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This section provides a medium through which Canadian surgeons can declare themselves, briefly and informally, on the day-to-day affairs of surgery.

Noninvasive Evaluation of the Carotid Circulation

Pasteur died of a stroke. So did Lenin, von Hindenburg and Franklin D. Roosevelt. Through most of medical history it was thought that strokes were cataclysmal intracranial vascular accidents, unpredictable and without satisfactory treatment or possibility of premorbid diagnosis. The recently appreciated fact that most patients with ischemic strokes have potentially operable extracranial carotid lesions has provoked interest in their early recognition and localization. Although arteriograms are necessary to define the anatomy of carotid bifurcation lesions prior to operation, it is desirable to be able to screen patients without the inconvenience, expense and small risk associated with arteriography, particularly when serial examinations are required. Patients with asymptomatic bruits, atypical neurologic symptoms and previous strokes are of special interest.

The noninvasive methods that have been developed have elucidated several clinical observations. As a stenosis increases the associated bruit becomes longer and of higher pitch, and as the occlusion becomes nearly complete, the bruit may no longer be audible. Carotid phonoangiography provides photographic representation of the waveforms produced by such bruits and allows their differentiation from transmitted cardiac murmurs or more proximal bruits. By comparing the waveforms with the arteriogram one can deduce the degree of stenosis represented on the former. A pansystolic bruit represents a 40% to 50% stenosis and a bruit extending into diastole indicates an even greater stenosis and a more marked pressure gradient.[1] The carotid vessels can also be studied with a directional Doppler flow probe to generate a flow map on the storage oscilloscope and thus provide a graphic projection of blood flow velocities, allowing localization of a stenotic lesion and an estimate of the amount of narrowing. At the same time, recordings can be made of the audiosignal for subsequent study and interpretation, and a tracing generated of the analog blood flow signals.[2,3]

The ophthalmic artery is a direct continuation of the intracerebral portion of the internal carotid artery and can be studied with a Doppler flow probe, as can its supraorbital branch. A hemodynamically significant internal carotid artery stenosis may be reflected by a reversal of ophthalmic or supraorbital artery flow.[4] Since the collateral circulation through the ipsilateral external carotid or the opposite internal carotid artery across the circle of Willis is quite variable, it may or may not allow normal or near normal pressure in the internal carotid artery distal to the middle cerebral artery to generate antegrade signals. Bone and Barnes[5] have added refinements such as carotid compression to the technique of Doppler ophthalmic examination and report a higher degree of accuracy; yet these additions add small but definite risks to an already complex technique and make its application as a simple screening test performed by a technician more difficult. Those noninvasive techniques that depend solely on evaluation of ophthalmic or supraorbital artery flow have been found to overlook a sizeable number of significant stenoses, and many give positive results only with near or total occlusion of the internal carotid artery.[6-8] The results of such determinations are helpful if positive but not of much value if they are negative.

Oculoplethysmography is performed by applying small suction cups to the cornea to record the volume changes in each globe produced by pulsatile arterial flow. At the same time recordings are made of ear lobe pulses to detect any delays between the internal and external carotid pulses which are indicative of an internal carotid stenosis. Such pulse delays are often minimal and the study may overlook patients with bilateral disease. In experienced hands an accuracy rate of 90% can be attained by combining oculoplethysmography with carotid phonoangiography, permitting greater discrimination in recommending arteriography and increasing the yield of those arteriograms performed.[1,8]

Prospective clinical studies[6,8] have compared the accuracy of several noninvasive studies. The clinical diagnosis of cerebrovascular disease was not always accurate, nor was the correlation between lesions and the presence of a bruit. None of the methods detected stenoses of less than 50%. With greater degrees of stenosis the methods were of varying accuracy and those studies that used more than one means of evaluation achieved maximum accuracy. Our own preference has been for the combined carotid Echo Doppler scan consisting of four parts: carotid bifurcation imaging, recording of carotid Doppler audiosignals, strip chart recording of analog blood flow signals and deter-

minations of ophthalmic artery flow direction. Using this combination, an accuracy of 93% of that attainable with arteriography has been possible, and lesser degrees of stenosis have been recognized.[9]

What are the uses and abuses of noninvasive studies? Patients with asymptomatic bruits, nonhemispheric neurologic symptoms, prior strokes, or known risk factors for cerebrovascular disease can be studied noninvasively in an attempt to identify those at particular risk of stroke and to improve the selection of patients for arteriography. Patients who require repeated examinations to follow the progression of asymptomatic bruits or nonhemodynamically significant stenoses obviously cannot be subjected to repeat arteriography at regular intervals, but can be studied noninvasively with no risk and minimal expense and inconvenience. The major limitation of noninvasive studies has been their inability to detect ulcerated plaques, particularly if they are nonstenotic. The most common cause of transient ischemic attacks (TIAs) is emboli, most of which originate from ulcerated plaques at the carotid bifurcation. Single or multiple TIAs represent a considerable stroke risk and are a *bona fide* indication for arteriography. If noninvasive techniques are used instead of arteriography in patients who present with TIAs a considerable number of patients who might benefit from carotid endarterectomy will be overlooked.

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Nerve Entrapment Syndromes

In this issue (page 354) Wiens and Lau draw attention to a particular type of peripheral nerve entrapment syndrome affecting the anterior interosseous nerve of the forearm. Although the article deals exclusively with a relatively rare form, it is well to be reminded of the existence of nerve entrapment syndromes.

The subject merits periodic emphasis in the literature because entrapment syndromes in general are not rare. The symptoms develop insidiously, are somewhat bizarre and frequently mimic those caused by other pathologic entities. An example of this mimicry is the resemblance between "spinal claudication", due to entrapment of the cauda equina and the lumbar nerve roots in spondylitic spinal stenosis, and vascular claudication. Only a careful and complete history and physical examination will make the distinction between them apparent. The symptoms of entrapment of the lateral femoral cutaneous nerve near the anterior superior iliac spine (meralgia paresthetica) can be confused with those of "atypical" vascular claudication. I have encountered many patients with this form of entrapment syndrome who have needlessly been shunted back and forth between a variety of health care professionals in the search for relief of their symptoms.

Awareness and recognition of nerve entrapment syndromes should therefore be of interest to surgeons as well as to primary care physicians. An excellent monograph[1] is available to those wishing to extend their knowledge of the subject.

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Parathyroid Hormone and Hyperparathyroidism: Current Concepts

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Our expanding knowledge of the physiologic and biochemical factors governing calcium homeostasis has improved our capacity to evaluate hypercalcemia, of which an increased incidence is being discovered through the widespread use of multiphasic screening. Consequently, we are diagnosing mild forms of hyperparathyroidism more often than formerly. The enhanced recognition of virtually symptom-free hyperparathyroidism presents a problem in patient management because the natural history of this form of hyperparathyroidism is unknown and the pathologic lesion underlying the condition may be ambiguous, resulting in difficult decisions in surgical management. Further study is required to resolve this issue in order to provide optimal care for the affected individual.

Notre connaissance croissante des facteurs physiologiques et biochimiques qui gouvernent l'homéostase du calcium a amélioré notre capacité d'évaluer l'hypercalcémie que l'on découvre maintenant avec une fréquence accrue grâce à l'emploi répandu des épreuves de dépistage. En conséquence, on diagnostique de plus en plus souvent les formes bénignes d'hyperthyroïdie. La reconnaissance plus fréquente d'un hyperthyroïdie virtuellement asymptomatique pose un problème de traitement puisque l'évolution naturelle de cette forme d'hyperthyroïdie est inconnue et que la lésion pathologique sous-jacente peut être ambiguë, entraînant de difficiles décisions de traitement chirurgical. D'autres études sont requises pour résoudre cette question de façon à assurer des soins optimums aux personnes qui en sont atteintes.

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The increase in our knowledge of parathyroid physiology and chemistry coupled with the widespread use of biochemistry to assess patients has greatly altered our understanding of the pathogenesis of hyperparathyroidism and our concepts regarding its management.

Calcium Homeostasis

The calcium of the extracellular fluid appears to be maintained in tight control by the net result of calcium fluxes across the intestine, kidney and bone (Fig. 1). The mechanisms influencing calcium transport in these tissues have come under intensive scrutiny in recent years, and considerable new insight has been gained into the actions of vitamin D and parathyroid hormone (PTH), the two major humoral factors controlling calcium homeostasis. Vitamin D has been shown to undergo metabolic transformation from a precursor of low potency to a highly active entity.[1] It is known that this sterol, ingested in food or converted by ultraviolet irradiation from an inert precursor, 7-dehydrocholesterol, is transported by a plasma protein to the liver where it is hydroxylated at the 25 position. This 25-hydroxy vitamin D derivative is then carried in the circulation as a protein-bound entity to the kidney (mainly), where one of at least two additional hydroxylations may occur. In association with states of hypocalcemia, phosphate depletion and PTH excess, the activity of a renal hydroxylase enzyme is augmented and a 1,25-dihydroxy vitamin D derivative is formed.[1,2] This is the most potent metabolite of vitamin D yet discovered. It acts chiefly on the intestine to enhance calcium absorption and restore normocalcemia; at least in pharmacologic concentrations it is capable of producing bone resorption as well. Additionally, perhaps by an indirect mechanism, the vitamin seems necessary for the full resorptive action of PTH on bone. In calcium-replete states, the major circulating dihydroxy metabolite is believed to be 24,25-dihydroxy vitamin D, the primary function of which is currently being evaluated. The major role of PTH in influencing absorption of calcium from the gut is therefore indirect through its "activation" of 25-hydroxy vitamin D to its potent, 1,25-hydroxy metabolite.

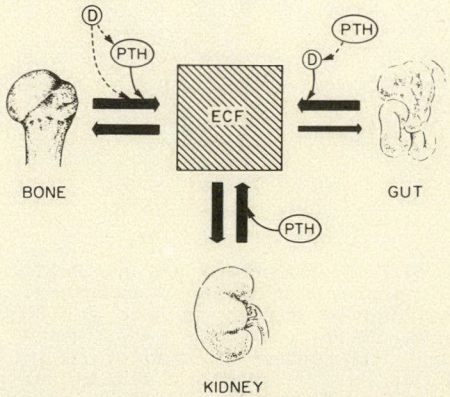

FIG. 1—Sites of known (→) and potential (- - ►) action of vitamin D (D) and parathyroid hormone (PTH) as mechanisms influencing calcium transport across gut, bone and kidney in maintenance of calcium of extracellular fluid (ECF).

In physiologic circumstances the major direct role of PTH in maintaining calcium homeostasis may be to enhance calcium absorption from the (distal) renal tubule and thereby to diminish calcium loss through the kidney.[3] In contrast, by interfering with phosphate reabsorption in the (proximal) tubule, PTH enhances phosphate loss through the kidney, so that in states of PTH excess the result is a well-recognized hypophosphatemia. A number of other influences of PTH excess on the nephron have also been observed, such as interference with bicarbonate reabsorption with resultant renal tubular acidosis.[4] These metabolic alterations induced by the hormone are all seen in accentuated form in clinical states of augmented PTH production.

The most notable effect of increased circulating PTH is enhanced bone resorption.[3] Although this is unquestioned in the elevated concentrations of the hormone seen in hyperparathyroidism, it has been observed that in much lower concentrations, such as occur in physiologic states, the hormone may be anabolic in bone.[5] Other agents inducing bone resorption, such as prostaglandins, have been identified and have occasionally been implicated (especially in association with neoplasia) in states of hypercalcemia and bone resorption simulating hyperparathyroidism.[6]

PTH Biosynthesis and Metabolism

Parathyroid hormone is an 84-amino acid single-chain polypeptide[3] synthesized in the parathyroid cell (Fig. 2).[7] The peptide product of the parathyroid ribosomes appears to have a 31-amino acid extension at the NH_2 terminus of the molecule and this elongated precursor is known as pre-proparathyroid hormone (pre-pro PTH).[8] The greater part (25 amino acids) of this precursor extension is most likely removed from the nascent chain by an enzyme as the newly-synthesized peptide passes into the cisternae of the endoplasmic reticulum, leaving a smaller precursor, extended by only 6 amino acids (pro PTH).[9] This peptide is converted to the hormone by a tryptic-like cleavage[10] probably within the Golgi complex, and the 84-amino acid hormone is then packaged into secretory granules and released in response to hypocalcemia. The biologic activity of pre-pro PTH and its fate (i.e., whether this entity is released into the circulation) are currently unknown. Pro PTH appears to have little if any intrinsic biologic activity until it is converted to the hormone,[11] and it is unlikely, although this has not been proved, that this precursor ever enters the circulation.

The extent to which further intraglandular metabolism of the 84-amino acid form of the hormone occurs is currently under intensive investigation. However, it is generally accepted that further metabolism in peripheral tissues, mainly liver[12] and kidney,[13] does occur. The consequence of the metabolism of the hormone is the production of hormonal fragments,[14-17] most notably an inert middle and carboxyl terminal fragment which, by virtue of its long half-life, is the form of parathyroid hormone generally circulating in highest concentration in the blood. The fate of the amino-terminal portion of the molecule is uncertain, yet is most important since the entire biologic activity of the hormone appears to reside in the amino-terminal-34 residues.[18] One group of workers[19] has reported the existence of a biologically active amino-terminal fragment (in addition to the intact hormone) in the circulation of man. This has raised the possibility that the 84-amino acid form of the hormone itself may be an inert precursor requiring conversion to an active amino-terminal fragment for hormonal action. However, recent evidence has indicated that cleavage of the 84-amino acid form of the hormone may not be required for at least some forms of biologic activity.[20] Consequently the apparently specific metabolism undergone by the 84-amino acid species may limit the quantities of biologically active circulating moiety or generate an amino fragment with a site or duration of activity different from what is possessed by the intact molecule.

Etiology and Pathogenesis of Hyperparathyroidism

The most common cause of hyperparathyroidism is still a solitary parathyroid adenoma in which the underlying disturbance appears to be a defect in cell growth localized to one gland whose proliferating cells maintain their biosynthetic function. However, the generalized abnormality resulting in hyperplasia of all four glands is now being recognized more often,[21] and appears to be inceasing in frequency as a cause of hyperparathyroidism recurring postoperatively.[22]

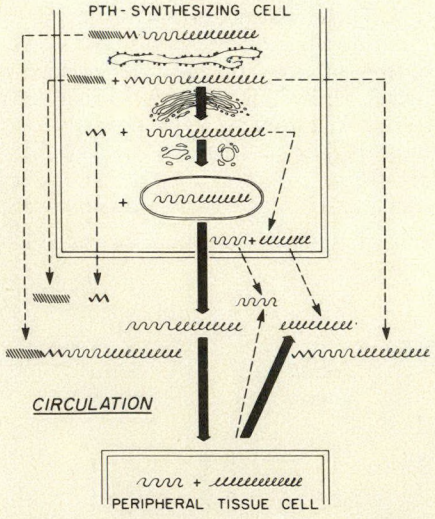

FIG. 2—Biosynthesis and metabolism of parathyroid hormone. Schematic representation of different portions of PTH molecule are as follows: ▭, 25-amino acid NH_2-terminal extension of pre-pro PTH; ▭, 6-amino acid NH_2-terminal extension of pro PTH; ▭, NH_2-terminal portion of major species of PTH containing biologic activity; ▭, inactive middle and carboxyl-terminal portion of major species of PTH. Both well-established pathways (→) and potential pathways (- - -►) of metabolism are noted.

Although one might suspect an external stimulus to be causative in at least some of these cases of hyperplasia, no such stimulus has yet been identified. Consequent upon the investigation of factors other than the calcium ion, such as β–adrenergic agents[23] and vitamin D metabolites,[24] which may influence glandular release of hormone (perhaps by modulating the effect of calcium), a subset of cases of parathyroid hyperplasia with a disordered external drive to parathyroid gland secretion may eventually be discovered.

An unknown controlling ionic or humoral factor need not be implicated if a defect in the "sensing" mechanism in glandular tissue is identified, whereby normal concentrations of ambient calcium are interpreted as low by the defective cells and consequently induce inappropriate glandular secretion of hormone. Such a mechanism has been postulated in certain cases of familial hyperparathyroidism.[25] Finally, those cases of four-gland enlargement associated with the multiple endocrine neoplasia (MEN) syndromes are believed to emanate from defects in embryogenesis, which subsequently manifest as disorders of cell growth in a number of endocrine glands (including all four parathyroid glands) to which the daughter cells with common defective ancestry migrate.

