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APPROVED: C. C. Thomas
REAR ADMIRAL, MC, U.S. NAVY
CHIEF OF BUREAU

DATE: JULY 1, 1949

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APPROVED: James V. Forrestal
SECRETARY OF THE NAVY

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Hemipelvectomy in Cancer: The radical resection of an innominate bone, its contiguous soft tissues and the subjacent lower extremity as a means of ablating cancer has received renewed interest recently. The decreasing mortality rate attendant upon the performance of this procedure has removed the diffidence which previously has been associated with hemipelvectomy. Since the first successful resection by Girard in 1895, 158 have been recorded exclusive of those in this series.

Hemipelvectomy (disarticulation of innominate bone) refers to that surgical procedure in which the entire innominate bone, contiguous somatic tissues (buttock), and the entire subjacent lower extremity are resected en masse. Because the cancellous nature of the innominate bone favors the wide dissemination of cancer throughout its structure, the entire bone should be removed. Not infrequently it is necessary to resect such other viscera as peritoneum, testicle and spermatic cord structures, intra-abdominal viscera, and periaortic lymph nodes.

Hemipelvectomy is indicated for those neoplasms which involve the hip joint, pelvic parietes, or soft tissues of the iliac region, and which cannot be surgically extirpated by more conservative methods. The various conditions in which this procedure may be indicated are: (1) Primary malignant neoplasms of the innominate bone such as osteogenic sarcoma, and periosteal fibrosarcoma. (2) Primary malignant neoplasms of the femur which have invaded the hip joint. (3) Cancer of the soft tissues of the upper thigh, inguinal region, or buttock, which have invaded the hip joint or extended through the obturator foramen to involve the pelvic parietes. (4) Metastases to the iliac region which have infiltrated the hip joint, the pelvic parietes, or which, because of local extension, have precluded extirpation of the disease by less radical procedures such as radical groin dissection. In this group are included: (a) metastases from primary epidermoid carcinomas or sarcomas of the lower extremity, (b) metastases from malignant melanoma which cannot be treated by hip joint disarticulation or radical groin dissection, (c) metastases from carcinoma of the penis or rectum in certain selected cases, and (d) metastases from certain distant primary tumors, as kidney carcinoma or thyroid carcinoma. In all instances in which the resection is performed for the treatment of metastases, the primary neoplasm must be controlled or controllable. (5) Certain massive benign tumors of the innominate bone, as chondroma, osteochondroma, or of the somatic tissue of pelvic area (neurofibroma) if they cannot be resected adequately by other less radical procedure. (6) For palliation in certain instances of general metastases: melanoma, Kaposi's hemorrhagic sarcoma, spindle cell sarcoma in which the lesion of the groin produces a bulky infected and painful mass, which cannot be controlled by any other modality. (7) Certain infections and trauma, which will not be discussed in this presentation.

In this series of 8 patients the resections were performed for synovial sarcoma, fibrosarcoma, periosteal fibrosarcoma, iliac metastases from a primary squamous cell carcinoma, Ewing's tumor, and metastatic hypernephroma. One palliative resection was performed for melanosarcoma.

The adequate control of fluid, electrolyte, and colloid balance as for any major surgical procedure and correction of anemia and other metabolic abnormalities are imperative. The patients are placed on an antibiotic regimen (penicillin, 50,000 units every 4 hours) one week before surgery. Two days before surgery they receive streptomycin (1 Gm. each day) and the day before operation, 6 Gm. of sulfadiazine are administered. The evening before operation a gentle enema is given. All of the patients were males, hence the authors have had no experience with vaginal preparation. Preoperative debridement, or cautery excision of certain lesions as described by Pack and Ehrlich, in the authors' experience is unnecessary. In bulky fungating tumors a small drapery is sutured over the lesion at the time of surgery. An indwelling urethral catheter is inserted before the patient comes to the operating room. Preoperative preparation of the psyche of all candidates for this operation is rewarded postoperatively by a grateful patient who bravely resigns himself to the deformity. None of the authors' patients regretted their decision to submit to this surgical procedure.

Endotracheal inhalation anesthesia (nitrous oxide, oxygen, and ether) was used in the earlier cases. Recently a combination of Baird's solution and nitrous oxide has been found a very satisfactory anesthetic agent. The patient can be moved easily when necessary and this mixture is desirable for the hypotension which not infrequently attends the operation.

There has been a steady and progressive decline in the operative mortality for hemipelvectomy. In 1909 the mortality rate when performed for cancer was 67 percent and Pringle in 1916 remarked on the achievement in decreasing the mortality rate to 56.6 percent in the intervening years. In 1935 the operative mortality of all cases performed to that date was 60 percent. In the subsequent ten years, 80 additional patients were treated and the reported mortality rate of that series was 18 percent. Recent reports by Morton, 4 cases; Pack and Ehrlich, 7 cases; and this series, 8 cases without an operative death suggests that the technic of conducting the patient safely through a hemipelvectomy has been achieved. Adequate pre- and postoperative care and special emphasis on supporative therapy (transfusion) during the operation, are the major factors contributing to the precipitous drop in the operative mortality rate. There is nothing to suggest that the patients of the 3 series cited above were better operative risks than in previously reported series; in fact, two patients were critically ill from widely disseminated cancer and the operative intervention was performed for palliation.

In this series the end results are not good. Four patients have succumbed. In one case in which the operation was performed for palliation, the patient succumbed two months postoperatively of diffuse melansarcomatoses. One patient, who had intraperitoneal invasion of a synovial sarcoma at the time of surgery, expired two months postoperatively with generalized visceral metastases. Two additional patients succumbed 5 months and 8 months postoperatively due to diffuse pulmonary metastases resulting from a spindle cell fibrosarcoma and synovial sarcoma respectively. A fifth patient has bilateral pulmonary metastases 24 months subsequent to surgery, and the remaining 3 patients are apparently free of disease, 2, 12, and 15 months respectively after surgery. In none of the patients who expired were local recurrences observed at postmortem examination.

Further review of this series reveals that in all 7 cases in which the operation was performed for curative purposes, there was a delay varying from 7 to 19 months from the onset of symptoms. The average delay in the group was 10.4 months. Moreover, the delay in certain instances was attributable to the medical profession. In two instances, a proper diagnosis was not established and no definitive therapy instituted for prolonged periods. In 3 instances, adequate therapy was delayed while conservative surgical measures or irradiation therapy were attempted by other physicians. It is probable that the delay in addition to the trauma of ineffective therapy contributed significantly to the poor results in 4 patients of this series.

It is difficult to determine the true accomplishment of exarticulation of the pelvis from published reports because of the inadequacy of the data. Pack and Ehrlich state that one third of the patients who submitted to the operation because of malignant disease were reported clinically cured, but state further that the follow-up in most instances was most inadequate.

A perusal of the literature reveals 9 instances of 5-year survivals with the following histologic diagnoses: 3 chondrosarcomas, 1 chondroma, 1 osteoclastoma, 1 osteogenic sarcoma ilium, 1 extraperiosteal sarcoma, 1 spindle cell sarcoma, and 1 epidermoid carcinoma.

It is suggested that the low survival in the reported cases may be the result of the following factors:

1. The previously high operative mortality rate.

2. Certain patients with neoplasms known to be radioresistant (spindle cell sarcoma, synovial sarcoma) received irradiation as the method of choice instead of surgical intervention. When hemipelvectomy was instituted finally, there had been a prolonged delay.

3. Conservative surgical procedures were attempted frequently before resorting to radical resection. The less radical procedures were utilized first because (a) they were being appraised, (b) the surgical inexperience of the physician precluded his performing a major procedure, (c) the humane attempt of trying to spare the patient the mutilation resulting from hemipelvectomy, and (d) the erroneous policy of trying a more conservative method first to see what it may accomplish before resorting to the radical curative procedure. Frequently it is possible to be more conservative in the long run by being radical at the outset.

4. Attempts to retain partial function have led certain surgeons to spare tissue which should have been resected. Sugarbaker and Ackerman stress this feature and have collected from the literature histories of 8 patients who developed stump recurrences. They point out that in 4 cases the innominate bone was incompletely severed and in one instance the gluteus maximus was preserved.

