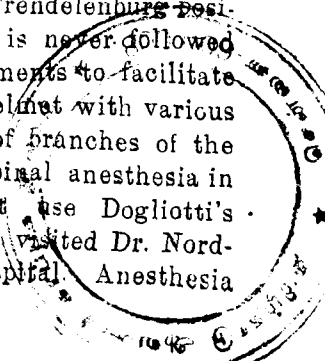
In Budapest I visited Dr. Adam at the University Hospital. He had many operations listed for that day. His first case was operation for goiter. He used 1:1000 pantocain by injection and deep block of the second cervical nerve. There was no pain except when there was traction on the gland. He used plenty of solution. Preliminary medication was barbital mixed with two other sedatives. The face of the patient was draped by using an ordinary sterile wire ether mask with a long piece of gauze to cover the face and head. For an operation for posterior excision of the rectum, anesthesia was produced by an assistant by field block around the rectum. Some of the solution was injected anterior to the sacrum and the patient was in the extreme lithotomy position. The injection was long but the patient did not seem to mind. The patient had been

given 2 mg. of pantopon before operation. This drug is not used for goiter cases. Dr. Adam does not use scopolamine. He has used local anesthesia 30,000 times and prefers it to general anesthesia. After infiltration Dr. Adam waits five minutes by the clock before making the incision and sometimes prefers to wait ten minutes. If the patient will not co operate at all he uses ether by the open drop method. In this hospital I saw a Haertel gas machine made in Berlin. It is seldom used. Transfusion of blood is done by the direct method and citrate is never used.

In Vienna I visited the Strauss Laboratories for a demonstration of the Kardiotron, a device which shows the pulse rate on a dial, blood pressure, and volume of respiration. It is operated by using a blood pressure cuff on the arm and long rubber tubings. The pulsation of the air is transmitted to a diaphragm which in turn presses on a Piezo crystal. The current is amplified electrically and the dials are calibrated to give the proper readings. Depth of respiration is shown in number of cubic centimeters per inspiration by using a mask containing a warm wire, which undergoes cooling with each respiration. Change in temperature is transmitted to the calibrated dial. There are two lights, the green one for large volumes of respiration, and the red one for small volumes of respiration.

I visited the St. Elizabeth Hospital and saw a vaginal hysterectomy done under infiltration of the perineum. Preliminary medication was dilaudid and scopolamine. In the same hospital I was informed that they do not use anesthesia for normal labor. In Dr. Denk's clinic I visited Dr. Frederick who was greatly interested in local anesthesia.

In Berlin I found that the German Surgical Congress had just closed and the Pharmacologic Congress had just opened. I attended a conference in the morning, together with Dr. Killian and Dr. Schmidt. The speakers were Professors Schaumann, Hochst, Kirschner, Heubner, and Flury. The discussion was on local anesthesia and thoroughly covered the fundamentals of the subject. Dr. Kirschner spoke at some length of his own methods of anesthesia, especially spinal anesthesia. He removes spinal fluid and injects air first, then the solution of nupercaine, and puts the patient in various degrees of Trendelenburg or reverse Trendelenburg position to get his results. He said that this method is never followed by headache. He has developed various instruments to facilitate his work. One of these devices is a metal helmet with various adjustments for guiding the needle for injection of branches of the fifth cranial nerve. He has used his method of spinal anesthesia in 5,000 cases and recommends it. He does not use Dogliotti's peridural method of anesthesia but described it. I visited Dr. Nordmann's clinic and the new Martin Luther Hospital. Anesthesia



there was the same as in the other hospitals. For local anesthesia procaine is employed. For general anesthesia eunarcon or evipal given intravenously or ether given by the open drop method is used. No chloroform is used and little gas, and then only nitrous oxide, oxygen and ether. For children alcohol, chloroform and ether mixture is employed. They do not use the intratracheal method. Transfusion of blood is done by the direct syringe method. The reason given for the lack of new things in inhalation anesthesia was that of expense and also that no individual is particularly interested in anesthesia until the time he must come to operation himself. In this hospital no anesthesia is used for normal labor.