The identification on histologic grounds of the underlying lesion of hyperparathyroidism, that is, the distinction between adenoma and hyperplasia, is extremely difficult and is made considerably more so when the hyperplasia is asymmetrical so that only one or two of the four glands may appear enlarged on gross examination. Nevertheless a means of making this distinction is of the utmost importance in deciding on an appropriate surgical approach to therapy. The recognition of distinguishing characteristics may have to await further insight into the mechanisms causing adenomas and hyperplasias.

Clinical Aspects and Differential Diagnosis

The widespread use of multiphasic screening has markedly altered the mode of presentation of primary hyperparathyroidism so that asymptomatic hypercalcemia appears to constitute a large proportion of the clinical instances of the disorder.[26,27] Renal manifestations, notably those of nephrolithiasis, are currently the most common form of symptomatic disease, while osseous abnormalities are detected relatively infrequently.[27] Gastrointestinal symptoms, including those of pancreatitis and dyspepsia, may quite

frequently accompany the hypercalcemia. However, proved peptic ulceration should alert the physician to the possibility of an accompanying Zollinger-Ellison syndrome,[28] and therefore of the MEN syndrome, type I. Other components of this syndrome, including other pancreatic islet-cell neoplasms and pituitary tumours, should then be considered (Fig. 3).

Alternatively, the association of hyperparathyroidism with thyromegaly and hypertension should raise the possibility of medullary carcinoma of the thyroid and pheochromocytoma(s) constituting the MEN syndrome, type II.[29] Although both syndromes are inherited as autosomal dominant entities, the only endocrinopathy shared by the two appears to be hyperparathyroidism. More recently patients with MEN syndrome, type II together with mucosal neuromas have been designated MEN, type III, partly in view of a reported lower frequency of hyperparathyroidism in the latter entity.[30] The importance of recognizing other endocrinopathies in association with primary hyperparathyroidism is not only of consequence to the affected patient, but obviously is of importance in the management of family members as well.

Causes of hypercalcemia that must be considered in the differential diagnosis of hyperparathyroidism can generally be grouped, on a pathogenetic basis, into those due primarily to excessive bone resorption, those due to excess absorption from the gut and those due to reduced renal excretion (Table I). Yet in view of our increased knowledge concerning the interaction of factors controlling calcium homeostasis, it is obvious that several pathogenetic mechanisms are generally involved in any single disorder; for example, in hyperparathyroidism, the increased bone resorption due to PTH excess may be accompanied by enhanced absorption of calcium from the gut owing to augmented concentrations of 1,25-dihydroxy vitamin D associated with increased PTH production. Similarly the hypercalcemia of vitamin D intoxication may result primarily from enhanced absorption of calcium from the gut, and also from increased bone resorption. Nevertheless a pathogenetic classification should provide a more rational basis for reaching the diagnosis in a given patient.

Establishing the diagnosis of hyperparathyroidism in the patient with hypercalcemia may not be exceedingly difficult if an adequate history is taken and physical examination is performed, inasmuch as many diseases associated with hypercalcemia may be thereby excluded. The absence from the history and physical examination of an adequate explanation for the presence of mild hypercalcemia (especially if this hypercalcemia can be documented as of long standing and is accompanied by few signs and symptoms) makes the diagnosis of hyperparathyroidism more probable. In contrast the investigation of severe hypercalcemia of recent onset should include consideration of neoplasia as a highly likely underlying cause.

Laboratory investigation should then permit the distinction of PTH-associated from non-PTH-associated hypercalcemia and also of excess PTH production from glandular as opposed to ectopic sites.

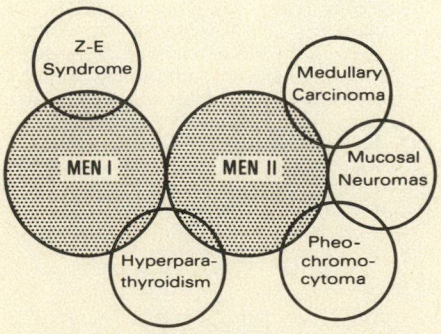

FIG. 3—Interrelation of endocrinopathies constituting multiple endocrine neoplasia (MEN) syndromes types I and II. Individual endocrinopathies depicted have been reported as occurring on occasion as familial diseases without other associated components of MEN I and MEN II. Triad of medullary thyroid carcinoma, mucosal neuromas and pheochromocytomas has occasionally been designated MEN III.

Laboratory Investigation

In view of the well-defined metabolic disturbances of hypophosphatemia and mild hyperchloremic acidosis induced by PTH excess, various combinations of serum phosphorus, chloride and bicarbonate concentrations have been advocated as indices to distinguish PTH-induced from non-PTH-induced hypercalcemia.[31] Their accessibility makes these values useful but they are not highly specific. Similarly the renal tubular reabsorption of phosphate, known to be diminished by PTH, suffers from lack of specificity, especially in view of the finding that hypercalcemia, in the absence of PTH, may induce phosphaturia.[32] The radiologic or pathologic demonstration, or both, of the pathognomonic skeletal lesion of hyperparathyroidism, osteitis fibrosa cystica (and especially subperiosteal resorption, a relatively early sign), is obviously helpful when present. However, because of the relatively low frequency of bone involvement in patients currently presenting with the disease, these signs are often not reliable. The use of a 10-day course of corticosteroids[33] in an attempt to suppress hypercalcemia has occasionally been useful in distinguishing PTH-related causes of the derangement (in which suppression does not occur) from non-PTH-related causes (in which suppression of hypercalcemia is often observed).

Table I—Etiology of Hypercalcemia

Excess bone resorption
Hyperparathyroidism
Malignant condition
Producing PTH
Producing other hormonal agents
Immobilization
Thyrotoxicosis
Excess absorption from gut
Sarcoidosis (other granulomas)
Vitamin D intoxication
? milk-alkali syndrome
? adrenal insufficiency
? idiopathic hypercalcemia of infancy
Excess renal reabsorption
? thiazide diuretics

Several newer tests have been introduced as diagnostic aids in distinguishing PTH-related from non-PTH-related hypercalcemia. These include measurement of urinary cyclic AMP and the radioimmunoassay for PTH. However, such measurements are rather difficult to obtain partly because special expertise is required to perform the tests and interpret the measurements. The measurement of urinary cyclic AMP is based upon the identification of this nucleotide as an intermediary in the mechanism of action of PTH, particularly at the level of the kidney.[34] Excess circulating PTH has been associated with increased concentrations of urinary cyclic AMP (relative to urinary creatinine excretion). However, amounts excreted by patients with hyperparathyroidism and by normal individuals may overlap.[35-37] The discrimination of this test might be enhanced by measuring specifically urinary cyclic AMP of nephrogenous origin (presumably related primarily to the action of PTH on the kidney), but this would demand associated assay of plasma cyclic AMP, an even more complex and meticulous process.

The radioimmunoassay for PTH provides the most specific means of establishing the diagnosis of hyperparathyroidism, yet problems of technique and of interpretation persist. Because the human hormone for development of antisera and use as reagent in the assay is not widely available, heterologous assays (usually employing antisera to bovine PTH) are generally used with a consequent lack of maximal sensitivity. A second problem, that of hormonal heterogeneity[6,17] (Fig. 2), relates to the several circulating forms of PTH (at least an 84-amino acid form and a

middle and carboxyl fragment). Because of this heterogeneity, species of the hormone recognized by antisera developed in one laboratory may not be recognized by those developed in another, and consequently different "levels" of hormone may be measured in the same blood specimen.

PTH concentrations are best interpreted in conjunction with simultaneous measurement of serum calcium[16] since detectable values of PTH that fall within the normal range would be considered inappropriately high if the serum calcium concentration was elevated. Such "normal" concentrations of PTH found concomitantly with increased concentrations of serum calcium are indicative of insufficient suppression of glandular secretion, consistent with the diagnosis of hyperparathyroidism. In contrast with other endocrinopathies, formal stimulation or suppression tests with measurement of hormonal response by radioimmunoassay have not generally been helpful. In some degree this is owing to the continued partial responsiveness of many parathyroid adenomas to the calcium stimulus.[38,39] Induced hypercalcemia (by infusion of calcium) in a patient with hyperparathyroidism may substantially suppress the abnormal gland and diminish radioimmunoassayable PTH. On the other hand, induced hypocalcemia (by infusion of ethylenediamine tetra-acetic acid) may stimulate the gland and augment radioimmunoassayable PTH. Sufficient data are not yet available to provide limits for normal as opposed to abnormal stimulation or suppression of radioimmunoassayable PTH in formal testing and this difficulty is compounded by the lack of interlaboratory uniformity of PTH radioimmunoassay methods and results. Consequently we depend on several basal values of PTH in conjunction with calcium determinations to provide sufficient information.

The usefulness of the assay has been extended by employing it in conjunction with selective venous catheterization for preoperative localization of the site of excess PTH production.[40] Several other techniques introduced for preoperative location of abnormal parathyroid tissue, including selenomethionine scanning and arteriography, have in general been less helpful. The technique of selective venous catheterization is arduous, requiring the interest and experience of a cooperative venographer. Catheterization of at least the inferior thyroid veins on both sides is required,[41] since excessive dilutional effects occur when larger veins are sampled.

In several centres this technique is now reserved for problem cases in which hypercalcemia has recurred after neck exploration and reintervention is required. Although most useful in these situations, the technique is also susceptible to failure because of the distorted venous architecture following surgery and requires close correlation of the site of sampling with the venogram. It should prove particularly useful for distinguishing glandular from ectopic sites of PTH production.

Therapy

If the underlying cause of the PTH excess is an intrinsic defect within parathyroid tissue, as may be true in the majority of cases of adenoma and hyperplasia, then the preferred treatment (in the absence of available medical therapy to diminish "uncontrolled" cell growth) is to diminish the quantity of hypersecreting tissue by excising it. On the other hand, if the underlying cause of PTH excess is a defect extrinisic to the parathyroid cells, as it may be in some cases of hyperplasia, then the rational solution would be to eliminate the external defect stimulating the gland; inasmuch as no such defect has yet been identified, the approach here also has been to excise excess tissue, although with a lower rate of cure. How much tissue to excise may be a hard decision in view of the difficulties in distinguishing modest glandular enlargement from normal glands[17] and parathyroid adenomas from asymmetrical hyperplasia.

Medical therapy for hyperparathyroidism is of limited value. One might expect three categories of agents to be helpful: those that interfere with hormone release, those that antagonize the action of the hormone and those that counteract the metabolic disturbances induced by the hormone. To date only agents in the last category are available, most notably the phosphate anion. However, with long-term oral phosphate therapy, although hypercalcemia may be reduced, PTH secretion continues unabated or even accelerated with the possibility of continued bone resorption and the danger of metastatic calcium deposition. This form of therapy therefore is less than ideal and is generally employed only when the degree of hypercalcemia itself represents a threat to the patient's well-being and surgical therapy for hyperparathyroidism is absolutely contraindicated.

The difficult decision in therapy arises in the patients discovered to have asymptomatic hypercalcemia as the only manifestation of hyperparathyroidism. Although prospective studies have conclusively demonstrated the hazards of other untreated conditions not initially recognized by the patients and considered to be asymptomatic (such as prolonged untreated hypertension), no such studies are currently available for patients found to have mild elevations of serum calcium. Furthermore, it is not certain whether hyperparathyroidism with asymptomatic hypercalcemia represents the same disease state as hyperparathyroidism with obvious osseous or renal manifestations. Nevertheless where such mild hyperparathyroidism has been reversed by parathyroid surgery, sensitive biochemical and morphologic indicators of calcium and skeletal homeostasis have been found to improve[42] and clinical well-being may be enhanced as well, indicating the benefit of the surgery.

The somewhat exacting technical requirements of parathyroid surgery leave open the question of whether or not to intervene in what may be a relatively benign disorder.

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SESAP II Question

20. A 42-year-old man had a Billroth II subtotal gastrectomy for duodenal ulcer two years ago. He is now asymptomatic. Laboratory studies disclose the following values: hemoglobin 10.0 gm/100 ml, hematocrit 30 per cent, normal leukocyte count and differential. Which of the following studies would be most useful in further evaluating this patient?

(A) Examination of the stool for occult blood

(B) Gastric analysis with test for occult blood

(C) Measurement of prothrombin time

(D) Determination of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)

(E) Erythrocyte fragility test

For this question select the *one* answer that is BEST from those noted above.

For the critique of Item 20 see page 329 of this issue.

Surgical Considerations in Hyperparathyroidism: Current Concepts

MARVIN J. WEXLER, MD, FRCS[C], FACS

The pathologic and histologic alterations seen in the parathyroid glands removed at operation have changed dramatically in recent years as a result of early diagnosis and treatment, often in asymptomatic patients. This situation has resulted in considerable disagreement over optimal surgical therapy and the number of parathyroid glands the surgeon should remove. These areas of controversy are analysed and current concepts critically reviewed.

Les altérations pathologiques et histologiques retrouvées sur les glandes parathyroïdes à la chirurgie ont changé dramatiquement au cours des dernières années, résultat d'un diagnostic et d'un traitement précoces, souvent chez des patients asymptomatiques. Cette situation a entraîné de sérieux désaccords en ce qui concerne le traitement chirurgical optimal et le nombre de glandes parathyroïdes devant être enlevées par le chirurgien. Ces sujets controversés sont analysés et les notions actuelles sont revues de façon critique.

Surgical interest in the parathyroid glands has grown phenomenally since 1925 when Mandl[1] first removed a parathyroid tumour from a patient with generalized bone disease and hypercalciuria. Once considered rare, primary hyperparathyroidism is now being diagnosed with greater frequency and at an earlier stage as clinicians become increasingly aware of its existence and varied symptomatology, and as use of the multichannel autoanalyser has become routine in the general medical investigation of most patients.[2] The advanced stages of this disease, characterized by extensive renal damage or widespread skeletal involvement with osteitis fibrosa cystica, multiple cysts and brown tumours, are rarely seen today. Patients now present with minimal or no bone changes and it is the discovery of renal calculi that generally initiates an investigation for hyperparathyroidism. Less commonly, patients present with symptoms relating to the gastrointestinal tract, the pancreas, or the cardiovascular or nervous systems.[3] Accordingly, the histopathologic features of the lesions in the parathyroid glands removed at operation have also changed notably. This situation has given rise to alteration in our pathologic and surgical concepts and, more recently, to considerable controversy over the basic clinical question: How many parathyroid glands should the surgeon remove?

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Incidence of Multiglandular Disease

The history of parathyroid surgery has followed closely the evolutionary pattern of other surgical endocrinopathies such as Cushing's syndrome, pituitary and thyroid disease and hyperaldosteronism. The pathologic condition initially suspected was either an adenoma or a carcinoma. Later, with increased knowledge and earlier diagnosis, surgeons recognized that these entities were possibly the later phases of an initial hyperplasia, so that they might expect to find a simple diffuse hyperplasia early in the course of the disease. Although the water-clear cell type of primary hyperplasia of the parathyroid was identified by Albright and associates in 1934,[4] chief cell hyperplasia of all four parathyroid glands was not described until 1958,[5] yet accounted for 25 of the subsequent 100 cases dealt with at the Massachusetts General Hospital.[3]

In the case of a neoplasm, the decision is simple—one removes the tumour, leaving the normal undiseased tissue behind. The hyperplasias demand more of the surgeon because he has to decide how much tissue to resect and how much to leave. Complete exposure and identification of each and every gland become crucial. The general practice in the past has been to remove 3½ glands in the belief that hyperplasia is always a diffuse process involving all four glands. Part of the most accessible and best vascularized gland was left behind to prevent the development of hypoparathyroidism.

As can be seen in Table I, the reported frequency of multiglandular disease varies considerably, ranging from 10% to 65%.[6-15] Clearly this is a reflection of the inconsistent criteria used for distinguishing between normal tissue, hyperplasia and adenoma. Authors who report a 10% to 20% frequency of multiglandular disease base their diagnoses on gross appearance, size and weight of the glands; those who claim rates from 40% to 65% rely on histologic distinctions that at best are less than pathognomonic and far from universally accepted.