Bulky benign lesions such as chondromas, osteochrondromas, neurofibromas, offer the best prognosis. Malignant neoplasms of low grade malignancy of bone (chondrosarcoma) or well differentiated malignant neoplasms of soft tissue (myxoliposarcoma, periosteal fibrosarcoma, extra-osseous osteogenic sarcoma) should offer a good prognosis. Osteogenic sarcoma of the innominate bone or extension from the femur into the hip bone does not offer a very good prognosis. Cures, however, have been reported. Primary epidermoid carcinoma arising from the skin of the groin and infiltrating deeply or metastases from carcinoma which infiltrate inguinal tissues may offer a good prognosis in certain instances. Sarcoma of soft tissue, especially fibrosarcoma rhabdomyosarcoma, and synovial sarcoma are the histological types for which hemipelvectomy has been performed most frequently and in which the end results have been poor (3 cases of this series). In 25 cases labeled sarcoma observed in the literature there is only one recorded instance of a 5-year survival rate. These figures should not deter one, however, from the performance of radical surgery when it is the only method that may completely extirpate the disease. Hemipelvectomies have been performed for Ewing's sarcoma and multiple myeloma, but no cures have resulted.

Since the manuscript was prepared for publication 3 additional hemipelvectomies have been performed. A 35-year-old white male had had a mid-thigh amputation performed for a fibrosarcoma about the left knee joint. Because of radiological evidence of sarcoma about the hip joint, a hemipelvectomy was performed and the patient is well and apparently free of disease one year postoperatively. Hemipelvectomy was performed on a 32-year-old white male for a chondrosarcoma involving the head of the left femur and producing a bulky gluteal mass. Symptoms had been present for one and one-half years. The patient is well 6 months postoperatively except for a low-grade osteomyelitis of the opposite pubic bone. A 38-year-old white female who weighed 203

pounds had pain of the left thigh of two and one-half years' duration, and a fracture one year before admission. A massive neoplasm involving the proximal part of the femur, left hip joint, and medial aspect of the thigh necessitated a hemipelvectomy. The histological diagnosis was chondrosarcoma with invasion of the femoral vein and erosion of the femur. Her obesity precluded good wound healing and a period of about two months was required before the patient walked. She is well and apparently free of disease two years after surgical intervention. (Ann. Surg., July '49, I. M. Ariel and F. W. Hark)

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Experiences with Fibrin Coagulum in Pyelolithotomy: The removal of multiple calculi from the renal pelvis and its calices for years has tried the ingenuity of the surgeon. Inadequate methods have resulted in undue trauma to the renal parenchyma, incomplete removal of calculi, recurrent nephrolithiasis, and at times even unnecessary nephrectomy. The use of the roentgenogram of the surgically exposed kidney was a great step forward in the accurate localization of calculi to facilitate their removal and also to demonstrate the incomplete removal of radio-opaque calculi. It is not a rare experience to find at operation more calculi in the renal pelvis than previously had been anticipated. This results from the interposition and superimposing of large and small calculi as well as their varying degrees of radio-opacity. A significant contribution to the surgery of renal calculus lies in the original work of Dees in the application of fibrin coagulum to pyelolithotomy. The method has not been more widely employed because of the unavailability of fraction I of human blood plasma. It is hoped that very soon materials for coagulum pyelolithotomy will be available for general distribution through commercial channels. In a recent panel discussion on renal liathiasis at a large surgical meeting in this country only a brief mention of the method was made which indicated that its merits are too little appreciated at the present time by even the most experienced surgeons.

Coagulum pyelolithotomy has been used for removal of a single calculus in the infundibulum of a calix, multiple calculi in the calices, single calculi associated with calcific debris in the renal pelvis, multiple calculi in the pelvis and calices, and for clearing the pelvis after complete obstruction by a single stone at the ureteropelvic junction. The method is particularly indicated when several small stones are demonstrable in the renal pelvis by roentgenogram and when multiple calculi are suspected though not definitely shown before operation. The removal of single inaccessible and multiple calculi has been greatly facilitated by the technic. Fragmentation of calculi during removal has been avoided. Trauma to the kidney has been reduced to a minimum and complete mobilization of the kidney was found to be unnecessary when this procedure was undesirable. Mobilization of the kidney was carried out when the extrarenal portion of the pelvis was small. Those calculi which are densely adherent to the mucosa of the pelvis, those which are trapped in calices having

constricted infundibula, the calcified renal papilla and the large branching calculus will naturally not be extruded in the coagulum and must be removed otherwise. However, even in such cases the coagulum may be helpful in removing other free calcareous components. It should be emphasized that fibrinogen and thrombin should not be used after the kidney has been traumatized by surgical removal of calculi which has resulted in bleeding into the pelvis lest intravascular injection occur. However, the coagulum may be formed in the pelvis prior to the removal of these fixed stones.

The fraction I of human blood plasma and thrombin which the authors have used was prepared and made available by the Department of Physical Chemistry, Harvard Medical School. According to the technic and instructions issued, a single unit of fraction I of human blood plasma is dissolved in 100 cc. of a buffer solution of sterile 0.15 M Na_2HPO_4 30 minutes before use. Physiological saline solution is now dispensed with the commercial preparation of fibrinogen as the diluent to dissolve the fibrinogen. When this is injected with thrombin or clotting globulin (Lederle) coagulation of fibrinogen occurs within 30 seconds and it has been shown that within 4 minutes the tensile strength of this coagulum is from 10 to 20 times as great as that of human blood clot. The production of this intrapelvic coagulum has no detectable effect on the kidney. In fact it is expected by the author that bovine fibrinogen may be safely and satisfactorily used instead of human fibrinogen.

The steps in operative technic outlined by Dees (see News Letter of 21 June 1946, Vol. 7, No. 13, p. 8) have been followed with success and are as follows: After exposure of the renal pelvis and ureter, stay sutures are placed on either side of the ureteropelvic junction in preparation for a vertical incision in the ureter 4-5 mm. in length. One of the advantages of the technic is that removal of multiple calculi from the pelvis may be accomplished without mobilization of the kidney. When the pelvis is chiefly intrarenal in type mobilization of the kidney is desirable and better exposure can be obtained by retraction of the parenchyma overlying the renal hilus. A soft rubber urethral catheter from 12 to 14 F is inserted through the opening in the ureter into the renal pelvis. The ureter is occluded distal to the opening by a rubber covered bull-dog clamp. The catheter must fit snugly in the ureteral incision to avoid leakage. The renal pelvis is emptied of urine and the catheter is adjusted so that it irrigates freely. The capacity of the renal pelvis is measured by instillation of normal saline which is completely aspirated. Dees has found the irrigation of the pelvis with a solution of 0.1 percent Aerosol O.T. to be useful when considerable infection has been present in order to dissolve tenacious exudate binding calculi to the mucosa.

Fibrinogen in solution in 0.15 M Na_2HPO_4 is injected into the renal pelvis to its maximum capacity and simultaneously human thrombin or clotting globulin (Lederle) is injected in from one tenth to one fifth the volume of fibrinogen

used by means of a different syringe into the lumen of the catheter. It is the authors' custom for the operator to inject the fibrinogen solution into the catheter which is held in place by smooth forceps while the assistant injects the thrombin starting its instillation after 5 cc. of the fibrinogen has been injected. After waiting for 5 minutes a firm clot has always been formed in the renal pelvis. Adequate distention of the renal pelvis can be easily determined by palpation. The catheter is removed. The necessary size of the opening in the pelvis depends upon the size of the calculi present. The coagulum is removed with stone forceps. By moderately overdistending the pelvis with slightly more fibrinogen solution than the estimated volume, complete filling of all calices with inclusion of all loose calculi is insured. Delivery of the coagulum is facilitated by spontaneous expulsion when pressure is released on opening the pelvis. After removal of the coagulum, digital exploration is necessary in searching for adherent calculi and in identifying calcified renal papillae. The pelvis is thoroughly irrigated with saline and a roentgenographic film of the kidney made. The opening in the ureter and renal pelvis is closed by loose approximation with 00000 catgut, unless acute infection or significant chronic infection is present, and the wound is closed in layers with interrupted cotton or silk sutures. The renal fossa is always drained through the posterior angle of the wound with a soft thin rubber drain.

Coagulum pyelolithotomy is not applicable in all cases of nephrolithiasis. The authors employed it in 10 cases of nephrolithiasis; in 8 instances the technic was definitely helpful and facilitated delivery of calculi. In two cases the method was not successful or helpful; in one this resulted from faulty technic and in the other failure resulted because calculi were walled off in calices in such a manner as to be inaccessible to the coagulum. (J. Urol., July '49, J. Harrison and B. E. Trichel)

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Aureomycin Treatment in Urinary Tract Infections: The patients selected for treatment with aureomycin were all adults and almost all of them had severe and long standing urinary tract infections which had failed to respond to treatment. Only one patient with a previously untreated acute pyelonephritis complicating pregnancy is included. The others all had various underlying defects along the urinary tract and had been subjected to numerous instrumentations and to various operative procedures either for diagnosis, for relief of symptoms or in an attempt to produce a radical cure. Most of the patients were in the older age groups. Only 4 of the patients, however, were hospitalized during the aureomycin therapy; the others were considered to be especially suitable for ambulatory therapy because they were highly intelligent, completely co-operative, and anxious to be relieved of the infection. The ambulatory patients were kept under close observation both before and after the aureomycin therapy.