Among many new things in Germany to which my attention was called was the manufacture of artificial albumin and the manufacture of clothing out of material similar to paper. I was also told that the number of degrees in a circle had been changed from 360 to 400, which they feel is a long needed correction.

In Hamburg I visited Dr. Nestmann at the University Hospital and also met Dr. Robbelen. They use scopolamine, eukodal and eponinin. They use pantocain or procaine for block and infiltration anesthesia and pantocain for urethral anesthesia. For spinal anesthesia they give pantocain for low operations and procaine with corbasil for high operations and for intravenous anesthesia, evipal or eunarcon. They use some vinesthene (divinyl oxide) for short operations and like it especially for children. They use also chloroform, ether, ethyl chloride, avertin, nitrous oxide and oxygen. Their carbon dioxide absorber is not the type used in the United States. They use both the Draeger and Haertel machines. The combination of local and gas anesthesia is not popular. Transfusion of blood is done by the citrate method. Occasionally they use the direct syringe method.

I saw one patient undergo a gastric operation; anesthesia was with nitrous oxide, oxygen and ether. The arrangement for adding ether is a device by which the ether is siphoned from a container and is added to the mixture of the gases a drop at a time. The rate of dropping is visible.

In Lubeck I visited the Draeger works and saw several models of gas machines which are manufactured there, gas and ether machines for dental and surgical cases and several models for the administration of oxygen and carbon dioxide. In one gas machine a device for artificial respiration is incorporated. The rate of respiration is controlled by hand. I also saw a new steel cylinder which is 60 per cent lighter and holds 80 per cent more gas than the old heavy ones that we use.

In Brussels I met Dr. Pierre DePage, Dr. Coryn, the surgeon, and the anesthetist, Dr. Enderle. We discussed anesthesia; it is carried out in a manner similar to that which I had seen elsewhere

on the Continent. Concerning transfusion of blood I was fortunate to find that Professor Hustin of Brussels was actually the first to publish a report of the transfusion of blood using the citrate method.

In Paris I was met by Dr. Sanders, formerly of Boston, who is specializing in general anesthesia. I visited the Ambroise Pare Hospital and there met Dr. Desmarset and Dr. Jacquot, who are editors of the French journal of anesthesia. Unfortunately Dr. Monod was ill and I did not meet him, but he is planning an international congress of anesthetists to meet in Paris in 1940. He hopes to have as many representatives as possible from the United States. At the American Hospital I saw Dr. deMartel operate and met Dr. Gros, the chief surgeon. Dr. Sanders administered cyclopropane, using to and fro breathing through the soda lime absorber. Little preliminary medication had been given and that only fifteen minutes before operation. Induction was carried out slowly which made it safe, and I was pleased with the technic. At the Leopold-Bellou Hospital I met the French anesthetist, Dr. Amiot, who has invented his own device for inhalation anesthesia. This consists of three bags. One of the bags near the mask contains loose soda lime. Cyclopropane was used, induction was smooth, and light anesthesia was maintained. There was no ether device on the machine so that to add ether he moistened a piece of gauze and dropped it into the breathing bag on the machine. I visited the Laennec Hospital, and there met Dr. Welti, surgeon, who has visited in Rochester and who is hoping to visit here again shortly.

In London I visited with Dr. Halliday, the principal of King's College, and his sister, Mrs. Constance Black, who is an anesthetist. I visited the Brompton Hospital and saw Mr. Edwards perform a thorocoplasty for tuberculosis on a fat middle-aged man, who was a very poor risk. Dr. I. W. Magill was the anesthetist and he used 250 mg. of 5 per cent pentothal sodium to induce anesthesia and maintained anesthesia with cyclopropane using the soda-lime absorption method. He used a small canister so that he can use a fresh one for each patient. He was using a Guedel black rubber airway and a headstrap of his own design on which was an extra strap for supporting the chin. I visited the London Clinic.