Essentially three surgical "philosophies" have evolved and enjoy current popularity. All have as their objective the removal of abnormal and potentially abnormal tissue without creating hypoparathyroidism yet obviating the

Table I—Incidence of Multiglandular Disease in Selected Series

Author	Total no. of patients	No. with multiglandular disease, %
Paloyan, Paloyan and Pickleman[6]	98	65
Muller[7]	352	50
Haff and Ballinger[8]	38	50
Esselstyn and colleagues[9]	100	49
Bruining[10]	267	45
Block and colleagues[11]	182	20
Palmer and colleagues[12]	250	15
Myers[13]	82	13
Clark, Way and Hunt[14]	295	12
Davies[15]	350	10

necessity for future re-exploration with its inherent difficulties. Fundamental differences in theories of the pathogenesis of hyperparathyroidism and conflicting data regarding success in achieving the stated objectives underlie these alternative approaches. These are best summarized as follows:

The "Right" Approach

The conservative approach advocates that at first only one side of the neck should be explored. If one enlarged and one normal gland are found on gross examination, the "adenoma" is excised and the operation terminated. Roth, Wang and Potts,[16] the principal proponents of this mode of surgical treatment, offer evidence that over 80% of primary hyperparathyroidism is due to a solitary adenoma, excision of which results in a very low recurrence rate. These workers claim that double adenomas, if they ever exist, are very rare.[17] The coexistence of a grossly enlarged and a normal-sized gland is assumed to refute the diagnosis of hyperplasia. In the uncommon event of a recurrence in such a circumstance, one side of the neck remains for easy exploration and a healthy, functioning, normal gland remains undisturbed on the side originally operated on. Unnecessary trauma to normal glands is avoided and the very real danger of permanent hypoparathyroidism associated with re-exploration is eliminated. If it is necessary to explore both sides, clinically enlarged glands can be removed without the need for biopsy of apparently normal glands.[18]

The "Left" Approach

The radical approach, first urged and still championed by Paloyan,[6,19] Haff and Ballinger[8] and others,[20] is based upon these workers' own data, which indicate that recurrence of disease after simple excision of an adenoma is frequent, and on the premise that hyperparathyroidism is a secondary manifestation of chronic extrinsic stimulation. Accordingly, prophylactic near-total removal of the end organs is necessary. In all patients 3½ glands are excised, leaving 75 to 100 mg of well-vascularized glandular tissue. If a gland cannot be located, ipsilateral thyroid lobectomy and thymectomy are performed.

According to proponents of this approach, gross inspection is unreliable in distinguishing normal from abnormal tissue and they suggest that the true incidence of multiglandular disease is high. The pathologist must be supplied with sufficient material to permit a comparison of the changes in the various glands. Finally, this technique provides irrefutable proof that the surgeon has visualized all glands.

The "Middle" Way

Advocates of a moderate, middle-of-the-road, selective approach as represented by Palmer and associates,[12] Myers[13] and Clark, Way and Hunt,[14] argue that persistence rates due to technically inadequate primary exploration are unacceptably high. True recurrence rates, due to misinterpretation of diffuse hyperplasia, are low. Therefore, an uncompromising effort is made to identify all parathyroid tissue, including exploration of the common sites of ectopic or supernumerary glands as Palmer and Sutton advocate in this issue (page 350). Only grossly enlarged glands are excised and biopsy of one or more seemingly normal glands is done for positive identification, but routine biopsy of all glands is not performed. This approach, like the more conservative one, is also based on the belief that one can tell by its appearance whether a gland is abnormal, that a gland of normal size does not and will not have abnormal secretory function. This selective surgery is associated with a low rate of postoperative hypocalcemia.

Four important questions must be answered to reconcile these conflicting approaches:

- What is hyperplasia?
- Is histologic evidence of hyperplasia in a normal-sized gland of clinical importance?
- What is the true incidence of polyglandular disease and is all multiglandular disease hyperplasia?
- Can the surgeon distinguish between normal and abnormal glands by their gross appearance at operation?

Adenoma versus Hyperplasia

Prior to the general recognition in the 1960s of chief cell hyperplasia of all four parathyroid glands as a clinical entity, most surgeons were content to seek and remove only one enlarged gland and made little or no attempt to determine the status of the remaining normal-appearing glands, or even to identify them at all. According to some,[21] this practice accounted for the popular figure of 80% for adenomas reported in most series of that time.[22] In an attempt to solve this problem Esselstyn and colleagues[9] routinely did biopsies of all four glands in 100 patients with primary hyperparathyroidism and subjected the tissue to histologic study. They reported hyperplasia in 49% of this group. They rigidly defined an adenoma as a "discrete, usually diffuse lesion" of a single parathyroid gland; the presence of a definite rim of normal capsule tended to confirm the diagnosis but was not absolutely essential to it. Nonadenomatous glands could show no morphologic evidence of hyperfunction and in cases where the cells of two or more glands showed evidence of hyperfunction, the diagnosis of adenoma was not applied. Paloyan, Paloyan and Pickleman[6] defined cases of hyperplasia as those in which there is either gravimetric and histologic evidence of cellular overactivity in more than one gland, hyperplasia alone, an adenoma coexisting with hyperplasia, or multiple parathyroid adenomas. The mere existence of the latter entity is now disputed by some.[17,23] Clearly, arguments for surgical management based on reported rates of multiglandular disease or hyperplasia are factitious. It is now recognized by pathologists that the entire spectrum of adenoma, hyperplasia, transitional cells and normal histology may be present not only in a single patient, but in some instances in a single gland.[21]

Most pathologists experienced in parathyroid histology concede that there are few, if any, reliable histologic criteria that permit consistent and precise differentiation between normal parathyroid tissue and hyperplasia and between hyperplasia and adenoma.[11,24,25] Furthermore, the surgeon cannot rely on frozen sections of biopsy specimens in making the diagnosis; the pathologist can do little more than confirm the presence of parathyroid tissue.

The concept of an abnormal external stimulus bringing about early hyperplasia of all parathyroid glands, with the later development of an autonomous adenoma in one that causes suppression of the remainder, is undoubtedly too simplistic. Primary hyperparathyroidism probably represents a collection of diseases of varied etiology and pathogenesis. Abnormal stimuli may originate from without and perhaps also within a single gland and hyperplasia need not be a process affecting all four glands (Fig. 1). Whether the surgeon can distinguish between normal and abnormal glands at operation is a question difficult to answer. This does appear possible from a clinical and functional aspect, but cannot be done on histologic grounds. Evidence

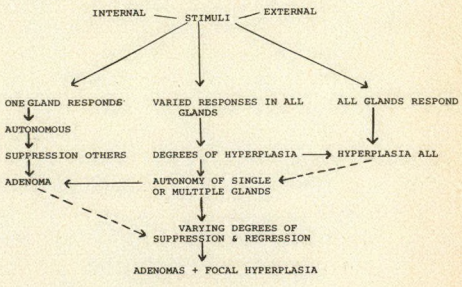

FIG. 1—Pathogenesis of hyperparathyroidism. Possible interrelation between adenoma and hyperplasia.

continues to mount that microscopic hyperplasia in a normal-sized or even a suppressed gland is common but of no functional importance and of no clinical consequence.[23,26] Alternatively, diagnosing hyperplasia in slightly enlarged glands without histologic support can also lead to error owing to varying amounts of surrounding fatty tissue.

Persistent versus Recurrent Hyperparathyroidism

From a clinical standpoint, the answer to the dispute over how much and how many glands to remove lies in the outcomes of the various surgical approaches. Unfortunately the relevant data are imprecise because of the failure of most surgeons to distinguish clearly between persistent disease and true recurrence following surgical treatment. This accounts for reported "recurrence" rates ranging from 0.4%[14] to 19%.[20]

Persistent disease is considered by most surgeons to represent overlooked disease. Recurrent disease, defined as return of hypercalcemia at least 6 months after a period of normocalcemia, implies newly developed pathologic change. Clark, Way and Hunt[14] recently summarized all reports in the English literature of surgically treated hyperparathyroidism since Paloyan and colleagues[19] first advocated routine prophylactic subtotal parathyroidectomy in 1969. In this collected series of 3204 patients, treated by the selective approach described earlier in which only abnormally enlarged parathyroid glands were removed, recurrent hyperparathyroidism developed in only 24 (0.7%). This low figure suggests that true recurrence is rare, even with a selective approach, but persistence may be common owing to an inadequate primary operation. It must be recognized, however, that most reported series consist of retrospective reviews in which follow-up data are incomplete and are often based upon an isolated serum calcium determination. In reports of follow-up studies as long as 15 to 40 years after operation,[12,14,15] patients lost to follow-up are infrequently acknowledged and the majority of patients have usually been under observation for less than 5 years. Even in a recent prospective study of 198 patients with hyperparathyroidism from whom a single enlarged gland was removed between 1968 and 1970 and who were kept under surveillance to the end of 1975, 25% either died or were lost to follow-up within 5 years and a further 25% were under observation for less than 5 years.[27] Reliable long-term and prospective follow-up studies with regular monitoring of serum calcium and parathyroid hormone (PTH) concentrations are needed. Recurrences reported 5 to 15 years after the initial operation are not unusual. Monitoring on a regular basis, particularly if sensitive PTH assays are included, may provide earlier evidence for recurrence. It is still possible that recurrent disease is the result of a physiologically insignificant amount of hyperfunctioning tissue being left at the first operation and later proliferating to produce eventual recurrence. As such it represents unrecognized abnormal tissue and therefore persistent disease. However, as shown by the data currently available, true recurrent disease as distinct from persistent disease is relatively uncommon even with the most conservative of selective approaches. On this basis, there is no support for routine prophylactic subtotal parathyroidectomy except in patients with multiple endocrine adenomatosis type I, familial hyperparathyroidism, or secondary hyperparathyroidism in which recurrence rates are reported as high as 33% with lesser surgery.[14] The hypothetical possibility of producing delayed recurrence of hyperparathyroidism from eventual autonomy of an overstressed remnant remains if we elect routine subtotal parathyroidectomy. Total parathyroidectomy with auto-transplantation of tissue to the forearm as described by Wells and colleagues[28] may prove to be the ultimate solution in such cases. At present the indications for this procedure are unclear.[29,30]

Unfortunately a recent clinical and pathological study of 112 patients requiring parathyroid reoperation[17] did not distinguish between persistent and recurrent disease. Nevertheless, the findings supported the concept that persistence due to a technically inadequate operation and failure to find an adenoma is the major problem of postoperative recurrence rather than misinterpretation of diffuse hyperplasia and failure to perform routine subtotal excision. Of the causes of unsuccessful parathyroid exploration, the commonest was the failure of the surgeon to be familiar with the normal location of the parathyroid glands and the way a gland may be displaced when diseased. In this series 66 adenomas and 7 carcinomas were found. In only 29 patients was the histology that of primary hyperplasia, which had continued despite excision of one or more diseased glands at the initial operation. It is also notable that in more than half the unsuccessful cases attributed to technical incompetence the initial diagnosis of parathyroid tissue was later revised when, at histologic examination, the tissue was found to be lymph node or fat or thyroid.

Assuming that the surgeon is competent in this area, aberrant locations of glands and supernumerary glands (fifth or sixth) overlooked at the initial exploration are the principal causes of reoperation in patients treated according to traditional surgical guidelines.[30] Recurrent hyperparathyroidism due to enlargement of a parathyroid gland previously observed to be normal is rarely documented.

Postoperative Hypocalcemia

The biggest argument against routine prophylactic subtotal parathyroidectomy is the high incidence of postoperative hypocalcemia (13% to 30%) reported by some[10,18,26,31] compared with a negligible incidence (1% to 4%) when only glands that are enlarged are removed.[10,12,14,26,27] Close scrutiny reveals that the high figures usually include a group of patients in whom the hypocalcemia is transient and who are easily treated until sufficient compensation is afforded by the remaining tissue. The greater the amount of residual tissue, the less the likelihood that hypocalcemia will occur and the faster the recovery if it does occur. It is important to caution against the overzealous administration of calcium during the early postoperative period. This may suppress the remaining parathyroid function and eventually produce atrophy. Variations in the degree of treatment with calcium may also account for reported discrepancies in different series. Paloyan, Paloyan and Pickleman,[6] while they reported only two instances of hypoparathyroidism in 100 patients who underwent subtotal parathyroidectomy, disregarded this group in which hypocalcemia is transient and considered only those with permanent hypoparathyroidism. In the evaluation of postoperative calcium problems it is important to recognize that these are not necessarily the result of excision of excessive amounts of parathyroid tissue. They can occur after removal of only a single large adenoma, as a result of rapid bone absorption of calcium subsequent to removal of the influences of excessive PTH. Calcium taken orally is usually sufficient to correct symptoms and is rarely required for more than a few weeks. In a recent study,[26] 12 of 50 patients who were operated upon by a "radical" surgeon required treatment for symptomatic postoperative hypocalcemia. However, only five had had a formal subtotal parathyroidectomy; the others had had only one or two glands removed and biopsy of a varying number of the remaining glands. These results suggest that biopsy alone may induce postoperative hypocalcemia owing to manipulative damage, since the incidence was re-

duced to 2% in a subsequent 50 patients in whom a conservative approach was used and only the enlarged gland(s) removed.

As clearly stated by Ballinger,[20] the crucial question is whether the risk of hypocalcemia is greater than the risk of leaving hyperfunctioning parathyroid tissue in situ with development of insidious nephrocalcinosis and the increased danger of permanent hypocalcemia resulting from subsequent explorations. It would appear that, taken in proper context, the risk of either eventuality is extraordinarily small. The patients at highest risk for the development of permanent hypocalcemia are those with either previous incomplete neck exploration for hyperparathyroidism or previous or concomitant thyroidectomy. It is in this latter group that parathyroid autotransplantation may find its role.

Conclusion

"The success of parathyroid surgery must lie in the ability of the surgeon to know a parathyroid gland when he sees it, to know the distribution of the glands, where they hide, and also be delicate enough in technic to be able to use this knowledge."[3] Resolution of the controversy over the frequency of recurrent disease is, at least in part, dependent on clearly distinguishing it from what is actually persistent disease and on eliminating the latter as far as possible at the primary operation.

The question of whether surgeons, even those most experienced in parathyroid surgery, can identify a parathyroid gland without confirmation by biopsy is paramount. Frequently the answer must be in the negative.[17] It would therefore appear to be vital to visualize all four glands and to do a biopsy of all glands that appear normal to confirm their identification. This can be accomplished easily with iris scissors with little apparent damage to the residual tissue but with full knowledge, as emphasized by the study of Edis and associates,[26] that the frequency of postoperative hypocalcemia will be increased although it will usually be temporary and easily managed. Clearly the major problem is that of continued hyperparathyroidism where the risk at a subsequent operation far outweighs the morbidity of temporary postoperative hypocalcemia. All glands that appear abnormal should be removed and weighed by the pathologist after removing extracapsular fat; there should be dialogue between pathologist and surgeon. Glands with a normal gross appearance do not require excision.

There does appear to be an increasing proportion of patients with what might be termed a mixed bag of one or two grossly enlarged glands suggestive of adenoma, perhaps one normal-sized gland that is hypercellular on biopsy and one gland of normal histology.[32] This combination is consistent with the pathogenetic concepts proposed earlier (Fig. 1). The nature and course of these variants remain unclarified and it seems necessary to relate the gross and microscopic findings of all four glands to a definitive approach to surgical treatment and then to a long-term follow-up over many years. Inclusion of electron microscopy may further aid this process.

More pressing problems are the course to be followed when one gland cannot be definitely located, perhaps even after hemithyroidectomy and transcervical thymectomy, and the approach to be taken for recurrent disease. The ultimate success in the management of the patient with continuing hyperparathyroidism depends upon the surgeon. He must know what the abnormality is and how to correct it. In the hands of an accomplished surgeon with detailed knowledge of the numerous anatomical variations of the parathyroid glands,[33] the success rate is high, even without sternotomy. As previously noted, persistent disease usually reflects some lack of competence on the part of the surgeon at the time of the primary operation rather than an inability to distinguish between adenoma and hyperplasia or to perform routine prophylactic subtotal resection. A density test recently described by Wang and Rieder[34] may prove valuable in the intraoperative differentiation of primary parathyroid hyperplasia from neoplasia and may call for further modification of surgical attitudes and approaches.

It is important to recognize that an adenoma may be located in an ectopic fifth parathyroid gland. It is noteworthy that of 14 patients with mediastinal parathyroid tumours reported by Scholz and associates,[35] 5 had previously had four glands identified in the neck. Others[6,12,14,17] have reported similar experiences. In such circumstances, while removal of a single "suspicious" enlarged gland or subtotal removal of the normal four may result in transient normocalcemia, the remaining tumour will surely declare itself, perhaps to be misinterpreted as recurrent disease. The periodicity of hyperfunction must also be considered. Light may be shed on these concepts and controversies by more routine use of sensitive assays for PTH. Purnell, Scholz and Beahrs[27] have measured serum PTH values after parathyroidectomy and found that in some patients these remained elevated. The importance of the increased PTH concentration in the presence of normal serum calcium concentration is not certain. This subject has been more extensively reviewed in this issue of the Journal by Goltzman (page 285).