The antibiotic was provided as a powder in capsules, each containing 50 milligrams, and was given by mouth. Most of the patients received 10 capsules (0.5 Gm.) morning and night for about a week, but 0.5 Gm. 4 times a day (before each meal and at bed time) was given for varying periods in some of the patients and in almost all of those who were given a second course. In 7 patients a second course of aureomycin was given, usually after an interval of 2 weeks, either because the infection was not completely eliminated or because it recurred. The predominant clinical symptoms prior to the aureomycin therapy were dysuria, poor sphincter control, frequency, nocturia, and cloudy urine. Some had had recurrent attacks of severe costovertebral angle pain and tenderness. The urine was loaded with pus cells in every case.

In general, the pyuria diminished during therapy and disappeared entirely in about half of the patients while treatment was still being given. Symptomatic relief occurred at the same time in most instances, the burning on urination, frequency, and nocturia all diminished or subsided. The urine became highly acid and remained so throughout the treatment. Cultures obtained immediately before treatment usually revealed only a single strain of organisms but in those who received a second course of aureomycin, organisms other than those initially present had appeared during or after the first course. The cultures usually became sterile during the aureomycin treatment. In some of the patients, however, Proteus vulgaris or Pseudomonas aeruginosa and in 2 instances Escherichia coli either first appeared or persisted during aureomycin treatment. Infection recurred within a few days in most instances, with either the same or with different organisms. The P. vulgaris was the most persistent but Ps. aeruginosa also could not be eradicated. Good results of a permanent nature were, therefore, infrequent in these cases of chronic urinary tract infections. Temporary relief, either slight or moderate, resulted in about two thirds of the patients. The patient with the acute pyelonephritis complicating pregnancy responded promptly with both symptomatic relief and a bacteriologic cure.

Most of the organisms were quite sensitive to aureomycin and were completely inhibited by concentrations ranging from 6.3 to 50 micrograms per milliliter, but the strains of P. vulgaris and Ps. aeruginosa required from 125 to 250 micrograms per milliliter for complete inhibition. Partial inhibition usually occurred in one half or one fourth of the concentrations which were needed for complete inhibition. The more resistant organisms persisted or appeared in the cultures during and after the aureomycin treatment. All of the strains of the same organism that were isolated from the same patient, however, were equally sensitive to aureomycin. There was no evidence of any tendency for resistant variants to develop during therapy.

The aureomycin activity in the urine, demonstrated by methods that were rather crude, was equivalent to concentrations of from 32 to 256 micrograms per milliliter in specimens obtained during treatment and between 2

and 12 hours after a dose of 0.5 gram. Of interest is the fact that concentrations of 16 micrograms per milliliter, and sometimes more were obtained as long as 48 hours after the last dose and smaller concentrations were demonstrable for more than 72 hours. The errors involved in the methods were such as to suggest that the actual concentrations were considerably higher, because the antibiotic tends to deteriorate rapidly on standing and even during the course of the tests. Blood levels were usually 2 micrograms per milliliter or less but concentrations of 8 micrograms per milliliter were obtained in one patient while he was receiving one gram every 12 hours.

Toxic effects were minimal. The most common complaint was looseness of the bowels with frequent (from 2 to 4 daily), bulky, and soft stools but not true diarrhea. This was more frequent and was accompanied by some nausea and occasional vomiting when doses of 2 grams a day were given. In some of the patients with cystitis, a disagreeable sensation as of something drawing or squirming in the pelvis was sometimes noted. This may have been related to the high acidity of the urine during ingestion of large doses of aureomycin. There were no other symptoms in these or in other patients, nor was there any laboratory evidence of renal or liver damage or of any toxic effects on the blood. There were no fevers or rashes attributable to the antibiotic.

These cases were chosen deliberately because, with the exception of the patient with acute pyelonephritis, they represent the types of urinary tract infections which are usually refractory to the chemotherapeutic and antibiotic agents that have been available. When all of the clinical and bacteriologic findings are taken into account, the results in these cases may be considered to be quite satisfactory, although they still leave much to be desired. The results are probably as good as, if not better than, those usually obtained in similar cases with sulfonamides or with streptomycin. Because most of these patients had previously proved to be refractory to these agents and some were relieved of symptoms and pyuria for the first time in many months while they were taking aureomycin, this agent may prove to be a useful addition to the therapy of urinary tract infections. Aureomycin has several advantages over other agents used in this field in that it can be given by mouth, it is effective against both Gram-positive and Gram-negative organisms and from present indications it can be given for long periods without significant toxic effects and without giving rise to resistant variants. It is relatively ineffective, however, against P. vulgaris and Ps. aeruginosa.

The authors further state that since submitting this paper, they have treated more than 50 additional patients with urinary tract infections. One third of these patients had acute pyelonephritis, cystitis, or both and all but one were cleared of bacteriemia and pyuria. The results in the chronic cases were the same as those noted in this report above. (Surg., Gynec. & Obstet., July '49, H. S. Collins and M. Finland)

Experience with a New Insulin: Specially modified insulin, designated by the manufacturers as NPH 50, is a neutral crystalline protamine zinc insulin with an action intermediate between that of soluble (regular) insulin and protamine zinc insulin.

With the use of insulin mixtures as first proposed by Lawrence and Archer in 1937, the control of severe diabetes was finally accomplished with one injection of insulin a day. The intermediate type of action of the mixtures largely eliminated the glycosuria in the daytime so frequently observed with the use of protamine zinc insulin alone. The results of treatment by this method in large series of patients have been most gratifying. Nevertheless, this method has projected definite clinical problems because premixed insulins are not stable enough for general use, and mixing the insulins in the syringe represents a technic which is difficult to teach to many patients. Therefore, many physicians have continued to advise the use of protamine zinc insulin alone in spite of serious objections to it.

At the Mayo Clinic the practice has been to use protamine zinc insulin only for patients who require 20 units of insulin or less a day. Patients who require more than 20 units have been treated with insulins mixed in the syringe. This method has required the expenditure of a considerable amount of time on the part of the staff and the patients. Additional objections to the procedure include (1) increased chance for error in dosage, (2) dislike of some patients for the additional daily inconvenience, and (3) unsuitability for patients with limited intelligence or poor vision. Nevertheless, the reasonably satisfactory control of the diabetes that usually results from properly adjusted tailor-made mixtures has justified their extensive use.

In the designation for this new insulin, NPH 50, the N stands for neutral. The pH of this insulin is 7.2, whereas soluble (regular) insulin is acid, its pH is about 3.0, and that of protamine zinc insulin is about 7.2. The P is for protamine; the H is for Hagedorn, who with his associates Krayenbuhl and Rosenberg developed the method of preparing crystals of protamine zinc insulin as used in NPH 50. The figure refers to the approximate quantity (0.50 mg.) of protamine that has been used in the preparation of 100 units of this insulin. The crystals of protamine zinc insulin are described as beautiful tetrahedrons with shiny faces and sharp, smooth edges. According to Peck they are extremely stable under proper conditions, and from them suspensions can be made to which soluble (regular) insulin can be added without loss of the quick action characteristic of soluble insulin.

Some time ago the author and his co-workers were supplied (Lilly Research Laboratories) with limited quantities of NPH 50 for clinical trial. The available information about the product was meager, consisting primarily of preliminary data on determinations of blood sugar in a few treated patients.

Diabetic patients using insulin who lived in Rochester or near by, who were under supervision and who were willing to try it were given this insulin. Nearly all of them were engaged in their usual occupations and eating at home. The diabetes of nearly all of them was severe and nearly all of them had obtained reasonably satisfactory control with tailor-made mixtures of soluble and protamine zinc insulin. The patients tested freshly secreted specimens of urine before each meal and at bedtime for a period before, and in the period during which, they received NPH 50 insulin. They also reported at regular intervals for supervision.

After use of the new insulin for a period of from two to 6 months, each patient was asked for his opinion of the comparative value of NPH 50 insulin and the insulin he had been using previously. At the same time comparison was made between the adequacy of control during and before the use of NPH 50 insulin; this comparison was based on control of glycosuria and avoidance of reactions.

The results of the study are shown in the table below.