At the Gordon Hospital for Rectal Diseases I saw Mr. Abel and Dr. Jarman using narkogen, a new thiobarbiturate from Germany. It does not seem to me to be as potent as pentothal sodium or so useful in the cases in which I saw it used.

In Birmingham I met Dr. W. J. McCardie, said to be the senior practicing anesthetist in the British Empire. He has a wonderful collection of old English books and gave me an autographed reprint on ethyl chloride as a general anesthetic, published over thirty years ago, which he says is the first article in English on the subject. I visited the General Hospital of Birmingham and saw

Mrs. Sanders anesthetize a six-year-old child for pneumonectomy. The surgeon was Mr. Scott Mason. I met Mr. Stammers, the neurosurgeon, who had part of his training in Rochester. I stayed at the home of Dr. and Mrs. Featherstone. He is the leading anesthetist of Birmingham and the backbone of organized anesthesia in England.

Back in London again I visited the Royal Free Hospital and saw Mr. Joll operate on several patients for goiter. The anesthetic was carried out by Drs. Morris and Goldman, and their assistants. They use intratracheal nitrous oxide, oxygen and ether for goiters, or ethyl chloride with ether maintenance, using the intratracheal tube. They also administer a basal anesthetic dose of avertin and infiltrate the line of incision with procaine solution. The anesthetists prefer nitrous oxide and oxygen to the ethyl chloride-ether combination as they feel that the gas is safer. I visited St. Bartholemew's Hospital and met Dr. Evans, and saw Mr. Shaw do an abdominal hysterectomy. The anesthetic was given by inhalation. The machine used was Boyle's. The gases are supplied to each operating room in the new portion of the hospital from a central supply in the basement, and suction and positive pressure are supplied also. At Guy's Hospital I met Dr. Marston, senior anesthetist, Dr. Scott, another senior anesthetist, and Dr. McConnell, associate anesthetist. I saw Mr. Slesinger operate on a patient for goiter. They used avertin, 100 mg. per kilogram, plus nitrous oxide and oxygen without the intratracheal tube. Dr. Marston has developed a rest which grasps the head securely in rubber covered steel fingers; it seems to be satisfactory.

England was the only place where general inhalation anesthesia was preferred to local anesthesia by the surgeons.

Extract.

LATE RESULTS IN THE TREATMENT OF AMEBIC ABSCESS OF THE LIVER AND HEPATITIS.

C. H. Hodgson, M.D., Fellow in Medicine, The Mayo Foundation, and P. W. Brown, M.D., Division of Medicine: In reviewing the records for the past eighteen years they have found thirty-five cases of hepatic involvement by the *Endamoeba histolytica*. Eighteen of these have come to operation while the remaining seventeen have presented such characteristic clinical and laboratory findings as to warrant the diagnosis of amebic infestation of the liver. Although

an unquestioned diagnosis can be made only on recovering the *Endamoeba histolytica* in pus from the liver, nevertheless, they feel that an entirely justifiable diagnosis can be made when the history and clinical findings point toward it and the patient makes a prompt recovery following specific therapy.

The incidence of amebic infection of the liver in relation to all cases of amebiasis is small, approximately 2 or 3 per cent of the cases of amebiasis encountered at the Clinic. It was surprising, however, to find that among 125 surgical cases of abscess of the liver eighteen or 14 per cent were attributable to amebae. The infrequent occurrence of this condition in women is again brought out in this series; only four of our thirty-five patients were women. Age of the patient does not seem to be a factor, since the ages ranged from seventeen to fifty nine years.

In going over the histories of these patients one is impressed by the wide differences in the duration of symptoms. Some had evidence of infection for only a few days and others most certainly had hepatic involvement for many months. Although a history of diarrhea is important and usually gives the first clue to the diagnosis of amebiasis, it is noteworthy that eight of these patients did not have diarrhea at any time. Pain was the most common symptom and usually occurred in the right upper quadrant of the abdomen, but it was also noted in the epigastrium, left upper quadrant and the right lower part of chest. Nine of these patients had pain referred to the shoulder, indicating diaphragmatic irritation. The majority had fever and fifteen had chills.