Subtotal parathyroidectomy is mandatory in patients with multiple endocrine adenomatosis, familial hyperparathyroidism, or secondary hyperparathyroidism. If a question of viability or sufficiency of residual tissue arises, as is often encountered in patients reexplored for recurrent disease, parathyroid tissue should be transplanted to the forearm where monitoring and subsequent removal can be performed if necessary.

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Glimpses of Surgical History: V for Venesection

DAVID A.E. SHEPHARD

Blood has so profound a meaning for man that bleeding, both natural and accidental or induced (as with VENESECTION), early took on deep significance. Menstruation suggested that blood could, maybe should, be shed periodically; and, in a strange twist of sexual behaviour, monkish males subjected themselves to a regular regimen of blood-letting to counter the supposedly harmful effects of accumulation of semen and to help them battle fleshly temptation. In other realms of Hygeia, the revulsive effects of accidental hemorrhage were also recognized by primitive people. So blood-letting became one of the earliest forms of therapy: as an old verse put it, "It maketh cleane your braine, releeves your eie, / It mends your appetite, restoreth sleepe"—and evidently much else besides.

We still practice venesection: transfusion and autotransfusion require venesection, and polycythemia, hemosiderosis, arterial hypertension and pulmonary congestion were treated by venesection until quite recently. Such treatment seems rational, very different from that of the barbers of two or three centuries ago who let blood flow freely (the red of the barber's pole reminds us of this) and from that of the owners of "bleeding shops" that people, well or ill, visited regularly to be "blooded" or to "breathe a Vein". To be bled—without medical advice—was for many an everyday custom.

What we consider rational venesection did not replace the maniacal approach until the mid-19th century. The practice of barbers, bath-keepers and sow-gelders collapsed into desuetude only with the rise of experimental physiologists like Magendie and Bernard and with the scepticism of therapeutic nihilists like Skoda. As today's operators (and their head-of-the-table colleagues) watch for the ebb and flow of blood in a patient "etherized upon a table", let thought be given to the many who laboriously laid the lore and learning of blood over the centuries, so that modern "Surgeons. . . trust to the Blooding" in rational care of their patients.

Clinical Experience with the Newer Hepatobiliary Radiopharmaceuticals

L. ROSENTHALL, MD

Technetium 99m-labelled hepatobiliary imaging agents provide high resolution images not previously possible with rose bengal labelled with iodine 131. This has prompted a re-examination of the utility of these radioactive pharmaceuticals. We have found that the newer methodology provides a rapid, innocuous and accurate means of excluding acute cholecystitis from the diagnosis in patients with symptoms suggestive of this disease and of assessing surgically altered biliary anatomy. In the presence of moderate bilirubinemia, up to about 85.5 to 103 μmol/L (5 to 6 mg/dL), a definitive distinction can be made between medical and surgical jaundice.

Les agents de contraste marqués au technétium 99m servant à la mise en évidence des voies hépatobiliaires offrent des images à contraste marqué qui n'étaient pas possibles avec le rose bengale marqué à l'iode 131. Ceci nous a incité à ré-examiner l'utilité de ces produits pharmaceutiques radioactifs. Nous avons trouvé que la nouvelle méthodologie offre un moyen rapide, nonenvahissant et précis d'exclure du diagnostic la cholécystite aiguë chez les patients ayant des symptômes suggérant cette maladie, et d'évaluer les modifications chirurgicales de l'anatomie biliaire. En présence d'une bilirubinémie modérée allant jusqu'à 85.5 a 103 μmol/L (5 à 6 mg/dL), une distinction définitive peut être faite entre l'ictère médical et l'ictère chirurgical.

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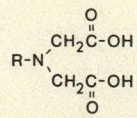
Rose bengal labelled with iodine 131 was the standard hepatobiliary imaging agent after its introduction in mid-1950. The principal limitation of this agent is the radionuclide ^{131}I which has an 8-day physical half-life, a high-energy photon emission that is inefficient for gamma camera imaging and a beta emission that does not contribute to the imaging process but rather adds unnecessarily to the body radiation-absorbed dose. To stay within acceptable limits of radiation burden the administered dose was kept low and this resulted in liver and biliary tract images of low information density and, consequently, poor detail. Technetium 99m is a radionuclide with the desirable physical qualities of being a pure gamma emitter and possessing a short (6-hour) half-life which aid in delivering a low radiation-absorbed dose even when administered in millicurie amounts. Unfortunately, it has not been possible to label the hepatocyte-seeking rose bengal with ^{99m}Tc. An alternative radionuclide is ^{123}I, which has physical properties somewhat akin to those of ^{99m}Tc, but is cyclotron-produced, expensive and inappropriate for general use in the form of a simple kit.[1] A variety of radioactive pharmaceuticals concentrated by hepatocytes have therefore been developed employing the inexpensive and ubiquitous ^{99m}Tc as the label in millicurie doses to provide images of high information density in short imaging times.[2-10] Two of these have undergone considerable clinical investigation, ^{99m}Tc-pyridoxylideneglutamate[11] and the ^{99m}Tc-labelled N-substituted iminodiacetic acid (IDA) derivatives[12-14] (Fig. 1), but the others are still at the experimental stage. The IDA derivatives are believed to possess some advantages over pyridoxylideneglutamate,[15] but both are rapidly concentrated by the hepatocytes, and subsequently excreted into the biliary tract, gallbladder and gut within an hour of intravenous administration. The analogues of N-substituted IDA vary in their transit time through the liver and in the degree of renal excretion. ^{99m}Tc-dimethyl-IDA (^{99m}Tc-dm-IDA) has the most rapid transit through the liver, but about 15% is excreted by the kidneys; in contrast, ^{99m}Tc-parabutyl-IDA (^{99m}Tc-pb-IDA) has a slower hepatic transit time and a 2% renal excretion, not unlike ^{131}I-rose bengal. The disparate properties of these two radioactive pharmaceuticals assume importance in the presence of hyperbilirubinemia as will be shown later.

This review relates our experience with ^{99m}Tc-dm-IDA, and to a lesser extent ^{99m}Tc-pb-IDA, in the diagnosis



N-SUBSTITUTED IMINODIACETIC ACID

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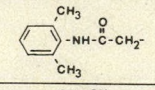
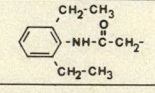
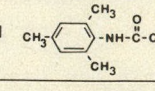
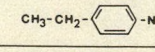
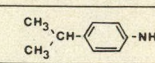
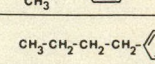
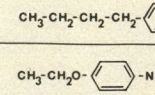
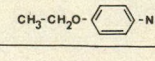
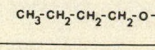
2,6-dimethyl	
2,6-diethyl	
2,4,6-trimethyl	
p-ethyl	
p-isopropyl	
p-butyl	
p-ethoxy	
p-butoxy	
o-butoxy	

FIG. 1—Various acetanilide iminodiacetic acid (IDA) derivatives.

of acute and chronic cholecystitis, the differential diagnosis of jaundice and the assessment of the postsurgical bypass pathways of the biliary system.

Technique

Gallbladder Assessment

Food is withheld for 2 hours prior to the examination. About 5 mCi of ^{99m}Tc-dm-IDA or ^{99m}Tc-pb-IDA is injected intravenously and radionuclide images are obtained at 15-minute intervals for the first hour until the gallbladder is visualized. Nucleographs are procured at 30-minute intervals thereafter if necessary. The study is terminated when most of the radiotracer is excreted into the gut if the gallbladder cannot be visualized.

In the presence of liver disease and jaundice the slower excretion of the radioactive pharmaceuticals will extend these temporal relations.

Differentiation of Jaundice and Determination of Surgically Altered Anatomy

No food restriction is necessary. After an intravenous dose of 5 mCi of ^{99m}Tc-dm-IDA or ^{99m}Tc-pb-IDA nucleographs are obtained every 30 minutes for the first 4 hours or less if the diagnosis becomes apparent. In severe hepatobiliary disease a 24-hour image is obtained to determine whether excretion into the gut has taken place.

Results and Discussion

Normal Gallbladder

In normal subjects the gallbladder is visualized within 30 minutes of the intravenous injection of ^{99m}Tc-dm-IDA provided food is withheld for 2 hours before the examination. With ^{99m}Tc-pb-IDA the time to visualization may be longer because of its slower transit time, but does not exceed 1 hour. Entry into the gut can be appreciated about the same time as the gallbladder is visualized or soon after (Fig. 2).

In an earlier study all 43 patients with a normal gallbladder as demonstrated by oral cholecystography and the results of routine liver function tests (total serum bilirubin, protein, transaminase and alkaline phosphatase values) showed gallbladder filling on the ^{99m}Tc-dm-IDA images.[16] These patients did not require cholecystokinin, as advocated by others,[17] to induce emptying of the gallbladder prior to administration of the radioactive phar-

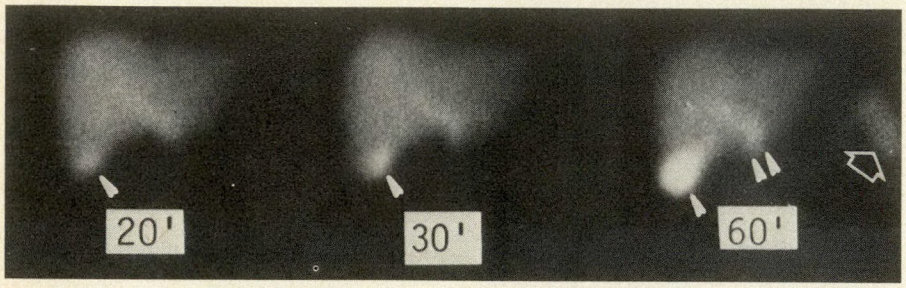


FIG. 2—Normal gallbladder. ^{99m}Tc-pb-IDA images were obtained at 20, 30 and 60 minutes. Gallbladder is identified as early as 20 minutes but is more clearly seen at 30 and 60 minutes (single arrow). Filling of common bile duct (double arrows) and gut entry (open arrow) are evident at 60 minutes.

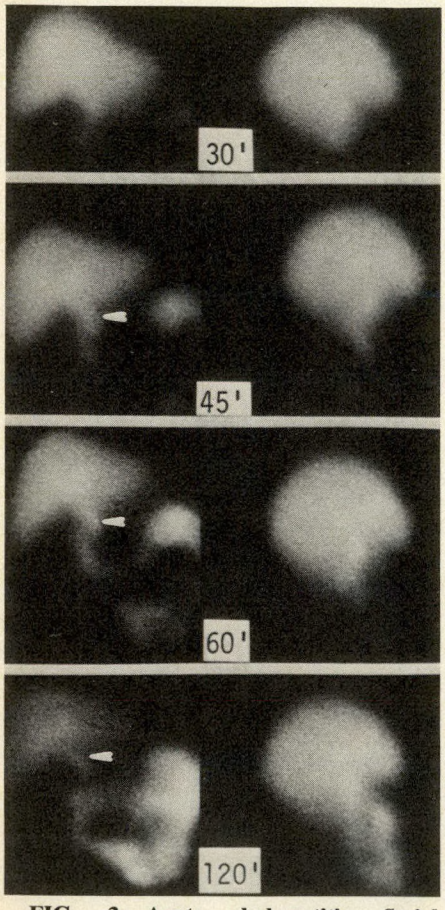


FIG. 3—Acute cholecystitis. Serial ^{99m}Tc-pb-IDA images fail to identify gallbladder over 2-hour period of observation. Bowel entry is observed as early as 30 minutes and common bile duct is seen at 45 minutes and later (arrow).

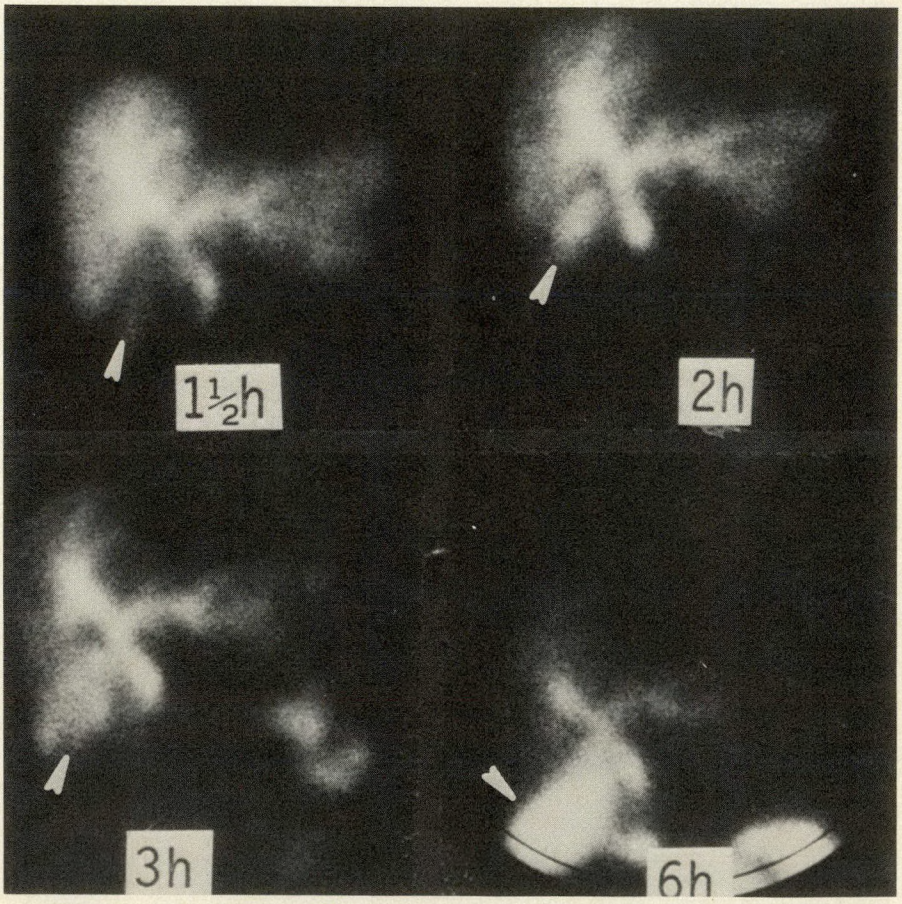


FIG. 4—Serial ^{99m}Tc-dm-IDA images in case of partial extrahepatic biliary obstruction in patient with acute pancreatitis. Biliary system is dilated and can be seen extending into branches of right and left hepatic ducts. Bowel entry is delayed as it is only apparent at 3 hours. Gallbladder is visualized by 1½ hours and enlarges progressively (arrow), thereby excluding a diagnosis of acute cholecystitis, particularly the clinically suspected hydrops.

maceuticals in order to facilitate visualization.

Abnormal Gallbladder

Failure to visualize the gallbladder in the presence of normal excretion into the gut indicates either acute or chronic cholecystitis (Fig. 3).

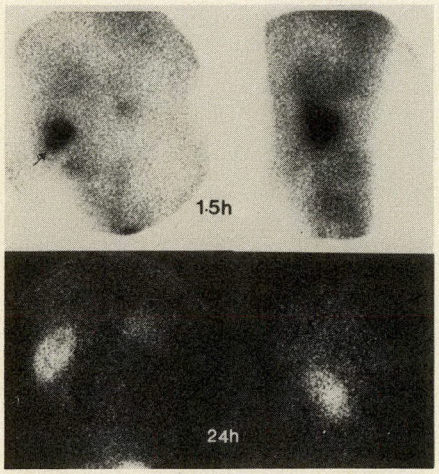


Fig. 5a

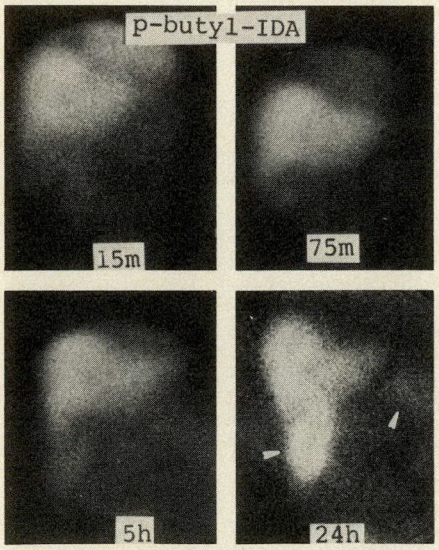


Fig. 5b

FIG. 5—Comparison between images obtained using ^{99m}Tc-dm-IDA and ^{99m}Tc-pb-IDA in patient with complete obstruction of common bile duct secondary to carcinoma of colon. Serum bilirubin value was 205 μmol/L (12 mg/dL). (a) Frontal and lateral ^{99m}Tc-dm-IDA images at 1.5 and 24 hours, respectively. There is exceedingly low liver concentration at 1.5 hours and complete absence at 24 hours. Most is excreted through kidneys. Of incidental note is obstruction of right kidney at ureteropelvic junction (arrow). (b) Frontal ^{99m}Tc-pb-IDA images at 15 and 75 minutes and at 5 and 24 hours. Much greater concentration is registered in liver at 15 minutes with less renal excretion than of ^{99m}Tc-dm-IDA at 1.5 hours. At 24 hours liver is well demonstrated and there is no appreciable gut entry; only kidneys are visualized (arrows). This is consistent with complete obstruction.