Comparison of Control of Diabetes With NPH 50 Insulin With Previous Insulin Programs in 20 Cases of Severe Diabetes[1]

Criteria	More satisfactory	Same	Less satisfactory	Incomplete data
Urine tests	9[2]	5	1	5[3]
Convenience[4]	18	2	0	0
Satisfaction[4]	17	2	1	0

1. Insulin reactions were less of a problem in 12 patients, the same in 6 patients, and more troublesome in 2 patients.
2. Six of these 9 patients required supplementary regular insulin for adequate control of glycosuria.
3. The 5 patients with "incomplete data" in respect to their urine tests gave as their impressions of the tests: more satisfactory 3, same 2.
4. Evaluation by the patient.

No untoward effects were noted and no local or general allergic reactions were encountered in these patients. Insulin reactions from overdosage of NPH 50 were more easily recognized than those provoked by protamine zinc insulin. Symptoms most frequently noted with NPH 50 overdosage were hunger, perspiration, palpitation and restlessness.

From this limited experience, the author and co-workers are led to hope that the control of diabetes obtainable with this new insulin will prove to be at least as satisfactory as that obtained with the insulin mixtures used before. Control with it is certainly more satisfactory than that obtainable with protamine zinc insulin alone. For control of diabetes of considerable severity additional soluble (regular) insulin seems to be required. Even so the new insulin is more convenient to use than mixtures made in the syringe of soluble (regular) and protamine zinc insulin. Of these 20 patients only one expressed a preference for the earlier procedure. (Proc. Staff Meet., Mayo Clin., 6 July '49, N. R. Kirkpatrick)

Dihydrostreptomycin in the Treatment of Pulmonary Tuberculosis: The authors, S. T. Allison et al., working in the U. S. Veterans Administration Hospital, Rutland Heights, Massachusetts, a 600-bed hospital for the treatment of veterans with tuberculosis, have treated 19 patients with pulmonary tuberculosis and one with generalized miliary tuberculosis with dihydrostreptomycin. Ten patients received 2 Gm. of the drug daily, and 10 received 3 Gm. daily, for a period of 90 days. It was the main purpose of the authors' study to evaluate any toxicity that the drug might possess in the dosage given. Accordingly, numerous laboratory tests were carried out at regular intervals, for the most part at weekly intervals. The authors also evaluated subjective symptoms and signs indicative of toxicity. The early symptoms of paresthesias in 6 patients, at first thought to be evidences of neurotoxicity of the drug, now appear to be evidences of impurities in the first lots of drug administered because subsequent lots failed to produce these symptoms. Tinnitus, which developed in 4 patients, may well have been a true neurotoxic manifestation because this symptom appeared later in the course of treatment. Audiometric observations were little changed from pretreatment readings. The nausea reported in 2 patients was an early symptom and may or may not have been significant. It does not appear to be a characteristic toxic manifestation of either dihydrostreptomycin or streptomycin. Because one patient receiving 3 Gm. daily practically lost vestibular function and had to be dropped from the course on the sixtieth day, this demonstrates the possibility of specific toxic effects on the vestibular nerve.

Compared with streptomycin in similar dosage, vestibular-nerve toxicity appears considerably less in this group receiving dihydrostreptomycin. In previous studies with streptomycin, of a group of 20 patients receiving 1.8 Gm. for 120 days, 75 percent lost vestibular function by the end of the course, and most of these had lost function by the end of 60 days. In the subsequent group of 31 patients who received 2 Gm. of streptomycin for 60 days, 64 percent completely lost vestibular function.

Eosinophilia, which was common in the authors' series of patients receiving various dosages of streptomycin, occurred with much less frequency in the present group of dihydrostreptomycin-treated patients. For example, 30 percent of the latter showed eosinophil counts from 5 to 8 percent, whereas 75 percent of the former had counts that reached an upper limit of 17 percent. This is consistent with the lessened toxicity observed in the present study.

Renal damage has not been observed in the authors' study, and no evidence of renal irritation has been noted except in one patient who received 3 Gm. daily in contrast to from 40 to 50 percent who received 1.8 Gm. of streptomycin and showed frequent albuminuria and cylindruria - not in themselves evidences of renal damage but certainly of probable renal irritation.

There has been no lasting effect of the drug on the hematopoietic system. Prothrombin times were not altered significantly during treatment. No other liver-function tests were done, but no patient appeared to develop clinical evidence of liver damage. Improvement was manifested by weight gain, lessened cough and expectoration, and disappearance of fever in all patients. True evaluation of conversion of sputum cannot be made in this series because the time of observation is too short. At least 3 months of negative sputum should be required before one can consider a conversion definite. Erythrocyte sedimentation rates were significantly lowered in 65 percent of the group during treatment. This incidence is scarcely different from the decreases in the sedimentation rates that occurred in 75 percent of 20 patients who received 1.8 Gm. streptomycin for 120 days. Roentgenographic improvement was observed in 60 percent, and half of these patients showed only slight or minimal improvement. This is in contrast to the first group receiving 1.8 Gm. of streptomycin for 120 days, who showed roentgenographic improvement at the end of 90 days of treatment in 75 percent. In a series of 31 patients receiving 2 Gm. of streptomycin for 60 days, 90 percent showed improvement. In a group of 13 patients receiving 1 Gm. of streptomycin for 120 days, 84 percent showed improvement by roentgenograms. Therefore, not only the incidence of improvement but also the degree of improvement in the individual cases appeared less with dihydrostreptomycin. Resistance studies are completed and available on only 12 patients in the group at this writing, 5 of whom developed resistant organisms during treatment.

Because of the development of cochlear-nerve damage in 4 of the 20 cases reported subsequent to completion of the course of therapy, a brief description of the development of symptoms is important. Follow-up study on a patient with ataxia on the sixtieth day of treatment reveals that he has no residual dizziness or ataxia, but vestibular function, as interpreted by the caloric test, has not returned. One week after discontinuation of therapy, tinnitus developed, and this has become slowly more marked. This patient's audiogram was not quite as good after 60 days of therapy as it was before treatment, and it has become progressively slightly worse for 5 months.

A second patient, a 52-year-old man, received 2.0 Gm. of dihydrostreptomycin daily for 90 days. One month after completion of his course of treatment he complained of moderate tinnitus, which has remained unchanged 3 months after treatment. Concomitantly he complained of occasional staggering, and loss of balance when bending over, these symptoms being exaggerated in the dark. No deafness was noted, but at the onset of tinnitus slight impairment of hearing was shown by the audiogram.

A third patient, a 30-year-old man, received 3.0 Gm. of dihydrostreptomycin daily for a period of 90 days. There was no evidence of cochlear-nerve involvement until two months after treatment, and since then he has had occasional

tinnitus and some clinical impairment of hearing. His audiogram also showed some impairment of function at the time tinnitus developed.

A fourth patient, a 37-year-old man, received 3.0 Gm. of dihydrostreptomycin daily for 90 days. One month after treatment marked tinnitus and mild deafness developed, both of which increased markedly in severity for the following month. An audiogram taken at the onset of tinnitus showed impairment of function. The audiogram taken a month later showed increased impairment.

In addition to these cases, a patient came to the authors after receiving dihydrostreptomycin for about two months in another hospital. Because he had miliary disease, it was decided to continue antibiotic therapy but change to 2.0 Gm. of streptomycin daily. About a month after admission (a month after dihydrostreptomycin had been stopped), he began to complain of deafness, and during the next month he became almost totally deaf.

In this small series of 20 cases, 4 patients (20 percent) suffered cochlear-nerve damage, which became apparent only after dihydrostreptomycin therapy was completed. In 3 of these cases nerve damage was not apparent until at least a month after completion of treatment. Though streptomycin is a definite toxin to the eighth nerve, it more specifically attacks the vestibular branch, and much less often the cochlear division. Dihydrostreptomycin, on the other hand, appears to attack the cochlear division as frequently as the vestibular division of the eighth nerve, and much more often than streptomycin does. (New England J. Med., 14 July '49)

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Early Roentgen Recognition of Lower-Lobe Tuberculosis: Because of the old dictum that reinfection tuberculosis has a preference for the apices and immediately infraclavicular regions, lesions in other locations are too often missed or, if noted, are considered nontuberculous until a sputum test proves positive. Actually, lower-lobe tuberculosis is not at all uncommon. It has, moreover, characteristic roentgenographic features which the authors believe should suggest the true nature of the disease at an early stage.

The incidence of lower-lobe tuberculosis as reported in the literature varies from a small fraction of one percent, through a middle group of from 2 to 6 percent, to almost 30 percent in one series of nurses reported by Ross. As Reisner and Weidman and Campbell have emphasized, this discrepancy is due to three factors: first, failure to obtain a lateral view; second, examination late in the course of the disease; third, the confusion that exists in the use of the terms basal tuberculosis, lower-lobe tuberculosis, hilar tuberculosis, and perihilar tuberculosis. Actually the hilar and perihilar forms are in the apex or subapical region of the lower lobe. It is only the overlapping of shadows in

the postero-anterior view that makes the lesion appear to be connected with the hilus. In the lateral view it is seen to be well separated from the hilar structures. Inclusion of these perihilar lesions in the lower-lobe group greatly increases the incidence of the latter form of the disease.