When the prolonged illness of many of these patients was taken into consideration, their general condition was fairly good. On examination tenderness in the region of the liver was an almost universal finding in patients who had not been subjected to previous surgical procedure, and in many patients an enlarged liver or a mass in that region could be felt. In some cases the right side of the diaphragm was elevated and in a few cases there was evidence of fluid at the base of the right lung. In nine of the eighteen surgical cases a sinus drained through the wall of the chest or abdomen, the results of previous surgical drainage. In some of these considerable digestion about the walls of the sinus tract had taken place, a condition which improved markedly when specific therapy was instituted. Jaundice was present in less than a third of the cases and as a rule was not intense.

Definite evidence of amebiasis, namely, finding the ameba in the stools or pus from the liver, was present in thirty-two of the thirty-five cases. In the remaining three cases such marked improvement occurred within thirty-six to forty-eight hours after emetine therapy was begun that the diagnosis could not be

questioned. We know of no other condition which will respond to emetine therapy in the manner of amebiasis.

It is believed by most investigators that the infection in the liver arises from amebic infestation of the colon, but at the time the patient who has an abscess of the liver comes for examination, there may be no evidence of amebiasis on roentgenologic examination of the colon or proctoscopic examination. Two or three examinations of the stool may be negative for *Endamoeba histolytica*; yet repeated search should disclose the parasite.

This study was undertaken with the idea of determining the effectiveness of treatment and permanent recovery seems to be the rule. Of the seventeen patients who received medical treatment, fourteen were well an average of three and a half years after treatment. Two were not available for recent study. The remaining patient was admitted to the Clinic in extremis and died soon after admission. Necropsy disclosed perforating amebic ulcers of the cecum, peritonitis and amebic abscess of the liver.

Of the eighteen patients who were subjected to operation fifteen were well an average of seven years after treatment. One patient had had a recurrence of the abscess twelve years after treatment at the Clinic. Two patients died postoperatively. The diagnosis was made at operation in one of these cases but death ensued before specific therapy could be tried; in the other a prolonged downhill course followed the operation and an accurate diagnosis was not made until too late for specific therapy to be of assistance.

From analysis of these cases it appears that when the diagnosis can be established preoperatively, a thorough course of medical treatment should be tried. This will bring about recovery in the majority of cases. If the diagnosis is established after surgical intervention, specific therapy should be instituted as soon as possible. There are examples among our cases in which recovery did not take place following surgical intervention until specific therapy was given, and there is one case in which adequate treatment with emetine and treparsol failed to bring about improvement until surgical drainage was tried. In other words all patients should be given anti-amebic therapy and surgical treatment should be reserved for those who do not promptly respond.

THE USE OF HUMAN PREGNANCY SERUM IN THE TREATMENT OF STERILITY: REPORT OF THREE CASES

A. B. Hunt, M. D., Section on Obstetrics and Gynecology:
Human pregnancy serum was administered intramuscularly in a

small series of cases of menorrhagia attributable to ovarian failure in the past year and a half at the Clinic. Endometrial biopsy and hormone studies as well as clinical observations indicated this treatment in most instances. The results seem to be about as effective as other methods of ovarian stimulation or substitution therapy. All but one of the patients who had menorrhagia were unmarried or deliberately avoiding pregnancy. This one patient who had been sterile for three years became pregnant after two months of treatment. This prompted the use of the serum in another instance of infertility with successful results. In a third case injections have been given for three months without conception occurring. The two successful cases are reported.