In one study[16] of pathologically and surgically proved cases all nine patients with acute cholecystitis and seven patients with chronic cholecystitis and cystic duct obstruction failed to show concentration by the gallbladder of ^{99m}Tc-dm-IDA. There were an additional 11 patients with chronic cholecystitis and patent cystic duct who did not exhibit gallbladder filling with ^{99m}Tc-dm-IDA. The gallbladder in two of these patients actually did fill following a 5-minute 100-unit infusion of cholecystokinin and a second dose of ^{99m}Tc-dm-IDA. The presence of nonobstructing stones in the gallbladder cannot generally be demonstrated by radionuclide imaging.

The conclusions to be drawn from our experience with the use of hepatobiliary imaging in patients with suspected disease of the gallbladder are: (a) nonvisualization of the gallbladder after radionuclide injection signals either acute or chronic cholecystitis; (b) radionuclide visualization of the gallbladder excludes the presence of an obstructed cystic duct. Therefore acute cholecystitis can confidently be ruled out in patients presenting with symptoms suggestive of the diagnosis if the gallbladder is visualized. The technique is innocuous, noninvasive and rapid.

Differentiation of Jaundice

Partial extrahepatic obstruction is characterized by a dilated tract and delayed emptying of the system into the bowel (Fig. 4). Activity in the bowel without dilatation of the biliary tract identifies a jaundice of intrahepatic origin. Failure to detect entry of the radionuclide into the bowel within a 24-hour period of observation establishes a diagnosis consistent with complete extrahepatic obstruction provided the serum bilirubin concentration is only moderately elevated. However, when the degree of bilirubinemia is high, lack of excretion into the gut may also be associated with severe hepatocellular disease and intrahepatic cholestatic jaundice and the result is no longer definitive.

Experience with ^{99m}Tc-dm-IDA has shown that for serum bilirubin concentrations of 85.5 μmol/L (5 mg/dL) or lower, serial imaging can consistently distinguish between medical and surgical jaundice; in the presence of higher concentrations the degree of liver uptake of the radioactive pharmaceutical diminishes rapidly and the results are of only qualified value. The introduction of ^{99m}Tc-pb-IDA with its higher degree of liver concentration and lesser renal excretion than ^{99m}Tc-dm-IDA has improved the ability to differentiate between medical and surgical jaundice at more elevated values of serum bilirubin (Fig. 5). Clinical trials with this radioactive pharmaceutical are still under way and the precise limitations have not been fully defined.

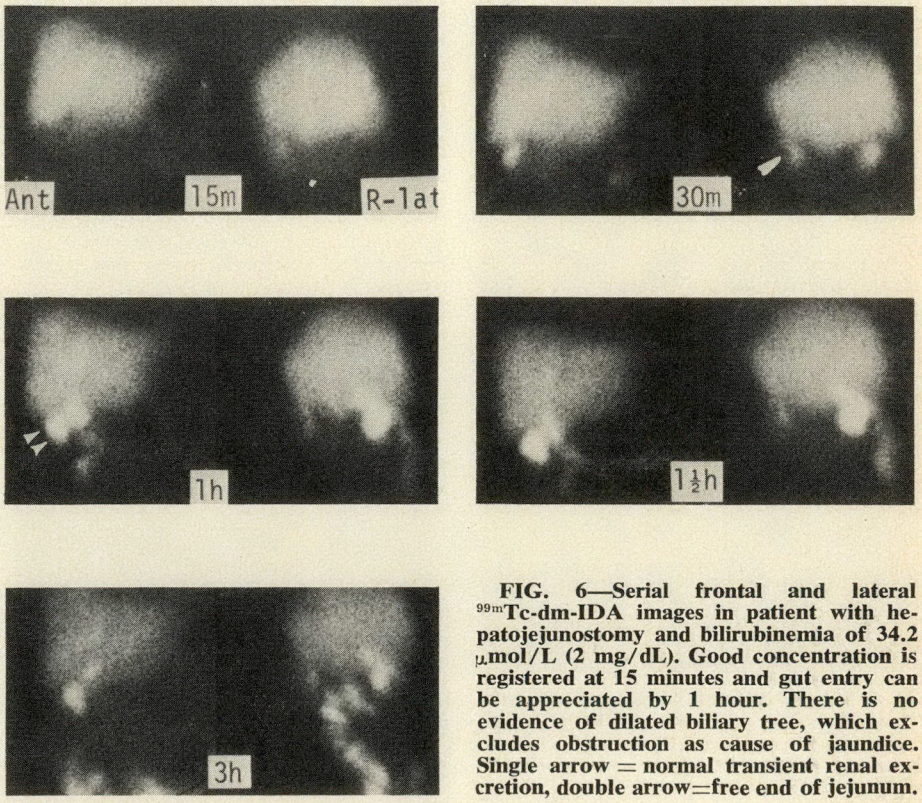


FIG. 6—Serial frontal and lateral ^{99m}Tc-dm-IDA images in patient with hepatojejunostomy and bilirubinemia of 34.2 μmol/L (2 mg/dL). Good concentration is registered at 15 minutes and gut entry can be appreciated by 1 hour. There is no evidence of dilated biliary tree, which excludes obstruction as cause of jaundice. Single arrow = normal transient renal excretion, double arrow=free end of jejunum.

Ultrasonography generally plays a primary role in evaluating the status of the biliary tract. However, in a small proportion of cases ultrasonography does not clearly define the status of the biliary tract and the disclosure of dilatation by itself does not necessarily imply obstruction, particularly if there has been previous surgical intervention. Radionuclide imaging helps by providing morphologic and dynamic information in these cases.

Determination of Surgically Altered Anatomy

The integrity of such operative procedures as choledochojejunostomy, cholecystojejunostomy and hepatojejunostomy (Fig. 6) can be assessed in the presence of moderate jaundice. Inlet and outlet obstructions of gastroenterostomies can be disclosed (Fig. 7) and intra-abdominal bile spills are easily detected (Fig. 8). Hepatobiliary imaging in the presence of these conditions offers a unique and noninvasive method of investigating the altered and disordered anatomy proximal to the gastroenterostomy.

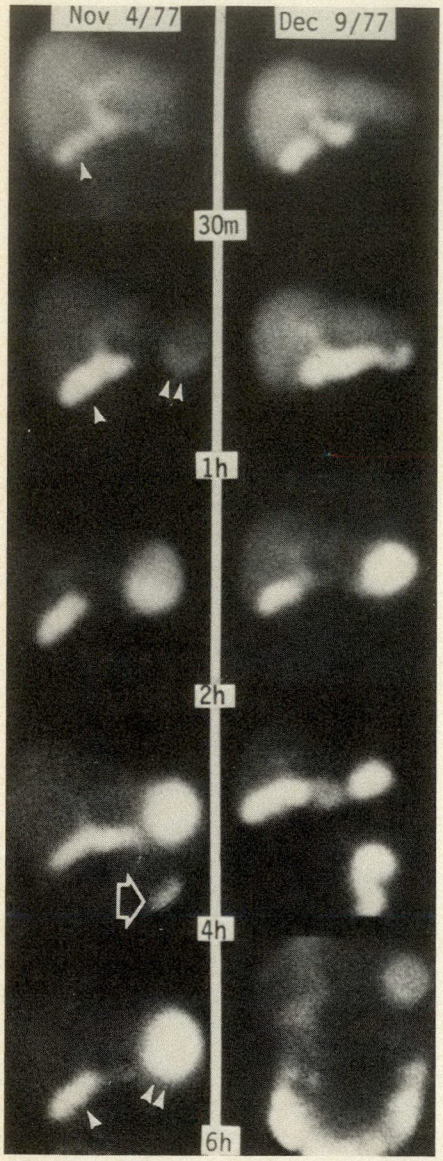


FIG. 7—Serial ^{99m}Tc-dm-IDA scans in patient with partial inlet and outlet obstruction following Whipple's procedure. Postoperatively patient suffered from copious bile emesis. On Nov. 4, 1977 undilated common duct is clearly seen at 30 minutes and there is entry into afferent portion of jejunum (single arrow). At 1 hour there is further accumulation in jejunum and reflux into stomach remnant is observed (double arrows) but no entry into efferent portion of jejunum. By 2 hours most of liver is drained and activity is divided between afferent jejunal loop and stomach with no gastric emptying. Efferent jejunal activity is apparent for first time at 4 hours (open arrow), but at 6 hours there is still grossly abnormal retention in afferent jejunum and stomach indicating both inlet and outlet obstruction. On Dec. 9, 1977, after conservative management, degree of obstruction had improved but obstruction was not totally relieved.

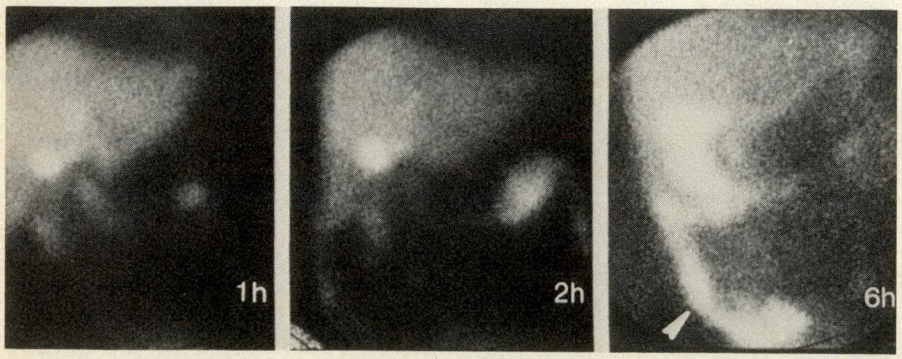


FIG. 8—Bile spill. This disoriented patient prematurely pulled out indwelling T tube and intra-abdominal bile spill occurred. At 1 hour ^{99m}Tc-dm-IDA image defines gallbladder and some gut entry. At 6 hours there is definite column of radioactivity coursing along right lateral abdominal wall towards pelvis (arrow), bearing no similarity to concentration in small bowel.

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Tantalum Angiography in the Study of Rejection of Pulmonary Transplants

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The results obtained in dogs after the use of pulmonary allografts from donors pretreated with cyclophosphamide were compared with those obtained after the use of unmodified and immunosuppressed grafts.

Tantalum angiography demonstrates the pulmonary vasculature in detail to precapillary levels. In normal lungs a uniform narrowing of vessels occurs ending in a fine precapillary rete. In rejected lungs the finer peripheral vessels are occluded by thrombi. Parenchymal spaces between medium-sized vessels are enlarged owing to expansion by hemorrhage, congestion and mononuclear cell infiltration. After pretreatment of the donor, the angiogram shows a normal appearance in the transplant up to 84 days after transplantation. The microvasculature demonstrates no vasoconstriction, thrombus formation or irregularities in vessel diameter.

Electron microscopy demonstrates persisting vessel integrity until late rejection when total disruption associated with thrombosis occurs. Immunosuppression markedly inhibits the early rejection response and donor pretreatment almost totally prevents it. Tissue disruption and thrombosis occur only at the stage of late rejection and terminal necrosis.

Les résultats obtenus chez le chien avec l'utilisation d'allogreffes pulmonaires provenant de donneurs traités à la cyclophosphamide ont été comparés avec ceux obtenus avec des greffes nonmodifiées et traitées aux immunosuppresseurs.

L'angiographie au tantale démontre en détail le système vasculaire jusqu'au niveau des précapillaires. Dans le poumon normal, un rétrécissement uniforme des vaisseaux survient, se terminant en un fin réseau de précapillaires. Lorsqu'il y a réaction de rejet, les vaisseaux périphériques les plus fins sont obstrués par des thrombi. Les espaces parenchymateux entre les vaisseaux de moyen calibre sont élargis à cause de l'expansion provoquée par l'hémorragie, la congestion et l'infiltration de cellules mononuclées. Après traitement du donneur, l'angiogramme montre l'apparence normale du greffon jusqu'à 84 jours après la greffe. Les vaisseaux microscopiques ne présentent aucune vasoconstriction, formation de thrombi ou irrégularité du diamètre des vaisseaux.

L'examen au microscope électronique démontre la persistance de l'intégrité vasculaire jusqu'au rejet retardé quand une séparation des tissus accompagnée de thrombose survient. L'immunosuppression inhibe fortement la réponse de rejet immédiate et le traitement du donneur la prévient presque totalement. Le détachement des tissus et la thrombose ne surviennent qu'au stade du rejet retardé et de la nécrose terminale.

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At present the outstanding problem in any transplantation program is adequate abrogation of the induced rejection response of the allograft. Prolonged survival is dependent upon inherent histocompatibility, attenuation of rejection by selective immunosuppression, and anticipation and treatment of any postoperative complications related to technique. Guttman[1-3] prolonged functional survival in animal and human renal allografts by pretreatment of the cadaver donor kidney with cyclophosphamide and methylprednisolone. Cytotoxic drugs decrease the immunogenicity of the graft by inactivating the donor's nonparenchymal passenger leukocytes. No agent or combination of agents has consistently inhibited the rejection response, but donor pretreatment has prolonged histologic integrity and functional survival as assessed by ventilation and perfusion scanning studies in canine pulmonary allografts.[4]

Tantalum angiography has been used specifically in experimental hyperacute rejection of renal xenografts.[5] This new radiologic procedure, which uses intra-arterial injections of tantalum particles, was compared with the standard replacement method of microphil injection. Tantalum angiograms vividly illustrated the subtle changes of decreased glomerular perfusion. The radiologic demonstration of decreased numbers of visualized glomeruli correlated with the physiologic, coagulation and pathologic studies and indicated localized obstruction of the microcirculation of the glomerulus by intravascular coagulation. The microphil injections into hyperacutely rejected kidneys were inferior in demonstrating these changes because of their complete filling of the postglomerular vascular bed, including the renal veins. With the technique of tantalum angiography the progressive destruction of the glomerular microcirculation demonstrated that this avascular bed was the prime target in the experimental model of hyperacute renal xenograft rejection. Arterial spasm was suggested by the segmental narrowing of the arteries early in the process of rejection, a feature that could not be demonstrated by microphil injections.

We attempted to correlate, in detail previously undescribed, the histologic features of abrogation with angiographic changes in the central and peripheral vascular bed of a pulmonary allograft using the new method of tantalum angiography.

Material and Methods

Left lung transplantation was performed in 41 dogs; 14 dogs underwent left autotransplantation and 27 underwent left allotransplantation (7 without immunosuppression, 10 with postoperative recipient immunosuppression and 10 following donor pretreatment and with postoperative recipient immunosuppression). Immunosuppression was induced by postoperative administration of methylprednisolone (2 mg/kg body weight) and azathioprine (1.5 mg/kg). Pretreated donors received a continuous infusion of cyclophospha-

mide (0.75 g) and methylprednisolone (2.0 g) for at least 6 hours prior to transplantation.

Lung biopsy specimens were obtained either in vivo or after the animal's death. Whole lung specimens were inflated with 10% buffered formalin by way of the bronchus at pressures ranging from 20 to 30 cm H_2O. After 24 hours' fixation tissues were dehydrated in graded alcohols, then embedded in paraffin and sectioned for microscopic study. Sections were stained with hematoxylin and eosin. When circumstances warranted, special staining procedures were also employed including trichrome, reticulin, periodic acid-Schiff and Gram's staining.