Infiltrations even in the infraclavicular regions may well be in the apices of the lower lobes, which quite frequently extend higher than is commonly supposed. The lateral view shows them to be well posterior, in the paravertebral gutter, below the interlobar fissure. These are true lower-lobe lesions, even though they are not in the very base of the lung. Less commonly, the disease may be confined to the extreme base, and many think of only this form as lower-lobe tuberculosis. Even this position is not exceedingly rare, but the lesions are usually misdiagnosed as bronchiectasis for a considerable period. The time of diagnosis must also be taken into consideration. A lesion which begins in the lower lobe frequently spreads to the upper, and the true sequence of events is then confused. The fact that so many lower-lobe lesions have been found in nurses may be partly accounted for by the fact of early diagnosis. On one point almost all observers have agreed, namely, that lower-lobe lesions are much more common in young females, and show a decided preference for the right side. The incidence is probably also higher in diabetics. The reasons for this are obscure.

Lower-lobe tuberculous lesions may be divided into two broad groups: first, transverse streaks of infiltration in the perihilar area, or just above or below it; second, smaller or larger areas of consolidation, often with cavity formation, sometimes involving the whole lobe. These types depend primarily on the stage in which the disease is first found. The rate of progression, as in tuberculosis elsewhere, varys extremely. A number of authors, however, have called attention to early cavity formation.

The authors' purpose in this report is to illustrate the first of the two types just mentioned, i.e., the early lesions which are present at the time the diagnosis should be made and treatment started. These early infiltrations consist of rather soft, transverse, often beaded lines extending, in the postero-anterior view, from the hilus or perihilar region transversely into the lung field, often to the periphery. At times they may be widely separated from the hilar region, occurring in the lateral portion only. It is the transverse appearance of these lines that the authors wish particularly to emphasize. In the lateral view, when the lesion is in the lower lobe apex, the infiltration is well posterior, near the posterior chest wall. It appears lower and more anterior when in the subapical portion. Very small lesions may be difficult or impossible to demonstrate in this projection. Fluid is apt to form early. As the disease progresses, nodular or patchy confluent areas appear. There is frequently early cavitation. Later, spread to the rest of the lobe occurs, either in the form of infiltrating streaks, which may also have the transverse

appearance, or as a massive consolidation. Finally, there is spread to the rest of the lungs.

There are many conditions which must be distinguished from lower-lobe tuberculosis. The authors discuss these only from the point of view of roentgenographic diagnosis. Obviously the final proof rests with the laboratory and the demonstration of the Mycobacterium tuberculosis or other etiologic agent. The clinical history and physical examination are equally important. In the very early case differentiation from normal lung markings is the most difficult problem. The shadows of the early infiltration of lower-lobe tuberculosis, however, are more transverse and extend transversely toward the periphery, rather than fanning out radially as do the bronchovascular markings. The lines also have a fine nodular or beaded appearance, which differs from that of the vascular shadows. Comparison with the opposite side is usually of help in differentiation.

In bronchopneumonia and bronchiectasis the shadows extend in a downward and outward direction toward the diaphragm rather than transversely. They are not as fine or beaded in appearance, and there is less involvement toward the periphery. Fungus infection and atypical pneumonia may also present problems in differential diagnosis, but these again do not show the characteristic transverse lines. In the presence of a nontuberculous abscess there is usually more pulmonary reaction surrounding the cavity. In the tuberculous form the transverse markings again may be helpful. Sputum studies are, of course, conclusive. The lymphatic permeation type of early metastatic cancer may be difficult to distinguish from lower-lobe tuberculosis. Segmental emphysema or atelectasis is usually associated with a primary neoplasm.

In this small series of 10 cases, as in the studies of others, it was observed that lower-lobe tuberculosis occurs predominantly in young women, with the incidence in nurses extraordinarily high. (Radiology, July '49, H. W. Ostrum and W. Serber)

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The Present Status of Vitamin B_{12} in Pernicious Anemia: Vitamin B_{12} is a red crystalline substance with a molecular weight of 1630. It contains cobalt, nitrogen and phosphorus but no sulfur. It is extracted from liver in exceedingly small amounts and can also be obtained from a variety of sources in nature, including the manure of cows, chicks, and other species and recently has been reported to be found in the liquor produced in the production of streptomycin. Its potency in the treatment of pernicious anemia was reported by West and confirmed shortly by Spies who also found it effective in sprue and nutritional macrocytic anemia. Its outstanding feature was its potency, doses as small as 4 micrograms being adequate to produce a maximal reticulocyte response.

The first person treated was a 66-year-old white female with pernicious anemia, a patient on the wards of the Kings County Hospital. Following a single injection of 150 micrograms a maximal reticulocyte response of 27 percent was observed and the blood count rose to normal and is still over 4 million, 10 months later, with no further therapy.

Having established the efficacy of the material, a series of trials was instituted to establish the limits of potency. It was found that a single injection of as little as from 3 to 6 micrograms produced a maximal reticulocyte response, and a total dose of 56 micrograms in one patient effected complete hematologic remission, which was maintained for 4 months before relapse, with no additional therapy. A dose of one microgram a day was found to give a maximal reticulocyte response and restore the blood count to normal. A daily injection of one tenth of a microgram was ineffective, but remission occurred when this was increased to three fourths of a microgram daily. One half a microgram daily gave a submaximal reticulocyte response. From these experiments the unit potency of B_{12} was fixed at approximately one unit per microgram, a unit being defined as the amount of antianemic substance required daily to effect and maintain hematologic remission in a patient with pernicious anemia.

The next problem to investigate was the effect of B_{12} on the neurologic lesions of combined sclerosis. One of the Bellevue patients had exhibited early cord lesions at the onset of treatment with one gamma a day, and at the end of 53 days of treatment had a negative neurological examination. Four patients with more severe neurological disease were treated at the Columbia-Presbyterian Medical Center by Doctor West. The dose employed here was 25 micrograms a week. There was marked improvement in ability to walk, and gain in subjective and objective motor strength and co-ordination. The neurologic signs such as Babinski and Romberg signs tended to diminish or disappear. Vibratory sense on the other hand improved slowly and only slightly. These patients have now been followed for 8 months, and on 25 micrograms a week have maintained their improvement and shown no sign of relapse. In general the neurological results of treatment with B_{12} seem to be as satisfactory as those that might have been obtained with vigorous liver therapy.

Meanwhile other workers have been investigating various aspects of B_{12} treatment and reporting their findings. Hall reported beginning disappearance of megaloblasts from the bone marrow as early as 18 hours after the injection of B_{12}. Bethell demonstrated that a substance probably the same as B_{12} was excreted in the stools of patients with pernicious anemia in relapse, and that this substance when extracted from their stools and given parenterally, caused remission. Berk et al. reported that when B_{12} was given by mouth it was ineffective unless gastric juice was given with it, an observation confirmed by Hall. From these facts it has been suggested that the role of the intrinsic

factor of Castle may be to promote the absorption of B_{12} from the gut, and B_{12} has been suggested to be the extrinsic factor.

The question will at once be asked about the relationship of B_{12} to folic acid. Bethell reported that the response to B_{12} was inhibited by folic acid antagonists. Sturgis has reported that B_{12} is ineffective in the so-called pernicious anemia of pregnancy, which is cured by folic acid, and Luhby reports that B_{12} is likewise ineffective in the treatment of acute megaloblastic anemia of infancy, which also responds to folic acid. Folic acid and B_{12} probably operate at different levels in the process of hematopoiesis.

It has been shown that thymine in a ratio of several thousand to one can replace folic acid in the growth requirements of Streptococcus lactis R and Lactobacillus casei. Spies gave thymine in similarly large doses to patients with pernicious anemia and sprue, and obtained restoration of the blood count. Like folic acid, however, thymine had no effect on the neurologic lesions in these conditions. Wright has shown that the growth requirements of L. lactis can be met by substituting thymidine for B_{12} in a ratio of 10,000 to 1. Thymidine is the desoxyriboside of thymine and from the foregoing evidence it is tempting to postulate that the role of folic acid is to act as a coenzyme in the formation of thymine, which is then converted to its desoxyriboside by the enzymatic action of B_{12}. The author and his co-workers have attempted to treat patients with pernicious anemia with thymidine in dosage up to 150 micrograms, without notable effect. Although such an hypothesis is attractive it is probably oversimplified and fails to take into account a wealth of accumulated evidence concerning the role in hematopoiesis of other factors, including xanthopterin and other pterins. Most recently, a highly potent hematopoietic substance called B_{14} has been announced, but this claim is awaiting confirmation at present.