REPORT OF CASES

Case 1:—A married woman, aged twenty-four years, came to the Clinic in April, 1936, because of a mild menorrhagia from the onset of menstruation. General physical and pelvic examinations gave negative results except that the uterus seemed a bit enlarged and irregular so that the question of the presence of a small fibroid was raised. The concentration of hemoglobin in the blood was 12.1 gm. per 10 c. c. (80 per cent); the erythrocyte count 4,580,000 per cubic millimeter and the basal metabolic rate was—1 per cent. There had been an involuntary primary infertility of three years' duration.

Substitution therapy, using progesterone (prolution), was then given in five injections of 1/25 international unit each with definite lessening of the flow. During the next cycle an oral preparation (sistomensin) was used for ten days without apparent effect on the menorrhagia. Treatment by progesterone was resumed with good results for the next three periods and as flow was not excessive, the patient did not return.

A recurrence of the menorrhagia in much greater severity necessitated a return of the patient to the Clinic in February, 1937. With the menorrhagia had appeared fatigue and premenstrual depression and nausea. General examination gave negative results but pelvic examination again raised the question of a small uterine fibromyoma. The concentration of hemoglobin was 13.6 gm. per 100 c. c. (89 per cent); the concentration of estrin in a twenty four hour specimen of urine fifteen days before onset of menstruation was 9 rat units and the results of tests for normal amount of prolactin were positive in the urine four days before onset of menstruation. Examination under anesthesia and dilatation and curettage were performed and the uterus and adnexa were found to be normal. The condition of the endometrium was diagnosed as a late differentiative phase of the menstrual cycle in a cystic polypoid menopausal type of endometrium.

Since the curettage had not controlled the menorrhagia, human pregnancy serum in doses of 20 and 18 c. c. respectively was administered intramuscularly midway between the menses for the next two cycles. The first injection improved the menorrhagia only slightly but the patient thought that the subjective symptoms were relieved. After the second injection a six weeks' period of amenorrhea occurred with subjective symptoms of pregnancy. A Friedman test for pregnancy gave positive results but the patient did not return to the prenatal clinic and a spontaneous abortion occurred at about two months' gestation. She has been observed on three occasions in the last four months and following the pregnancy her periods are normal in interval, amount and duration.

Case 2:—A married woman, aged twenty-five years, came to the Clinic in December, 1935, because of a primary sterility of about a years' duration. Irregularity of the menses varying from four to six weeks had been present since the onset at fourteen years of age and she had had an occasional scanty period. The history and general physical examination revealed nothing of note aside from a second degree retroversion of the uterus. The basal metabolic rate was 0. Examination of her husband revealed normal spermatogenesis. A tubal insufflation test gave evidence of normal patency of the tubes. A specimen of endometrium obtained for biopsy nineteen days after menstruation showed the endometrium to be in the normal early differentiative phase of the menstrual cycle. The second menstrual period after the insufflation did not appear and on March 6, 1936, pelvic findings were typical of pregnancy of seven weeks' gestation. Two weeks later the patient was said to have aborted spontaneously.

Following this episode the patient complained of severe dysmenorrhea and menstrual backache and on examination a fixed retroversion of the uterus was found. Suspension of the uterus seemed justified but the patient was observed through two more menses during which her symptoms became even more severe. Consequently, curettage, internal shortening of the uterine ligaments, appendectomy and myomectomy of a tiny subserous fibroid were performed on July 2, 1936. A specimen of endometrium removed just as the menses were due now revealed a polypoid endometrium.

The patient's only complaint aside from the infertility following this procedure and physiotherapy was a distressing menstrual migraine. As she was so desirous of children that steps for adoption had been taken, it was decided to reinvestigate the status of the tubes and endometrium. Therefore an insufflation and endometrial biopsy were done on April 16, 1937. Evidence of tubal patency was obtained at a pressure of 170 mm. of mercury. The endometrial specimen removed for biopsy twenty-six days after menstruation was diagnosed as in the late differentiative phase of the menstrual cycle in a cystic endometrium.