Electron microscopy was performed when light microscopy demonstrated an entity that warranted further investigation. For fixation by immersion, the lung tissue was cut into 1-mm blocks and immersed in cold phosphate-buffered 1% osmium tetroxide for 1 hour. After dehydration in graded alcohols and propylene oxide according to the method of Luft,[6] the tissue blocks were embedded in a mixture of epon–araldite.[7] Sections were cut with glass knives on an ultramicrotome (LKB Instruments, Rockville, MD); 1-μ sections were stained with toluidine blue. Thin sections for electron microscopy were stained with uranyl acetate and examined and photographed in the Philips electron microscope (model EM-301, Philips Electronic, Mahwah, NJ).

Tantalum pulmonary angiography was used to define minute changes in the microvasculature not previously identified by other angiographic techniques. The technique was applied to both normal and transplanted canine lungs. Fifteen grams of tantalum (size, 1 μ) was suspended in 30 mL of 0.9% saline. An effective method of obtaining a uniform suspension was aggressive manual agitation just prior to injection. The animal was killed, the lung removed and inflated and the bronchus clamped. Experience demonstrated that no matter how quickly the hilar structures were clamped after infusion of the pulmonary artery, tantalum was able to enter into either an alveolar or venous phase, thus destroying arterial definition. Therefore to ensure preferential back-up of tantalum in the arterial side of the lung the pulmonary veins were ligated before injection. The pulmonary artery was cannulated and the suspension slowly infused until greying became noticeable over portions of the lung surface, at which time the infusion was terminated and the pulmonary artery ligated. A water manometer was attached to a T limb of the infusion circuit to quantify injection pressures and to ensure that pulmonary artery pressures of 20 mm Hg were not exceeded.

Two high resolution industrial films (Cronex NDT, E.I. DuPont De Nemours Inc., Wilmington, DE), speeds 65 and 45, offering complementing degrees of resolution and penetration were used. Lung tissue was placed in direct contact with the film and exposed in a "Faxitron" unit. An exposure of 30 kV for 1.5 minutes for the canine lung tissue was adequate. Films were then developed in the automatic processor for 7 minutes at 31.7°C.

Results of Histologic Studies

Autotransplantation

Three hours after operation a "reimplantation response" was identifiable. Focal areas of interstitial and alveolar edema and a moderate degree of congestion were present. There was neither a granulocytic nor a lymphocytic response and the bronchial wall distal to the anastomosis was intact with no ischemic change. Presumably the reimplantation response is due to operative trauma, lung ischemia (increased pulmonary capillary permeability and pulmonary edema), or to a denervation-resistance response attributed to outflow obstruction of the small veins.[8-10]

At 21 days mild peribronchial edema was present and fibrin deposition was found both in alveoli and in bronchial lumina. In both sites the fibrin was accompanied by minimal infiltration by nonspecific inflammatory cells. At 35 days only patchy focal areas of edema in alveoli were present along with compensatory emphysema. There was no perivascular or peribronchial lymphocytic aggregation.

Electron microscopy beyond 30 days demonstrated only a very few focal areas of interstitial edema and congestion. Alveolar type I and type II pneumocytes and endothelial cells with adjacent basement membrane were all normal. The remaining portions of lung showed no abnormality.

Allotransplantation

Four days after unmodified allotransplantation, light microscopy showed both perivascular and peribronchial infiltration with mononuclear cells, presumably T-lymphocytes (Fig. 1). At times the lymphocytic infiltrate was predominantly peribronchial with edema in the perivascular space. Occasionally lymphocytic infiltrates were also seen in the alveoli, the bronchi and the interstitium. Submucosal edema, congestion and mild infiltration by mononuclear cells were found at the bronchial anastomosis, but no evidence of impaired viability or ischemic change was demonstrated.

At 7 days the perivascular lymphocytic infiltrate became more intense, as did the hemorrhage into the alveoli, bronchi and interstitium. A fibrinous exudate into the alveoli was seen initially and became more pronounced with time. There was no desquamation

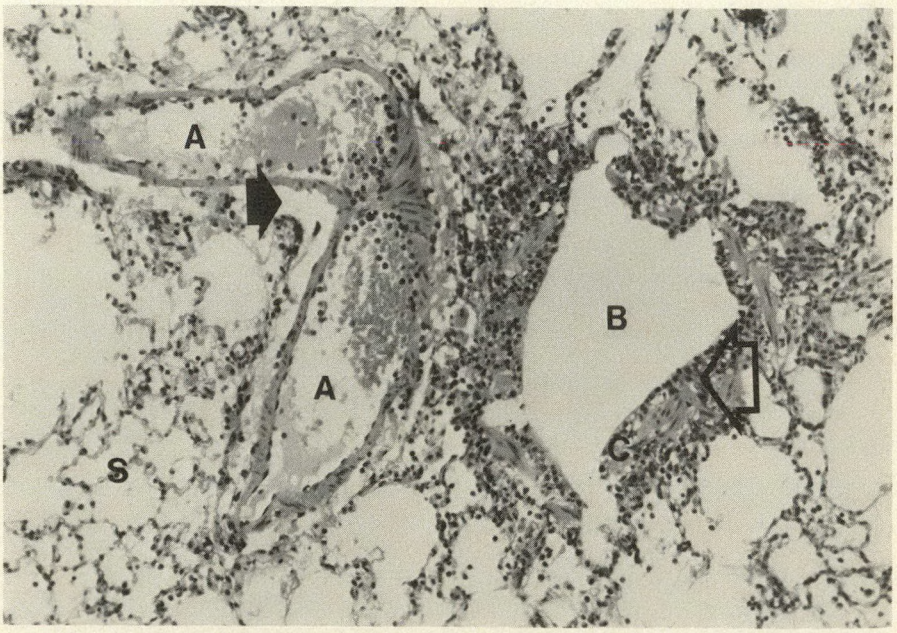

FIG. 1—Photomicrograph of canine lung 4 days after allotransplantation without immunosuppression. Bronchus (B) is cuffed by infiltrates of mononuclear cells (open black arrow) which extend through bronchial wall into submucosa. Medium-sized artery (A) is surrounded by edema (black arrow) and little cellular infiltrate. Mild congestion and edema are present in alveolar septa (S) (hematoxylin and eosin, reduced by 27% from ×20).

of any of the alveolar lining cells, nor was there evidence of arteritis or vasculitis. Thrombosis of vessels was a terminal event associated with necrosis and total disruption of lung architecture. In early rejection the leukocyte response was predominantly lymphocytic but during the necrotic stage at 7 to 9 days cellular infiltrates were mainly polymorphonuclear.

Electron microscopy at 4 days revealed lymphocytes containing active cytoplasmic organelle systems. No abnormalities were found in either the endothelial cells or the adjacent basement membrane. Small lymphocytes were present in the interstitial and intravascular compartments. Occasionally there was focal disruption of the endothelial basement membrane which allowed perivascular migration of lymphocytes with subsequent interstitial infiltration. Lymphoblastic transformation of T-lymphocytes was readily identified in capillaries adjacent to endothelial basement membranes. In all instances type I and type II pneumocytes remained intact; there was no baring of the basement membranes and no generalized disruption of the endothelium (Fig. 2). Seven days after operation there were more extensive areas of intra-alveolar and interstitial hemorrhage, severe congestion and edema. At this stage there was disruption of basement membranes and lung architecture (hemorrhagic necrosis). The mononuclear cell infiltration became less conspicuous and was replaced by an infiltrate of polymorphonuclear cells and macrophages that were actively consuming debris and erythrocytes.

In cases of allotransplantation with postoperative immunosuppression light microscopy suggested the entire spectrum of acute rejection described above but the period over which these changes occurred was greatly prolonged. The degree of response, as estimated by the absolute number or volume of lymphocytes, was depressed at any arbitrary time postoperatively when compared with the unabrogated response. End-stage infections and sudden terminal venous thrombosis were commonly seen in the immunosuppressed animals. The rejection response identified by electron microscopy was similar to the unabrogated response but the period over which these changes occurred was prolonged. When acute rejection was present the alveolar type I and type II pneumocytes, endothelial cells and basement membranes were all intact. It was only in the end stage of necrosis that changes in these and all other structures were present.

In allotransplantation with postoperative immunosuppression and donor pretreatment light and electron microscopy demonstrated an even greater abrogation of the rejection response than in the other two groups. Appearances in light and electron photomicrographs were entirely within normal limits in most long-term survivors. The findings of light and electron microscopy identify neither the lung's antigenic stimulus, which elicits the cellular response, nor the target organ or organelle to which the T-lymphocytes react.

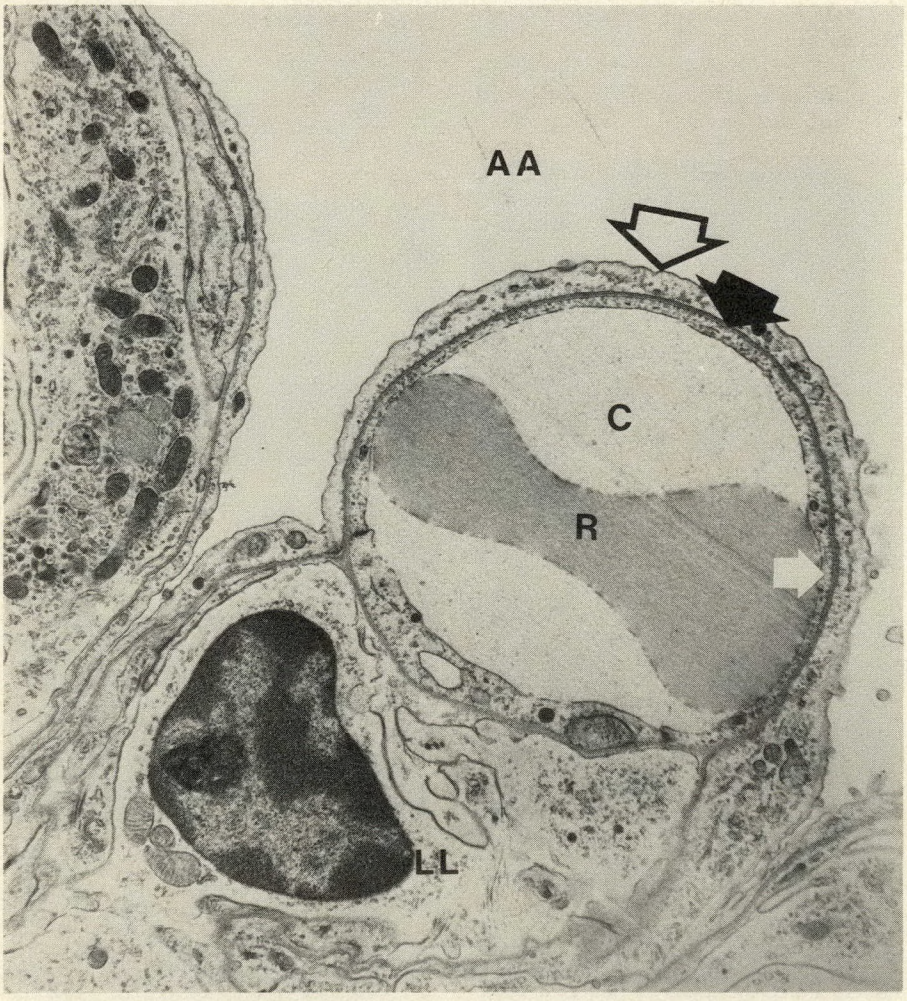

FIG. 2—Electron micrograph of lung 80 days after allotransplantation and postoperative immunosuppression. Capillary (C) contains single erythrocyte (R) and is lined by normal endothelial cells (white arrow) interconnected by normal electron-dense junctions. Adjacent basement membrane (black arrow) and type I pneumocytes (open black arrow) lining alveoli (AA) are intact. Representative infiltrative T-lymphocyte (LL) is positioned in mildly edematous interstitial compartment. Architectural integrity is present (reduced by 23% from ×4500).

Results of Angiographic Studies

A normal angiographic pattern was

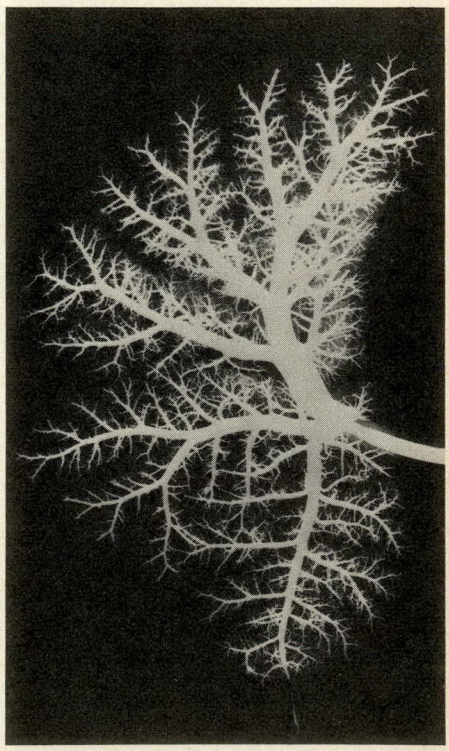

FIG. 3—Tantalum angiogram of canine lung 68 days after allotransplantation and postoperative immunosuppression with pretreatment of donor. Normal asymmetrical dichotomous arterial branching pattern is illustrated to sixth generation (precapillary) levels with total patency and normal, uniform tapering. No attenuation of or encroachment upon peripheral precapillary branches and no intraluminal filling defects are present.

identified in autografts and allografts with abrogated rejection responses. An asymmetrical dichotomous arterial branching pattern was visualized to the sixth generation, with total patency and normal uniform tapering and branching patterns. No distortion of or encroachment on peripheral precapillary branches and no intraluminal filling defects were present (Fig. 3).

With rejection the vasculature showed a loss of normal tapering of various arterial and arteriolar branches coupled with multiple filling defects representing thrombus formation. The absolute number of branches also diminished and there was visualization only to the fourth generation, producing the typical appearance of a "pruned tree". These changes may be asymmetrical since various portions of the allograft may be rejected at different rates, thus producing a range of histologic and angiographic changes in any one allograft (Figs. 4 and 5).

When rejection was at its end stage, multiple filling defects representing thrombus formation occurred in all the visualized branches. There was filling to second generation arteries producing a complete pruned tree appearance. These branches showed irregular and ragged intimal surfaces and loss of normal tapering. The lung parenchyma demonstrated total consolidation with parenchymal infiltration encroaching on the smaller arteries and arterioles which, together with the intraluminal thrombus formation, prevented distal filling of the pulmonary vascular tree (Fig. 6).

Discussion

Most methods of graft immunosuppression inhibit the sensitization phases of the afferent arc, or the effector phases of the efferent arc, of the immune response. Results depend upon depression or inactivation of sensitized lymphocytes and plasma cells. The exact mechanisms by which immunosuppressive therapy acts upon both the cellular and humoral phases of immunity have not yet been determined.

In canine pulmonary allotransplantation, immunosuppression has been effected by methotrexate alone,[11,12] methotrexate in combination with other agents,[13,14] azathioprine alone[15-18] and azathioprine and methylprednisolone.[14,19,20] Cyclophosphamide and actinomycin C can also markedly alter the immune response. Pretreatment of the donor with cyclophosphamide and methylprednisolone has prolonged histologic integrity and functional survival in canine pulmonary allografts when compared with other immunosuppressive regimens.[4] This effect is caused by a reduction in graft immunogenicity following the destruction of nonparenchymal cells of hemopoietic origin (mobile passenger leukocytes), which are the stimulus of allograft immunity and possibly the targets for certain effector mechanisms.