Finally, the presence of cobalt in B_{12} is certain to excite interest because of the fact that this element has been implicated for many years in the production of experimental polycythemia. With the aid of its isotopes it is now possible to learn more about the fate of cobalt in the body, and the presence of this inorganic ion in B_{12} may ultimately be of great help in studying the formation and role of this vitamin. Two of the author's patients were treated by West with cobaltous chloride with no effect, before they responsed to B_{12}. (Bull. N. Y. Acad. Med., July '49, E. H. Reisner, Jr.)

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Observations on the Macrocytic Anemia Associated with Pregnancy: The relationship of anemia in the mother and the young infant is close, closer perhaps than has been realized. For a number of years the author and his co-workers have been studying the anemia complicating pregnancy, which

some call the pernicious anemia of pregnancy. It is a macrocytic anemia with a high color index and it responds to liver, folic acid, or yeast. If the mother is not treated while pregnant, the infant also may have anemia later, especially if the infant's diet is poor in substances which contain folic acid or substances which act similarly. The important thing is to realize that there is an association between anemia in the mother and the early development of anemia in the child and to understand the necessity of administering, in many instances, yeast, folic acid, meats and meat products, or various mixtures of these materials. For years it has been recognized that certain infants have megaloblastic anemia and some of these infants have been treated successfully with liver extract. More recently Zuelzer and others described a syndrome of this type which responds to folic acid therapy. It has also been observed that folic acid is effective in this type of anemia in infants and children. The important point is that if treatment is administered to the mother and if the baby is fed a diet containing adequate folic acid or substances acting similarly, anemia of this type does not develop.

Six patients were selected for study using the following criteria: (1) the patient must have been pregnant within a few weeks prior to the initiation of the study. (2) She must have a macrocytic anemia with red blood cell counts of 2.5 million or less and a color index greater than one. (3) She must have megaloblastic arrest of the bone marrow. (4) She must have free hydrochloric acid in the gastric juice. (5) She must be untreated or must not have been treated recently enough to interfere with folic acid as a therapeutic agent.

The patients were admitted to the hospital and throughout the course of the study were maintained on a diet which was devoid of meat, meat products, fish, poultry, milk, and eggs. Daily hematologic examinations included leukocyte and erythrocyte counts, hemoglobin determinations, and reticulocyte counts. A Leitz colorimeter was used for determining in grams the hemoglobin content of the blood. The reticulocytes were counted in wet preparations by the use of a modified brilliant cresyl blue solution of Dameshek. Cell volumes were determined frequently on oxalated venous blood by Wintrobe hematocrit tubes. Bone marrow was obtained by sternal aspiration prior to therapy and at the peak of reticulocytosis. Differential counts were made on preparations stained with both supravital and Wright's stains. After the baseline determinations were completed, the patients were given folic acid by mouth.

The author and co-workers have made many studies on the specificity of the folic acid molecule. Various fragments of the molecule are ineffective when given alone or in any combination. The change of the glutamic acid to aspartic acid also makes it ineffective. Folic acid either in its conjugated form or in its free form is effective in producing reticulocytosis, an increase in white blood cells, hemoglobin, red blood cells and platelets in persons who have pernicious anemia, nutritional macrocytic anemia, and the macrocytic anemia of pellegra, pregnancy, and sprue. Folic acid should be considered

a member of the vitamin B complex, as are thiamine, niacin, and riboflavin. The author believes that the pregnant woman should have 2 milligrams of folic acid daily during the latter months of pregnancy. (Surg., Gynec., & Obstet., July '49, T. D. Spies)

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Internal Radiation Hazards from the Use of Polonium in Static Eliminator Devices: Radioactive materials have been used effectively in static elimination devices. Although such equipment is efficient, inexpensive and easily produced, the internal radiation hazards involved with the commercial distribution and industrial application of such apparatus have neither been sufficiently described nor completely investigated. Elimination of static electricity generated by leather belts moving over cast iron or steel pulleys, paper passing over metal rolls, and film over metal or plastic rolls has been a problem in industry for many years. Lately, radioactive materials have been used to produce a layer of ionized air between the dielectric material, and some metal portion of the machine which can be grounded easily. Because the usefulness of this type of device depends on the degree of ionization produced in the air, the most effective ionizing agent should be used.

The types of radiation which emanate from natural radioactive substances such as radium or uranium or from artificially-produced isotopes are gamma radiation which is an electromagnetic type and resembles x-rays, beta radiation which is a flow of negatively charged electrons, and alpha radiation which is a flow of alpha particles (helium nuclei). Any one or a combination of these types of radiation will produce ionization in the air. However, the most efficient ionizer for this purpose is the alpha particle.

Both radium and polonium are active alpha emitters and have an energy of approximately 5 million electron volts. Radium has slightly less energy than this value and polonium slightly more. In principle and theory, the use of these substances in static eliminators is excellent. It would seem from these facts that the major problems in static elimination have been solved. However, serious difficulties remain regarding important industrial hazards associated with the employment of these radioactive substances commercially. The most energetic alpha particles are barely able to penetrate the keratinized layers of the skin. Nevertheless if alpha particles enter the blood stream either by way of the intestinal tract or through the lungs during inhalation, they may produce some of the most serious types of radiation damage. Therefore, internal radiation hazards from polonium must be considered carefully by all concerned before and continuously during the production and use of this type of static eliminating equipment.

Radium has an atomic number of 88 and an atomic weight of 226. It has a half life of 1590 years. The energy of the alpha particles emitted is 4.79 million electron volts. A weak gamma photon is produced (0.19 million electron

volts). Polonium or radium F has an atomic number of 84, an atomic weight of 210, and a half life of 140 days. Its alpha radiation has an energy of 5.30 million electron volts. A gamma photon of 0.8 million electron volts is also emitted.

Because both radium and polonium emanate strong alpha rays, they are effective static eliminators. However, polonium is preferable, because on the basis of weight, the strength of the alpha emission is inversely proportional to the half life. Therefore, minute quantities of polonium emanate relatively large amounts of radiation. Also polonium decays into stable lead with an atomic weight of 206, whereas radium decays through a long chain of reactions. In these disintegrations, alpha particles are emitted along with many gamma and beta rays which are not so desirable for this use because only energetic alpha rays are needed. It was noted previously that polonium produces gamma rays of only 0.8 million electron volts. This is in the proportion of one gamma photon for every one million alpha particles emitted. Therefore, the gamma radiation is negligible for all practical purposes. Thus, polonium is an ideal antistatic material because it emits energetic alpha rays, has high specific activity, and its decay product is the stable element lead.

With nonpenetrating radiations such as the alpha rays emanating from polonium there are two main systems through which such material may enter the human body and cause radiation damage. First, and most important, is absorption from the lungs. When polonium is electro-plated on metal strips for use in static eliminator devices, its strong alpha activity produces a constant bombardment resulting in a continuous release of tiny particles of the gold plate over the polonium film into the surrounding atmosphere. These minute metal particles usually have small particle size that may cause serious inhalation hazards because they remain suspended in the air for long periods and may be airborne to the terminal pulmonary passage. When such radioactive particles enter the lungs, they have direct contact with the mucous membranes. Their alpha emission causes intense ionization in these tissues which may destroy cells locally or produce chemical changes in these cells. Later it may cause similar damage in other areas after entering the blood stream either directly through the capillary walls, or indirectly via the lymphatic system. Polonium is excreted in the urine and is a renal toxin. The metabolism of polonium is not completely understood. To date there are no exact data regarding the effects of polonium on the blood forming cells in the bone marrow.

Studies by K. Z. Morgan indicate that approximately 5 percent of polonium entering the body through the bowel is localized in the kidneys. The estimated tolerance value for alpha activity is 0.010 microcuries. Using this figure, the total whole body tolerance would be approximately 0.20 microcuries, or calculated by weight, approximately 4.5×10^{-11} grams of polonium. The concentration of alpha particles in the air which man may tolerate is

estimated to be approximately 10 micromicrocuries per liter of air. For polonium this would be equivalent to 2.2×10^{-15} grams per liter of air.