Two injections of pregnancy serum (23 c. c. and 18 c. c. respectively) were given intramuscularly between the June and July menses in the hope that such ovarian stimulation might allay the menstrual migraine or result in conception. No other therapy was employed. A normal menstrual period began July 23, eleven days after the second injection of serum, but the August and subsequent menses did not occur. A Friedman test for pregnancy on September 18 was positive. Weekly injections of 1 rabbit unit of progesterone (prolution) were given until October 20, when they were discontinued because of mild redness and soreness at the site of injection. Some painless vaginal bleeding occurred November 1, but subsided after injections of 1 rabbit unit of progesterone on four days and one injection of pregnancy serum. A normal gestation is now progressing into the sixth month.

A third case of infertility with ovarian failure has been treated for three months without success.

COMMENT

Infertility when not due to organic causes such as tubal occlusion or faulty spermatogenesis probably results from primary or secondary ovarian failure; namely, lack of ovulation, or failure of nidation because of progesterone deficiency. Defective transportation of the ovum into the tubes and uterus may also be a factor.

Efforts to stimulate normal ovarian function are not new. Roentgenray stimulation has proved of definite value and preparations of prolan have been given with varying success.

The two successful cases and the one failure in the use of human pregnancy serum reported herein warrant no conclusions as yet but some interesting observations may be noted. In case 1, the curettage no doubt may have had an influence on conception as it preceded it by only three months. However, the curettage failed to arrest the menorrhagia. In both of the successful cases biopsy had revealed a cystic, polypoid endometrium, one of the menopausal type. These findings are consistent with a condition of ovarian failure. The tendency of both individuals to abort early in pregnancy has been mentioned. This tendency has been attributed to recurrence of ovarian failure such as occurs in cases of habitual abortion. One reason for this view is that, in other cases, the stimulating effect of human pregnancy serum has been only temporary (three to four months). If this view is correct continued administration of progesterone or renewed ovarian stimulation by administration of prolan seems indicated well into the period of gestation. In both instances pregnancy resulted in the third month of treatment, a time when the maximal effect of the serum had been noted previously in the cases of menorrhagia.

In cases 1 and 2 pregnancy occurred before the recent report of Davis and Koff on the use of pregnant mares' serum in the treatment

of sterility and are of interest in the light of this communication. The action of human pregnancy serum is probably similar to that of pregnant mares' serum.

Assays of individual samples of our pregnancy serum for prolactin are now in progress. The Smiths found concentration of prolactin in the blood in the first half of pregnancy of from 40 to 1,000 rat units per 100 c. c., averaging about 300 rat units per 100 c. c. It is known to be higher early in pregnancy. Evans and his coworkers showed the normal occurrence of transient extremely high levels of prolactin in the blood and urine of pregnant women at about eight weeks' gestation. Our donors have, therefore, been selected from patients who have not reached the fourth month of pregnancy. A negative serologic test for syphilis is required of each sample of serum and rigid aseptic technic is necessary in the preparation and preservation of the serum.

Human pregnancy serum, while possibly lacking in potency as compared with pregnant horse serum, has the advantage of being of little or no potential danger, especially to allergic subjects, with regard to foreign protein or anaphylactic reactions.

No final conclusions can be drawn from these three cases of infertility treated with human pregnancy serum. More extensive, carefully controlled use of human pregnancy serum in the future will evaluate its merit. Conservatism is necessary in evaluating the results of such therapy, for Hamblen and Ross failed to find satisfactory evidence of the production of ovulation or formation of corpus luteum in eighty-five cases treated with sizeable doses of prolactin.

Medical News and Notes.

THE TINNEVELLY DISTRICT MEDICAL ASSOCIATION, PALAMCOTTAH.

(Tinnevely Branch of the Indian Medical Association.)

The Tenth Annual gathering organised by the Tinnevely District Medical Association was held on Saturday the 3rd of December 1938, in the Subrahmanya Karayalar Public Library, Palamcottah. Members numbering 75, including 7 women doctors were present. Two members of the Independent Medical Practitioners' Association, Tinnevely also attended the function.