The pathogenesis of allograft rejection of the canine lung remains controversial and our results differ somewhat from those generally described. Three phases of rejection have been described: alveolar, vascular and necrotic. The alveolar phase, occurring 2 to 3 days postoperatively, is characterized by a fibrinous exudate into alveoli, with swelling of type I pneumocytes followed promptly by their dissolution. The vascular or cellular phase, occurring 2 to 5 days postoperatively, is characterized by segmental peripheral arteriolar narrowing due to perivascular cuffing by mononuclear cells, endothelial swelling and intimal hyperplasia. Platelet thrombi occur late in this phase, well after vascular obstruction is visualized angiographically. The final necrotic phase is a consummation of the first two phases, with further architectural disruption and supervening infection.[20-22]

Our findings suggest that architectural integrity of the lung persists until terminal necrosis occurs irrespective of the presence or absence of infection. No histologic changes have been seen on light or electron microscopy in type I and type II pneumocytes, in endothelium, or in basement membranes until the final necrotic event produces rapid and total parenchymal dissolution. Acute and chronic rejection differ only in the quantity of T-lympho-

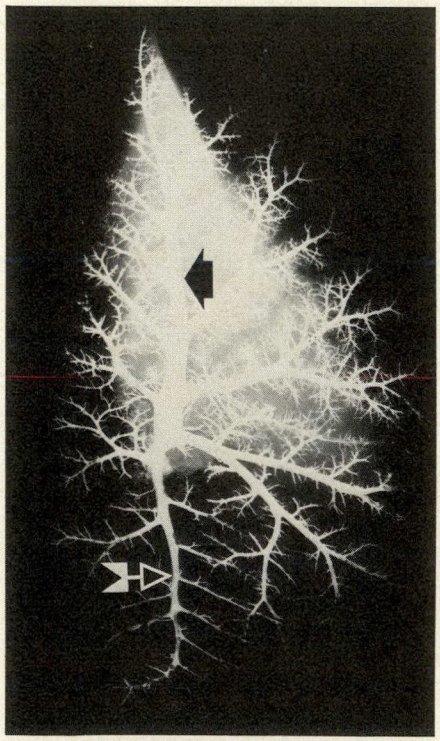

FIG. 4—Tantalum angiogram of lung 7 days after allotransplantation and postoperative immunosuppression in pretreated donor. Vasculature of upper half of the lung (black arrow) is normal. Arteries of lower half (open white arrow) show loss of uniform tapering, and several filling defects representing thrombus formation are present intraluminally. Absolute number of branches is diminished and filling occurs to fourth generation branches ("pruned tree" appearance).

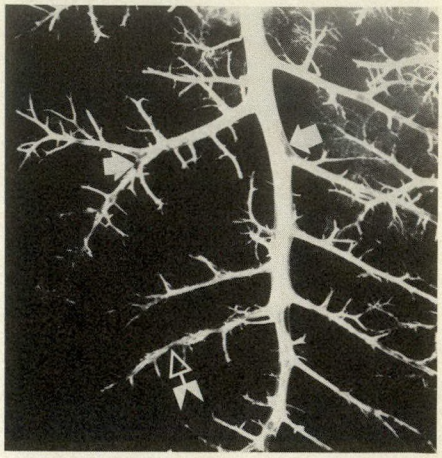

FIG. 5—Magnification of angiogram of Fig. 4 in area of rejection. Thrombi are present (white arrows) in both major and minor arteries. Loss of regular tapering (open white arrow) occurs and precapillary vasculature is compromised creating pruned tree appearance.

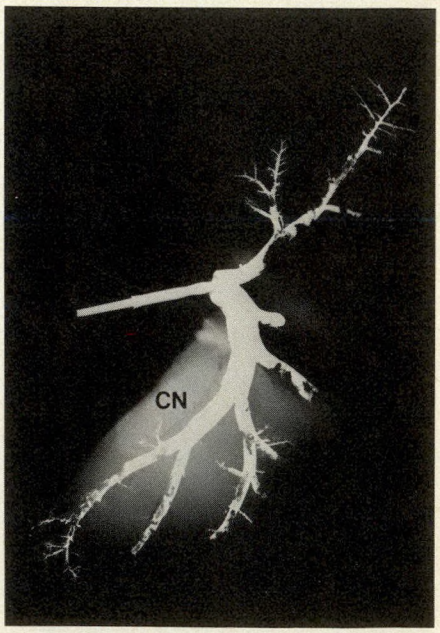

FIG. 6—Tantalum angiogram of lung 9 days after allotransplantation without immunosuppression. At final stage of rejection, many filling defects representing thrombus formation are present in all visualized branches. Filling to only second generation branches produces complete pruned tree appearance. Arteries have irregular and ragged intimal surfaces and abnormal tapering. Lung parenchyma shows consolidation (CN) with parenchymal infiltration encroaching upon smaller arteries and arterioles which, together with thrombus, prevents distal perfusion.

cytes present in a unit of lung volume.

Tantalum, a radiopaque transitional metal that is physiologically inert, can be injected intravenously into laboratory animals and selectively deposited on injured vascular endothelium.[23] Particles of tantalum show virtually no tendency to attach to normal or growing vessels or to leak from capillaries or from small venules. Following injury, however, tantalum adheres to the endothelial wall or to formed elements and appears to be transported by circulating phagocytic cells. Tantalum particles are easily visible in capillary beds in vivo and in histologic sections prepared for light or electron microscopy. Intravenously injected tantalum particles are useful in identifying a variety of vascular abnormalities in large vessels and in the peripheral microcirculation.

Conventional pulmonary angiography using radiopaque fluids has been performed at varying stages after lung transplantation in order to demonstrate any abnormalities that may suggest the pathogenesis of rejection. Two days after transplantation the angiogram demonstrated a normal pattern, that is, a venous appearance time of less than 2 seconds, an arterial phase of less than 3 seconds and a normal vascular pattern. After 6 days the pulmonary transit times increased during the arterial phase (3 to 5 seconds) and there was a delayed venous filling time. The vascular pattern became abnormal as evidenced by terminal arteriolar non-filling after more than 1 minute. During chronic rejection there occurred a retrograde progressive obliteration of the pulmonary tree.[20,24-26] Conventional angiography is useful only in detecting the cause of impaired perfusion in a transplanted lung but in no way casts light on the more detailed and intricate pathogenesis of the decrease in perfusion.

Correlated histologic and angiographic data in our study suggest several novel concepts. Rejection may progress at different rates in various portions of the allograft and at any one time a range of events can be identified. Electron microscopy has been valuable in showing that previously suggested target organs (endothelium, basement membrane, pneumocytes) remain intact during rejection which is only identified by a progressive increase in the volume and number of infiltrative lymphocytes. As infiltrates increase, the interstitium becomes expanded and encroaches upon arteries producing progressive obliteration of the peripheral microcirculation. T-lymphocytes produce thrombokinins and perhaps when they reach a certain titre (dependent upon total numbers) acute thrombosis occurs. At this end stage necrosis and disruption of parenchymal architecture results from sudden thrombosis in all arteries.

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continued on page 315

Recurrent Duodenal Ulcer

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STEPHEN MORGAN, MD, FRCS[C] AND DENIS BERNARD, MD, FRCS[C]

In the past 6 years 26 patients underwent operation for recurrent duodenal ulcer after what was considered to be an "adequate" initial operation. In such patients it is necessary first to demonstrate the recurrent ulcer and then to determine its cause. Endoscopy was the best means of confirming the diagnosis. The cause of recurrence was determined by tests for gastric acid secretion; 70% of patients had hyperacidity and 80% had positive results of the Hollander test. Treatment is always surgical but varies depending on the type of initial surgery, the primary cause of recurrence and the condition of the patient. Ten patients underwent vagotomy, 12 had vagotomy with antrectomy and 4 had antrectomy alone. There were no operative deaths but nine (35%) patients experienced 11 significant postoperative complications.

Vingt-six malades ont été réopérés au cours des 6 dernières années pour récidive d'ulcère duodénal. Chez ces malades il faut d'abord faire la preuve de la récidive et en établir la cause. L'endoscopie est le meilleur moyen diagnostic. Par la suite la recherche de la cause se fait à l'aide des tests de stimulation gastrique; 70% ont démontré une hyperacidité et 80% un Hollander positif. Le traitement a toujours été chirurgical mais varia selon le type de chirurgie initiale, la cause première de récidive et l'état du patient. Dix malades ont subi une vagotomie seule dont 6 par voie thoracique, 12 une vagotomie avec antrectomie et 4 une antrectomie. Aucune mortalité opératoire n'est rapportée mais neuf (35%) malades ont éprouvé 11 complications postopératoires significatives.

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Recurrent ulceration following "adequate" surgical treatment of duodenal ulcer still represents a major challenge for the surgeon. Not only does he have to determine the cause of the recurrence, but he must also treat each patient by the means least likely to lead to further recurrence and associated with the least morbidity and mortality. We report our experience in the management of the condition accumulated over a period of 6 years.

Patients and Methods

Between Apr. 1, 1971 and Mar. 31, 1977, we treated 26 consecutive patients with demonstrated recurrent ulcer following what is generally considered "adequate" surgical treatment of duodenal ulcer (Table I). In this retrospective study we excluded patients who underwent simple suture and epiplooplasty for perforation or gastroenterostomy without vagotomy, patients with stomal ulcers that developed after a procedure not primarily directed to an ulcer, such as a pancreaticoduodenectomy, and patients with recurrent ulcer after surgery for a primary gastric ulcer.

Our series comprised 22 men and 4 women with an average age of 44 years (range, 23 to 69 years). Almost two thirds belonged to type O blood group which is similar to the usual frequency of that blood group in patients with duodenal ulcer. The duration of the symptoms varied widely from 2 months to 14 years. Symptoms tended to reappear early following the primary operation; more than two thirds of the patients became symptomatic within 2 years. Patients generally sought medical advice without delay when their symptoms recurred. Seventy percent underwent repeat operations less than 1 year after recurrence of symptoms and altogether 61.5% of the patients underwent a second operation within 3 years of the first one (Table II). In only 6 of the 26 patients was the initial operation performed as an emergency procedure, in 2 for hemorrhage and in 4 for perforation. The site of the recurrence varied widely according to the type of initial surgery (Table III). Pain was

Table I—Distribution of Recurrences According to the Type of Primary Operation

Primary operation	No. of patients (and %)
Truncal vagotomy and pyloroplasty	13 (50.0)
Truncal vagotomy and gastroduodenostomy	1 (3.8)
Truncal vagotomy and gastrojejunostomy	1 (3.8)
Selective vagotomy and pyloroplasty	6 (23.1)
Truncal vagotomy and antrectomy (Billroth I)	1 (3.8)
Partial gastrectomy (Billroth II)	4 (15.4)
Total	26 (100.0)

Table II—Time Interval between Operations in Patients with Recurrent Ulcer

Interval, yr	No. of patients (and %)
< 1	4 (15.4)
1	5 (19.2)
2	4 (15.4)
3	3 (11.5)
4	1 (3.8)
5	2 (7.7)
> 5	7 (26.9)
Total	26 (100.0)

Table III—Distribution of Recurrences According to Anatomical Site

Site	No. of patients
Duodenal	8
Pyloric	4*
Prepyloric	7
Antral	2*
Stomal	
Billroth I	1
Billroth II	4
Gastrojejunostomy	1
Total	27

*1 patient had 2 ulcers.

the most frequent complaint (88%), followed by hemorrhage (42%), obstructive symptoms (15%) and perforation (3.8%). Recurrent ulceration had a deleterious effect on nutritional status; 10 (38%) patients lost from 2.25 to more than 9.07 kg.

We attempted first to demonstrate the ulcer and then to determine its cause. Roentgenography after a barium meal revealed an ulcer in 76% of the cases in which it was done. Endoscopy was diagnostic in 90% of cases. While endoscopy showed a recurrent ulcer in five patients whose roentgenogram was normal, it could not demonstrate an ulcer in one patient whose roentgenogram had previously been positive and also overlooked an ulcer on the lesser curve which had been seen on the roentgenogram and was confirmed at operation. The etiology of the recurrences was determined by gastric acid secretion tests: basal acid output (BAO) and maximal acid output (MAO) after pentagastrin stimulation, by the Hollander test and by the serum gastrin concentrations. For circumstantial reasons, all these studies were not done in every patient. The Hollander test showed that the vagotomy performed in 20 patients had been incomplete in 16. The serum gastrin concentration was normal in 12 of the 13 patients in whom it was determined. One patient, after a subtotal Billroth II gastrectomy, had a baseline gastrin value of 442 ng/L, leading us to suspect the presence of a gastrinoma. No gastrinoma was found and she was asymptomatic 18 months following vagotomy. Results of gastric secretion tests are shown in Table IV; 70% of patients had hypersecretion.

Table IV—Distribution of Recurrences in Relation to Gastric Acid Output (μmol/s)

Gastric acid output, μmol/s (meq/h)	No. of recurrences
Basal acid output	
< 0.8 (3.0)	3
> 0.8 (3.0)	11
Maximal acid output	
< 5.6 (20.0)	5
> 5.6 (20.0)	8

Treatment and Complications

All patients with a recurrent ulcer following adequate surgical treatment underwent a second operation. The type of surgery performed took into consideration the following: (a) the nature of the primary operation, (b) the probable cause of recurrence, and (c) the patient's general condition. Table V lists the various secondary operations performed in relation to the primary procedures. Ten patients had vagotomy alone, 12 had vagotomy and antrectomy and 4 had antrectomy alone. All vagotomies were of the truncal variety; in 6 a thoracic approach was used. We had no 30-day operative mortality but morbidity was high. Nine (35%) patients had 11 serious complications (Table VI); six patients had complications after antrectomy and three after thoracotomy.

Discussion

Recurrent ulceration is the most frequent complication that requires a second operation following surgical treatment of duodenal ulcer. The wide variety of procedures still used to cure duodenal ulcer indicates that no single operation is without failure. In a randomized study, Postlethwait[1] determined the 5-year recurrence rate following vagotomy and drainage (6.2%), vagotomy and antrectomy (0.7%), vagotomy and hemigastrectomy (0.9%) and subtotal gastrectomy (3.7%) for treatment of duodenal ulcer. These results are comparable to those reported by Goligher and colleagues.[2] The newer procedure of highly selective vagotomy also has a recurrence rate of 6% to 7% as the duration of follow-up increases.[3-8]

In our retrospective study, most of the findings were comparable to those recently reported.[9-14] Recurrent ulcers occurred more commonly in men in a proportion of five to one. The latent period was short (less than 2 years in 66%) and so was the symptomatic pe-

Table VI—Postoperative Complications in Relation to Type of Surgery*

Complication	Type of surgery
Pulmonary atelectasis	Antrectomy (Billroth II)
	Repeat vagotomy, thoracic approach (2 patients)
Pulmonary atelectasis and pancreatitis	Antrectomy (Billroth I)
Gastric atony and retention	Repeat vagotomy and antrectomy (Billroth I) (2 patients)
Gastric hemorrhage and dysphagia	Vagotomy, thoracic approach
Duodenal fistula	Repeat vagotomy and antrectomy (Billroth II)
Subphrenic abscess	Antrectomy (Billroth II) (catheter duodenostomy)

*There were 11 complications in 9 patients.

Table V—Surgical Treatment in Relation to the Primary Procedure

Second operation		First operation, no. of patients						
No. of patients	Procedure	TV + P	TV + Jab	TV + GE	SV + P	TV + A (BI)	PG (BII)	Total
10	ReV—thoracic approach	2	1	—	2	—	—	5
	abdominal approach	1	—	—	—	1	—	2
	V—thoracic approach	—	—	—	—	—	1	1
	abdominal approach	—	—	—	—	—	2	2
12	ReV + A—Billroth I	6	—	—	1	—	—	7
	Billroth II	1	—	—	3	—	—	4
	V + A—Billroth I	—	—	—	—	—	—	0
	Billroth II	—	—	—	—	—	1	1
4	A—Billroth I	2	—	—	—	—	—	2
	Billroth II	1	—	1	—	—	—	2
Total		13	1	1	6	1	4	26

ReV = repeat vagotomy, V = vagotomy, A = antrectomy, TV = truncal vagotomy, P = pyloroplasty, Jab = Jaboulay gastroduodenostomy, GE = gastroenterostomy, SV = selective vagotomy, BI = Billroth I, PG = partial gastrectomy, BII = Billroth II.

riod (less than 1 year in 70%). Furthermore, 60% of the patients were reoperated on within 3 years of their initial operation. Our patient population was relatively young (average age, 44 years) and 66% belonged to blood group O. That the primary procedure was done as an emergency does not explain a recurrence, for 77% of our patients had an elective primary operation.

Endoscopy is the best way to demonstrate a recurrence. It should be performed in any case in which recurrence is suspected but not demonstrated by roentgenography. Interpretation of the roentgenogram after a barium meal is often misleading after any operation for duodenal ulcer except parietal-cell vagotomy. Even when the roentgenogram is positive, endoscopy still provides useful information. For instance, it is the only means of demonstrating esophagitis or biliary gastritis, and the finding of a concomitant disease can change the surgical approach.

Most (80%) of the recurrent ulcers occurred after vagotomy and a drainage procedure. This is in accordance with the findings of others.[1,4] In our series the main factor in producing most of such recurrences was failure to achieve a complete vagotomy[14] as shown by a positive Hollander test in 80% of the patients in which it was done. Although a positive Hollander test indicating incomplete vagotomy does not mean that a duodenal ulcer is sure to recur, we find it valuable in determining the cause of a proven recurrence. Four of our patients with a negative Hollander test after vagotomy and drainage were explored through the abdomen for residual vagal fibres. In one patient an intact posterior vagal trunk was found. In all four patients, antrectomy was performed. In the presence of a negative Hollander test and high basal acid secretion, one should still suspect incomplete vagotomy.