A large printing company had recently received, by railway express, two packages containing several metal bars. No information was enclosed with the material and no warning notices were placed on the packages. No labeling was done regarding the identity of the contents. It was known by the company that these bars were to be used on the printing presses as electrostatic eliminators. The company officials contacted the California State Department of Health and were made aware of the possible radiation hazards. Therefore, consultations were made with the members of the Radiological Safety Unit at the University of California at Los Angeles Atomic Energy Project in conjunction with members of the California State Department of Public Health. A complete radiological survey of the area was conducted. The metal bars were measured for alpha and beta activity with a Victoreen 356 Alpha Survey Meter over the active and inactive portions of the bars. It was immediately apparent that the supposedly inactive surfaces were grossly contaminated by an alpha emitting substance. One of the members of the State Health Department handled two of the bars, touching only their inactive surfaces. His hands were surveyed with the alpha meter and the alpha activity registered represented an equivalent of 25,000 counts per minute. Calculations, using this value, showed that approximately 0.02 microcuries of radioactive polonium had been transferred to his hands during this short exposure. Three vigorous washings with borax soap and water reduced the activity to one third of its initial value. Continued scrubbing with a hand brush and soap reduced the amount of contamination further but did not completely remove it after 15 separate washings. The office where the metal bars had been stored for a few days without any unusual amount of handling prior to the survey was shown to be contaminated in many places. The arms of the desk chair, the telephone earpiece, and the inside door knob showed definite alpha activity.

In another specific case some small foils were brought to the authors by an individual who had been using them in his research problem on a study of antistatic devices. This individual had accepted the basic information of literature distributed with the material, which proclaimed these foils as non-hazardous. Accordingly, he used no handling precautions. The foils were brought in wrapped in tissue and placed in letter envelopes. This person's hands, the outsides of the envelopes, the coat pocket he carried them in, his trouser pockets and his personal effects such as keys, wallet, comb, etc. were highly contaminated. This person and one other associated with him, and who had also handled the active foils, both showed alpha activity in 24-hour urine specimens. The urine specimens were collected in such a manner that no outside alpha contamination was possible. The results show that transfer from hands to mouth is quite possible and occurs with surprising ease.

Inside of each of the envelopes the tiny gold flakes could be seen. One of these flakes was removed, and one attempt to check its activity indicated that it was so high that it was off scale on the insensitive range of a Victoreen 356 Alpha Survey Meter. The contamination potential of one of these foils was checked by placing it on a piece of filter paper with the supposedly non-active side in contact with the paper. A radioautograph was made of the filter paper after the foil was carefully removed. The radioautograph indicated that the so-called protective layer of gold had been almost completely removed along the edges of the foil by previous handling. Also, at one end of the small foil strip where there was originally an inactive area for handling the radioautograph indicated that the highest contamination was present.

Apparently in the production of these antistatic devices, polonium is obtained from radiolead or radium D. The strips and foils examined showed an appreciable amount of beta radiation which suggests that the polonium may have been contaminated with radium D and E. The half life of radium D is 22 years and it decays with the emission of 0.025 mev beta and a 0.047 mev gamma radiation to radium E. Radium E or radiobismuth has a half life of 5 days and decays with the emission of 1.17 mev beta to polonium. These more penetrating beta radiations emanating from the radiolead and radiobismuth contaminants in the polonium do not appreciably increase the external hazards from such devices but the presence of long life radiolead does increase the hazard from internal radiation. When radiolead is absorbed in the body, some is deposited and remains in the bones. Thus an exposed individual might store in his bones a producer of polonium which could cause serious radiation damage and associated depression of the blood forming cells.

Radiolead behaves like stable lead in the bones of the body. An intercurrent infection or any disturbance in metabolism which produces an acidosis or a diuresis results in mobilization of the lead from the bones into the blood stream and from there to the kidneys and other vital organs of the body. Thus radiolead is not only a serious continuous damaging agent to the bone marrow but intermittently it may cause injury to other vital tissues because of this periodic withdrawal from the bones into the general circulation followed by redeposition in the bones.

Apparently individuals who are studying the use of static eliminator devices and other persons who are involved in research with these radioactive materials have not been sufficiently instructed regarding the possible dangers to which they are subjecting themselves. In addition, it is also apparent that companies producing this equipment for commercial distribution have not been aware of all of the potential dangers. Plating a gold film over the radioactive polonium does not prevent the escape of radioactive material, because of the energetic alpha radiation emitted by polonium. From the authors' observations it is imperative that proper consideration be given to the potential internal radiation hazards in the industrial use of such static eliminating devices,

particularly in respect to inhalation and ingestion of these dangerous radioactive substances. (Univ. Calif. School of Med., Atomic Energy Proj. AT-04-1-GEN-12, Rep. No. UCLA 18, 28 Apr '49, F. A. Bryan and L. B. Silverman)

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Rabies Vaccine Encephalomyelitis in Relation to the Incidence of Animal Rabies in Los Angeles: In areas where rabies is endemic the management of persons bitten by animals is unsatisfactory. Any advantage gained from the use of vaccine must be balanced against the chance of resultant, postvaccinal encephalitis. The following indications for vaccination against rabies in human beings have been suggested: (a) the biting animal is clinically rabid, or (b) is proved rabid by laboratory tests, (c) is suspected of being rabid, (d) in an endemic area a stray animal escapes after biting, (e) an individual has handled an animal diagnosed as rabid and fresh abrasions of skin have been contaminated with saliva.

The number of persons who develop rabies after the bite of a rabid dog is not known with certainty but on the average may be from 5 to 15 percent; if vaccine is given, the number may be reduced by half. Too often, however, the situation involves categories (c) and (d) above. In such instances it is particularly necessary to estimate the likelihood of severe vaccination reactions. McKendrick's figures of 1940 collected from worldwide sources show that paralyses are attended by a fatality rate of 5 percent for the dorsolumbar type and 30 percent for the Landry type. Most of the vaccine used in this country is the Semple type and few data are available on the actual number of paralytic accidents here after use of such material. McCoy reported an incidence rate of 1:2,900 among 17,600 treated persons but because 4 of the 6 reactions were fatal this rate probably is too low. Among 24,000 treated persons, Horack recorded a rate of 1:1,200, 10 percent of which were fatal.

Rabies is endemic in Los Angeles. There were in 1946 approximately 3.5 million people living in an area of 4,000 sq. mi. in the county and almost 2 million in the 450 sq. mi. of the city proper. During the period of 25 years prior to 1947, there were 3,190 persons in the city bitten by dogs proved to be rabid, but 3,560 persons received rabies vaccine. Of 22 persons who died from rabies 14 had no vaccine. In 20 years of this period there were 14 cases of human rabies in the county exclusive of the city. In the city approximately 90 percent of the dogs over 4 months of age are licensed. On the basis of 125,000 licenses issued in 1946 the city's dog population exclusive of puppies may be estimated to be 140,000. On the average, a laboratory diagnosis of rabies is made annually on 40 dogs. Thus, at least one dog in 3,500 in the city becomes rabid. Because there are an unknown number of rabid dogs either not brought to examination or not detected if examined, the actual incidence is almost certainly higher. Approximately 150 rabid dogs per year are found

in the county outside the city but the total dog population in the county is unknown.

Some 10,000 animal bites per year are reported in the city; these are almost all by dogs. Approximately 70 persons per year are bitten by known rabid animals; thus, one bite in 140 is by a rabid animal. On the basis of a fatality rate in human beings of from 10 to 15 percent following the bite of a rabid animal,the chance of getting rabies from known animal bites in the city of Los Angeles is from 1:1,400 to 1:2,100. This does not include the numerous unreported bites which must occur.

During the 7-year period from 1940 to 1946, 9 cases of severe post-vaccinal reactions, including one death, occurred among 5,500 persons receiving vaccine (Semple) in the city and county, an incidence of 1:600.

Even the remote probability of developing rabies from a dog bite indicated by the rough approximation made here will not alter the necessity of employing vaccine for any person bitten by an unidentified dog. Certainly, however, many persons receive vaccine who do not require it. On the basis of data presented here and elsewhere it is apparent that the incidence of rabies vaccine encephalitis is a real contraindication to its indiscriminate use. Without discussing the theories regarding the etiology of this condition, it is likely that the incidence will be reduced markedly when a product more completely freed of brain tissue is produced; most present vaccines consist of approximately 10 percent suspensions of rabbit brains.

There is ample evidence that rabies can be controlled in the absence of any considerable wild animal reservoir by control of dogs. (Am. J. Pub. Health, July '49, C. F. Pait and H. E. Pearson)

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Autoantibodies in Different Phases of Human Glomerulonephritis: The authors have examined the sera of 51 patients with glomerulonephritis in all stages and of 126 controls for the presence of antibodies to human kidney. They found that in 72.7 percent of the tests done on the patients with nephritis, high positive titres can be obtained (average 1:412). The percentage of positive cases and the titres are higher in the later stages of glomerulonephritis than in the first month of the disease.