After Tea and music the Business meeting commenced under the Presidentship of Lieut. Col., T. S. Shastri, I. M. S. The Secretary Dr. K. Rama Ayyar, M.B.B.S., read the minutes of the last

monthly meeting held at Tuticorin and also the minutes of the Special Meeting held at Vannerpet.

Then the election of Office-bearers was proceeded with :—

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|---------------------------|-----|--|
| 1. President | ... | Lieut. Col., T. S. Shastri, I.M.S. |
| 2. Vice-President | ... | Dr. T. N. Govinda Iyer, M.B. |
| 3. Secretary & Treasurer. | ... | Dr. K. Rama Ayyar, M.B.B.S. |
| 4. For Women members | ... | Dr. Mrs. E. Bernard Carr. |
| 5. For the General Body | ... | Dr. L. Mahadevan, M.B.B.S.,
(Madras) D.O.M.S., (London),
Dr. N. Isaac, Dr. K. S. Subrahmanyam, L.M. & S. |

Member—Auditor ... Dr. K. V. Muthiah Pillai.

Resolved that the following be the Programme of Meetings for the year 1939 :—

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| 1. January | ... | Nanguneri (Temple). |
| 2. February | ... | Headquarters. |
| 3. March | ... | Tiruchendur (Sea side). |
| 4. April | ... | Headquarters. |
| 5. May | ... | Srivaikuntam (Temple). |
| 6. June | ... | Papanasam (Waterfalls) (Amba-samudram). |
| 7. July | ... | Courtallam (Waterfalls). |
| 8. August | ... | Headquarters (President's Function). |
| 9. September | ... | Sankarankoil (Temple). |
| 10. October | ... | Headquarters (Anniversary). |
| 11. November | ... | Koilpatti (Mills). |
| 12. December | ... | Headquarters. |

The following resolutions were passed unanimously.

1. Amending Rule No. 19 as follows :—

To have the power to alter the constitution at any one of its meetings after previous notice has been given where not less than one half of the number of members on the roll are present and three-fourths of the number present are in favour of the proposed change in the constitution.

New Rules.

2. Members whose subscription is in arrears for six months shall cease to be members, but they continue to be liable to pay the arrears.

3. Members who have lost their membership under the Bye-law shall not be re-admitted unless they pay all the arrears due from them.

4. A non-residential membership shall be instituted as follows :—

- (1) "It is resolved that the Association may institute a non-residential membership for the benefit of those members of our Association who get transferred or who have to

- move out of our District in the course of the Journal Year (1st of October to 30th of September following).
- (2) This non-residential membership applies only to such members as are residing and working in a District which has no branch of the Indian Medical Association.
 - (3) It is proposed that the Annual subscription for the non-residential members should be Rupee One for the membership plus a Journal subscription of Rupees Three per annum for the Journal. But since he has already paid Rupee One towards the Journal he should pay only Rupees Two for it for the current year.
 - (4) Before he leaves the District he should pay all the subscription and other dues due to the Association; and when he applies for non-residential membership he should pay in advance the subscription of Rupees Three for the current year.
 - (5) For the next year onwards he should pay Rupees Four in advance. If it is not paid in advance his name shall be removed from the list.
 - (6) His applications should be accepted by the Managing Committee and he should be enrolled as a non-residential member before, he gets the benefit of it, and the Secretary, of the Indian Medical Association, Calcutta, should then be informed to continue to send the Journal to such a member to his new address."
5. The "Association Year" shall be from the 1st of October to 30th of September the following to come into line with the Indian Medical Association.

Then Lieut. Col., T. S. Shastri, I.M.S., offered a hearty welcome to all the members and guests.

Annual Re-union.

Lieut. Col., T. S. Shastri, I.M.S., opened the proceedings of the Conference as the Chairman of the Re-Union.