Twenty-eight determinations were done in 12 cases during the first month of the disease, yielding an average titre of 1:107 with only 42 percent of the cases being positive more than 60 percent of the time. Two hundred and twenty-one determinations were done in 39 cases after the first month of the disease, yielding an average titre of 1:450 with 79.5 percent of the cases being positive more than 60 percent of the time. This difference may

be due largely to the fact that during the first few days of acute glomerulonephritis no antibodies can be found in the serum because they are completely absorbed in the kidney. Two hundred and five determinations performed on 126 normal controls yielded an average titre of 1:46 with only 17.5 percent of the cases positive 50 percent of the time or more.

Renal antigens obtained from infants or stillbirths show a much greater specificity and higher titres than antigens from adult renal tissue, a fact which may explain the high incidence of glomerulonephritis in young individuals.

The continuous presence of antibodies to kidney throughout all stages of the disease except the first few days indicates that human nephritis does not result from a single insult with subsequent scarring but rather from the constant presence and occasional stimulation of antibodies to renal tissue. Neutralizing these anti-kidney antibodies by means of kidney tissue emulsions or extracts should be carefully investigated as a possible therapeutic approach. The use of antihistaminic drugs to mitigate the vascular effects of such an antigen-antibody reaction should also be investigated further. (Bull. N. Y. Acad. Med., July '49, K. Lange et al.)

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Hypermetabolism Without Hyperthyroidism: It is an accepted fact that there are clinical conditions in which the basal metabolic rate is elevated in spite of the fact that none of the features of hyperthyroidism is present. Clinicians have known for a long time that many of the patients suffering from hypertension, polycythemia, leukemia, malignant lymphomas, generalized or localized malignant growths, Paget's disease of the bones, and other diseases frequently present an elevation of the basal metabolic rate. It is also well recognized that these patients do not present the classical signs of hyperthyroidism and the pathological changes in the thyroid gland do not suggest the typical hyperplasia and other alterations of Graves' disease. The authors have attempted to study thyroid function in this group of patients with elevated basal metabolic rates by determining the level of the nondialyzable (protein-bound) blood iodine and the urinary excretion of tracer doses of radioactive iodine (I^{131}). Both of these methods show constant changes in hyperthyroidism in which the hormone iodine is consistently elevated in the blood and the urinary excretion of tracer doses of I^{131} is reduced because of the increased avidity of the thyroid gland for iodine.

In a series of over 100 consecutive patients suffering from the diseases listed above whose metabolic rates were elevated and who presented no clinical signs of Graves' disease, the authors determined the blood iodine levels in all and the I^{131} excretion in some. Without exception, the blood iodine levels and I^{131} excretion were normal in spite of very marked elevations of the basal metabolic rate. (Bull. N. Y. Acad. Med., July '49, S. Silver et al.)

1-Methyl-2-Mercaptoimidazole - An Antithyroid Compound Highly Active in Man: The antithyroid compounds used for the treatment of hyperthyroidism were previously selected for clinical trial on the basis of high potency in the rat. Subsequent experience, showing that the rat assay was a poor index of effectiveness in man, led to the development of a method using I^{131} by which these substances were tested directly in normal human beings. Antithyroid activity determined in this way correlated quite well with clinical effectiveness. 2-mercaptoimidazole, which was found to be about 10 times as active as thiouracil, has now been used to treat 34 patients during a period of two years. The results obtained were quite in keeping with the predictions of its potency based on the iodine uptake test.

During the course of testing a limited number of further compounds by the radioiodine method, it was observed that 1-methyl-2-mercaptoimidazole was remarkably active. As little as 0.5 mg. exerted a pronounced inhibitory effect on iodine accumulation and doses of 5.0 mg. completely inhibited the uptake for nearly 24 hours. It was estimated that the activity of 1-methyl-2-mercaptoimidazole was approximately 100 times that of thiouracil. Preliminary studies on 30 patients with hyperthyroidism treated with this compound have confirmed a high degree of effectiveness. (Endocrinol., June '49, M. M. Stanley and E. B. Astwood)

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Observations and Recommendations Concerning the Use of Serum Albumin and Plasma: The Advisory Board on Blood and Blood Derivatives, BuMed, met on 13 July 1949, to consider the problem concerning the transmission of homologous serum jaundice or infectious hepatitis through the use of Stock Nos. 1-582-010, Albumin, Serum, Human, 1-582-045, Albumin, Serum, Human, Salt Poor, and 1-607-104, Plasma, Normal Human, Dried, and to decide upon the advisability of sterilization of existing stocks of these materials by irradiation.

The following excerpts from the minutes of the meeting of this Board are presented for the information and guidance of those concerned:

Observations:

1. There is an element of danger in the clinical use of dried plasma, human, inasmuch as it is known to transmit homologous serum jaundice. This has been the subject of numerous articles in medical journals since 1940.

2. Thus far no cases of homologous serum jaundice or infectious hepatitis are known to have occurred following the use of serum albumin, human. This is believed to be primarily a result of the method of preparation, namely, (a) the low temperature fractionation with alcohol and (b) the pasteurization at 60° C. for 10 or more hours which is made possible by the addition of acetyl-tryptophane.

Recommendations:

1. That use of indated plasma, human, dried, without irradiation, be continued, with the clinician weighing the possible beneficial effects of these therapeutic agents against the possible harmful effects, before administering them.

2. That the Materiel Division reprocess outdated plasma, normal human, dried, to serum albumin as such outdating and requirements beyond existing stocks occur.

3. That the advisability of irradiating plasma be deferred pending further study and more specific evidence concerning the efficacy of such treatment. (Professional Div., BuMed)

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Training Duty for Reserve Dental Officers: Training duty is again available for Reserve dental officers during the fiscal year 1950. Although not compulsory for retirement points, this duty will be necessary for future promotion points. During the fiscal year 1950 it is anticipated that the number of training duty billets ashore will be increased considerably and those afloat will be reduced accordingly. During the past fiscal year several Reserve dental officers requested training duty at activities for which no billets existed. For this reason, Reserve dental officers are reminded to submit their requests to their cognizant naval district offices early in the fiscal year.

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"Feel Alive": A brochure prepared primarily for use by Navy officers is now in the hands of the printers. The technical material is presented in an easily understandable style. The brochure is profusely illustrated, and contains facts and suggestions to assure the physical well-being of every Navy man and woman. Prepared by BuPers and BuMed, it encourages personnel on active duty to keep physically fit through proper exercise and diet. The brochure will be distributed throughout the entire Navy.

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ALNAV 73 27 July 1949

Subj: Presidon Tablets and Powder

Discontinue use immediately survey and destroy all stocks Hoffman-LaRoche Presidon tablets and powder. --SecNav. F. P. Matthews

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Op24B/cj, NH/A3-1, Serial 253P24 13 July 1949

To: All Ships and Stations

Subj: Command Relationships of U. S. Naval Hospital, Great Lakes, Ill.

Ref: (a) SecNav ltr, serial 84513 of 28 Mar 1944; AS&SL Jan-Jun 1944, 44-334, p. 8

1. The U. S. Naval Hospital, Great Lakes, Illinois, is hereby removed from the military command of the U. S. Naval Training Center, Great Lakes, Illinois, and placed under the military command and coordination control of the Commandant, Ninth Naval District. Reference (a) is modified accordingly.

2. Bureaus and offices concerned take necessary action.

--SecNav. F. P. Matthews

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BUMED CIRCULAR LETTER 49-89 25 July 1949

To: All Ships and Stations

Subj: Early Syphilis Treatment Failure Rates; Submission of Data with Reference to.

Ref: (a) BuMed C/L No. 47-149.

1. Data pertaining to early syphilis treatment failures is no longer required by the Bureau.

2. Reference (a) is hereby canceled. --BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-90 27 July 1949

To: All Ships and Stations

Subj: Transportation of Remains When Death Occurs Outside Continental U.S.

Ref: All Ships and Stations ltr dated 14 Aug 1947; AS&SL Jul-Dec 1947, 47-723, p. 49.

1. Reference is hereby cancelled. Detailed instructions relative to transportation of remains of deceased naval personnel will be issued in the near future. In the interim, surface transportation should continue to be utilized for movement of remains of deceased naval personnel to the United States. However, in any case where Government air transportation is readily accessible, such may be utilized with the Bureau of Medicine and Surgery being so informed together with information as to the date and time of departure and the place and time of arrival in the United States.

2. When death occurs at a place where facilities for embalming or encasement are not available, transportation by airplane to another overseas military activity, within practicable flying distance, where such services are available, may still be effected through the local command. Similarly, transfer of remains by air to another overseas activity for return to the United States by surface vessel may be arranged locally and the Bureau of Medicine and Surgery so informed. --BuMed. C. A. Swanson

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