Dr. K. Rama Ayyar, read out the messages of Good Wishes for the success of the Conference received from the following:—

The Hon'ble Dr. T. S. S. Rajan, L.R.C.P., M.R.C.S., Rao Bahadur C. B. Rama Rao, M.D., Dr. K. Raman Tampi M.D., Dr. P. Rama Rao, Radiologist, Madras, Dr. Noble, M.D., F.A.C.S., Nagercoil, Dr. K. R. Menon, I.M. & S., Dr. D. V. Venkappa, Madras, Rao Bahadur T. S. Tirumurti, B.S., M.B. & C.M., D.T.M. & H., (London), Dr. U. Krishna Rao, Madras, Dr. P. S. Srinivasan, Dharmashkodi.

Dr. M. Venkatachalam Chetty, read out the following interesting clinical cases which were successfully treated and operated at the Govt. Headquarters Hospital, Palamcottah:—

- (1) A case of Tumour (Right shoulder) (Not operated).

- (2) A case of perforating wound abdomen.
- (3) A case of undescended testis (left side).
- (4) A case of Traumatic dislocation hip (left side).

Dr. Mrs. A. Brown, Govt. Women and Children Hospital, Vannarpet read out a case of Tumour on the left side of the neck. A discussion of those cases followed, the Chairman of the Re-union contributing to the discussion and elucidating the therapeutics of the cases. The Grand Banquet was brought to a happy close at 11 P.M., after a grand dinner.

THE MEDICAL PRACTITIONERS' ASSOCIATION, NUZVID.

A monthly meeting of the above Association was held at Nuzvid on 20-11-'38 in Dr. Mrs. Seshagiri Rows' dispensary Dr. P. Anjaiah Presiding. Refreshments and tea were served to the members. Then the minutes of the previous meeting were read by Dr. N. Rama Rao which were accepted. The following case reports were discussed.

1. An early case of sarcoma of the thigh, and of criminal abortion resulting in Hyperpyrexia Tetanus and death. Medico legal aspects over the latter were discussed.

2. A case of Acute haemorrhage per rectum and vomiting of blood of a sudden onset resulting in collapse and necessitating administration of Saline, glucose, and cardiac stimulants and other Anti hemorrhagic remedies, in a primarily healthy adult male treated by Dr. N. Rama Rao. The possible causes of such a condition were discussed by the members, such as acute Duodenal or gastric ulceration, erosion of an aortic Aneurysm in the abdomen, ptomaine poisoning and the possible rupture of the anastomosis of vessels of the oesophageal branches of the thoracic Aorta and those of the subclavian Artery as a result of Hepatic congestion.

3. A case of Apoplexy with Hemiplegia of recent origin by Dr. V. Ananthachary, L.I.M.

4. A case of Ascites treated by Dr. S. Hanumantha Rao with Neptol and Decholine injections.

The members then passed the following resolution unanimously.

"As this Association is of opinion that the Honorary scheme now proposed for the Rural practitioners by the Government in their memorandum No. 34730-1-D 2 P H dated 30th September '38 will mar the prospects of the practitioners who have not been able to reach the expectations of the Government to stand on their own legs without the present emoluments; it resolves to request the Government to drop such an idea and to allow the Rural practitioners as at present."

Review.

M. & B. 693 IN GONOCOCCAL INFECTIONS.

We have received from Pharmaceutical Specialities (May & Baker) Ltd., a copy of another publication on that remarkable addition to chemotherapy, M. & B. 693. This 16 page booklet, which is entitled, "M. & B. 693 in Gonococcal Infections," is a complementary publication to "M. & B. 693 in Pneumococcal Infections," and "M. & B. 693 Biological and Biochemical Data."

We understand from the manufacturers that they delayed bringing M. & B. 693 to the notice of venereologists until they were satisfied that the use of this product marked a real advance in the chemotherapy of that disease. This booklet which they have now produced represents the pooled results of observations in over 1,000 cases.

Copies of this publication are available to medical practitioners on request.

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