Serum gastrin was determined in half of our patients. Fasting and 45-minute postprandial concentrations were not elevated enough to cause suspicion of Zollinger-Ellison syndrome or a G-cell hyperplasia in any patient. When a high gastrin concentration is found, investigation by secretin and calcium perfusion tests is called for. We have yet to discover our first gastrinoma.

The selection of the proper procedure for the second operation is determined by the nature of the first, the suspected cause of recurrence and the general condition of the patient. Other factors can also modify surgical planning, namely, several previous abdominal operations, obesity, advanced age and concomitant abdominal disease. Every patient in whom an incomplete vagotomy is suspected should have at least repeat vagotomy as part of the treatment. For recurrence after vagotomy and drainage when there is a normal serum gastrin concentration, transthoracic vagotomy is our procedure of choice when there is no obstruction, hemorrhage, or perforation.[15] It is most helpful in obese patients. Should there be a further recurrence, antrectomy could then be performed and would not be as difficult as if it were done as a tertiary abdominal procedure. The abdominal approach is mandatory for patients after vagotomy and drainage when there is obstruction, perforation or hemorrhage, marked hypersecretion, a suspicion of G-cell hyperplasia or concomitant abdominal disease. In any of these circumstances the procedure should be the most definitive available, namely, repeat vagotomy and antrectomy. This combination still offers the lowest known rate of recurrence in most centres.

If the first operation was gastric resection without vagotomy, then vagotomy should be performed. If antral exclusion and Zollinger-Ellison syndrome are not suspected and there are no complications of the ulcer, the thoracic approach may be selected.

If recurrence follows vagotomy and antrectomy, one should highly suspect a gastrinoma or antral exclusion after a Billroth II reconstruction. Examination of a frozen section of a duodenal biopsy specimen during the primary operation assures prevention of the latter. Even in the absence of hypergastrinemia, surgery should be performed using an abdominal approach to explore the pancreas, liver, stomach and duodenum. If such an exploration discovers no abnormality repeat vagotomy can then be performed.

We used antrectomy alone in the patients with a negative Hollander test and normal gastric acid secretion. In these cases, we still dissected the esophageal hiatus to make sure that no vagal fibres remained. Even though antrectomy "protects" against incomplete vagotomy,[13] exploration of the hiatus does not add to the morbidity, and making sure that the vagotomy is complete lessens the possibility of recurrence after vagotomy and antrectomy.

Most of our patients (21 of 26) were reoperated on in the past 3 years. Our follow-up is therefore short but includes 24 of the 26 patients. As yet there has been no known or suspected recurrence. The 30-day operative mortality was zero.

Conclusion

If a given percentage of recurrence following operation for duodenal ulcer is predictable, subsequent surgical treatment should aim at preventing any further recurrence while incurring the least morbidity and mortality. Thorough investigation is necessary to make an accurate diagnosis of recurrence and to determine its cause as precisely as possible. Attention should be directed not only to the completeness of the vagotomy but also to its efficacy. Endocrine-secreting tumours should be sought. The single common denominator of all the recurrences is insufficient primary treatment—gastric resection without vagotomy, incomplete vagotomy, overlooked endocrine-secreting tumour, or too limited surgery (e.g., vagotomy and drainage) for virulent duodenal ulcer disease.

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Immunologic Detection of Primary Carcinoma of the Pancreas

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The prevalence of carcinoma of the pancreas is increasing in North America. Primary prevention of this disorder is not yet possible and secondary prevention is difficult because most investigative procedures are either highly invasive or not universally available. The authors tested the efficacy of a simple immunologic assay, the leukocyte adherence inhibition (LAI) assay, in the detection of carcinoma of the pancreas. They investigated 55 patients who were divided into six groups—normal (control) patients (16) and those with carcinoma of the pancreas (9 patients), pancreatitis (15), other intra-abdominal carcinomas (9), obstructive jaundice (4) and pancreatic pseudocysts (2). The LAI assay proved highly effective in selecting patients who, at surgery, were shown to have carcinoma of the pancreas, but was not as effective in the other groups. This assay may therefore prove valuable in the early evaluation of patients with a suspected pancreatic malignant condition.

La fréquence des carcinomes du pancréas est en augmentation en Amérique du Nord. La prévention primaire de cette affection n'est pas encore possible et la prévention secondaire est difficile car la plupart des techniques exploratrices sont ou très envahissantes, ou pas généralement disponibles. Les auteurs ont testé l'efficacité d'un essai immunologique simple, le test d'inhibition de l'adhérence des leucocytes (IAL), pour la détection du carcinome du pancréas. Ils ont examiné 55 patients se répartissant en six groupes: les patients normaux (groupe témoin) (16) et ceux souffrant d'un carcinome du pancréas (9), de pancréatite (15), d'autres carcinomes intra-abdominaux (9), d'ictère par rétention (4) et de pseudokystes pancréatiques (2). L'épreuve d'IAL s'est avérée très efficace pour sélectionner les patients qui, à la chirurgie, ont présenté un carcinome du pancréas, mais elle ne s'est pas montrée aussi efficace pour les autres groupes. Cette épreuve peut donc être utile à l'évaluation précoce des patients chez qui l'on soupçonne une atteinte maligne du pancréas.

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The prevalence of carcinoma of the pancreas is reported to be increasing in North America.[1,2] This entity is now reported to be the fourth most common cause of death due to cancer, being exceeded only by carcinoma of the lung, colon and rectum, and breast.[3] Most patients who suffer from carcinoma of the pancreas die within 6 months of the diagnosis having been made. The mortality, therefore, very closely parallels the incidence.

Improved methods for early diagnosis of this fatal condition are clearly required. Many of the newer tests such as selective angiography, endoscopic retrograde pancreatography and computerized tomography are either invasive, technically difficult or not universally available. Such tests are not indicated in the evaluation of patients with minimal symptoms.

In 1972 Halliday and Miller[4] described a simple technique for the in-vitro determination of cell-mediated immunity to tumours. They demonstrated that the normal adherence of immune leukocytes on a glass surface could be inhibited by the presence of the specific antigen. This means of investigation was called the leukocyte adherence inhibition (LAI) assay. Numerous modifications have been described.[5-8] In our laboratory, we have adopted the tube LAI assay as described by Grosser and Thomson.[5] The present communication reports preliminary data on the diagnosis of carcinoma of the pancreas using this assay.

Patients and Methods

Patients were referred for study if they were suspected of having carcinoma of the pancreas on the basis of weight loss, epigastric pain, jaundice, or an abnormality evident in contrast studies of the stomach and duodenum. Patients with other pancreatic disorders were also assessed, as were a number of normal individuals and a few patients with obstructive jaundice due to lithiasis.

Patients were subsequently subdivided into six main groups:

- Patients with carcinoma of the pancreas confirmed at operation.
- Patients with clearly demonstrated acute or chronic pancreatitis.
- Patients with other malignant tumours of the gastrointestinal tract.
- Patients with obstructive jaundice due to stones, confirmed at operation.
- Patients with pancreatic pseudocysts confirmed at operation.
- Normal healthy persons (controls).

Antigen Preparation

Tumour tissue was usually obtained at autopsy and stored at –70°C. A pool of tumour tissue, usually from two to four patients, was taken from the freezer and thawed. All excess fat and normal tissue were scraped away. The pooled tumour tissue was then minced with a scalpel and with scissors. The minced tissue was diluted with five volumes of ice-cold phosphate-buffered saline at pH 7.3 and homogenized for 15 minutes at 40 000 rpm in a VirTis homogenizer (VirTis Co. Inc., Gardiner, NY). The homogenate was centrifuged at 20 000 *g* for 30 minutes. If a layer of fat was present on the surface it was removed and 2-mL aliquots of the clear supernatant were stored in small vials at –70°C.

Normal control antigen, usually normal liver tissue, was prepared in the same fashion and also stored in 2-mL vials. Before use in any assay, the protein concentration of an antigen extract was determined by a Lowry assay.[9]

Leukocyte Preparation

From patients selected for study 20 mL of blood was collected into vacutainer tubes containing heparin. These tubes were then incubated vertically at 37°C for 1 hour. The resulting leukocyte-rich plasma fraction was aspirated and centrifuged at 200 *g* for 5 minutes. The supernatant plasma was discarded. Erythrocytes contaminating the cell buttons were lysed by

adding tris-buffered ammonium chloride and the tubes were left at room temperature for 15 minutes.[10] The procedure was terminated by the addition of an equal volume of Medium 199 (Grand Island Biological Co., Grand Island, NY). The tubes were again centrifuged at 200 *g* for 5 minutes and the supernatant was removed and discarded. The cells were then washed three times with approximately 10 mL of Medium 199. Before the last wash a known volume of medium was added and a small aliquot of this cell suspension was withdrawn for cell counting. Cell counts were performed with a Coulter counter (Coulter Electronics, Hialeah, FL). Following the final wash the cells were resuspended in Medium 199 at a concentration of 1×10^7 cells/mL.

Antigen Specificity and Titration

The specificity of all antigens prepared was determined by performing a tube LAI assay with peripheral blood leukocytes from patients with known tumours. The appropriate protein concentration of the antigen was determined by constructing a titration curve of protein concentrations ranging from 50 μg to 400 μg for both test and normal antigens. Antigens causing a high degree of nonspecific release were discarded. In general, the appropriate protein concentration to yield optimal results was approximately 200 μg/tube.

LAI Assay

The LAI assay was performed in glass tubes 16 × 150 mm. All assays were performed in triplicate. The appropriate antigens to be tested in the assay were thawed and diluted to appropriate protein concentration, usually 2 mg/mL, using Medium 199. A 0.1-mL volume of leukocyte suspension (1×10^7 cells/mL) was carefully pipetted into the bottom of the glass tube. Then 0.1 mL of buffer, specific antigen, or control antigen was added to each set of triplicate tubes. Subsequently 0.3 mL of Medium 199 was added to bring the mixture to a final volume of 0.5 mL. Each tube was carefully mixed using a Pasteur pipette and the tubes were incubated horizontally. This incubation process was aided by using a styrofoam tray which is readily available in most hospital wards that use vacutainer tubes.

The tubes were incubated at 37°C in a humidified atmosphere of 5% carbon dioxide in air for 2 hours. Following this period of incubation the tubes were placed vertically and the number of nonadherent cells was counted using a Coulter counter. The data obtained were then converted to a nonadherent index (NAI) using the formula shown in Table I.

Results

The results of our assay are set forth in Table I. The specificity of the pancreatic tumour antigen is demonstrated by the fact that the NAI is significantly ($P < 0.01$) higher in patients with carcinoma of the pancreas than in those with other intra-abdominal malignant tumours. Also, the breast tumour antigen, which had previously been shown to be present in patients with breast carcinoma, was absent in patients with carcinoma of the pancreas and other intra-abdominal malignant lesions.

A positive NAI does not appear to be due to inflammation of the pancreas since in most patients with pancreatitis the index was not substantially elevated. Similarly, patients with obstructive jaundice not due to a malignant condition did not have a notably elevated NAI. These preliminary data, although small in number, suggest that the LAI assay may be a simple, noninvasive means of selecting patients with a possible malignant tumour of the pancreas who require further investigative procedures.

When an NAI index of 50 or greater was arbitrarily selected as indicating malignancy, it was shown to be so in eight of nine patients with surgically proven pancreatic cancer. The false-negative rate would therefore seem to be acceptably low. The false-positive rate, however, has been disturbingly high. Five of 15 patients with pancreatitits, 3 of 9 patients with other gastrointestinal carcinomas and 4 of 16 normal (control) patients had a positive index. Clearly, more patients must be studied to determine the efficacy of this assay.

Discussion

The preoperative diagnosis of carcinoma of the pancreas continues to be difficult to establish. Laboratory investigations that are said to be helpful in making this diagnosis include pancreatic function tests,[11,12] radionuclide scanning of the pancreas,[13] ultrasonography,[14,15] arteriography[16,17] and endoscopic retrograde pancreatography.[18-20] With the exception of ultrasonography, which is not universally available, each of these investigative procedures is relatively invasive. A recent report has suggested that the triple study by ultrasonography, pancreatic function tests and endoscopic retrograde pancreatography has an accuracy rate of almost 90% in either diagnosing or excluding pancreatic malignant lesions.[21]

Few immunologic tests have been described for the detection of carcinoma of the pancreas. The measurement of carcinoembryonic antigen (CEA) was once believed to be of value in the diagnosis of this disorder.[22] Unfortunately, various nonmalignant pancreatic disorders and other upper abdominal diseases produce measurable CEA concentrations resulting in a very high rate of false-positive results.[23] More recently the amount of CEA present in the pancreatic juice obtained at endoscopic retrograde pancreatography has been investigated. While the results are encouraging there is no evidence that this is of greater assistance in diagnosis than simple retrograde pancreatography.[12,24]

In 1974 Banwo, Versey and Hobbs[25] prepared an antibody to fetal antigen from the pancreas comparable to the CEA prepared by Gold and Freedman.[26] They called it a new oncofetal antigen for human pancreas and found it in the serum of 36 of 37 patients with carcinoma of the pancreas. However, a later report revealed that the pancreatic oncofetal antigen was also to be found in patients

Table I—Nonadherent Index (NAI)* Activity to Pancreatic and Breast Antigens of Patients with Pancreatic Disorders

Condition	Pancreatic antigen, 200 μg/tube		Breast antigen, 200 μg/tube	
	No. of patients	NAI ± SEM	No. of patients	NAI ± SEM
Carcinoma of pancreas	9	179 ± 34	7	23 ± 8.3
Pancreatitis	15	29 ± 26	6	−4 ± 9.9
Other carcinomas	9	29 ± 16	11	0 ± 14
Obstructive jaundice	4	−18.7		ND
Pancreatic pseudocyst	2	−46.5		ND
Control	16	24 ± 12	15	−1.6 ± 9

SEM = standard error of mean, ND = not done.

* $\dfrac{\text{No. of nonadhering cells in presence of specific antigen} - \text{No. of nonadhering cells in presence of nonspecific antigen}}{\text{No. of nonadhering cells in presence of nonspecific antigen}} \times 100$

with other types of abdominal carcinoma, pancreatitis and miscellaneous disorders.[27]

The present communication has described another immunologic assay for the detection of carcinoma of the pancreas. While the number of false-positive results in patients with other malignant tumours and with benign pancreatic disease has been disturbingly high, the rate of false-negative results in patients subsequently proved to have pancreatic carcinoma has been gratifyingly low. This suggests that the LAI assay may be of value in the early investigation of patients with suspected malignant tumours. Such patients whose LAI assay is positive should obviously be subjected to the more invasive tests that have been described. Patients whose LAI assay is negative may safely be kept under observation without any further investigative procedures being carried out.

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NOTICE

Canadian Association of General Surgeons Resident Research Contest

The Canadian Association of General Surgeons is awarding a prize of $500 to the resident in general surgery submitting the best abstract on a surgical topic. Included in the award will be an all-expenses-paid trip to Montreal to present the work at the annual meeting of the Canadian Association of General Surgeons, Feb. 6 to 8, 1979.

Eligibility

Any resident in general surgery conducting research during his residency training at a Canadian university is eligible to participate.

Abstract

The abstract must be submitted on the special form used by the Royal College of Physicians and Surgeons of Canada. The original plus five photocopies should be sent to: The research committee, Canadian Association of General Surgeons, c/o Dr. J.H. Duff, Department of surgery, University Hospital, 339 Windermere Rd., London, Ont. N6G 2K3. Abstract forms can also be obtained at the above address. The deadline for submission of abstracts is Sept. 1, 1978.

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Total Hip Prosthesis. Edited by N. Gschwend and H. U. Debrunner. 328 pp. Illust. The Williams & Wilkins Company, Baltimore; Burns and MacEachern Limited, Don Mills, 1976 $34.70, paperbound. ISBN 3-456-80241 2.

Reoperation Following Failure of Aortoiliofemoral Arterial Reconstruction

JOHN A. KNUDSON, MD* AND ALLAN R. DOWNS, MD, FRCS[C]†

Over a 19-year period, 729 primary arterial reconstructions for aneurysmal and occlusive disease of the aortoiliac arterial system were performed at the Health Sciences Centre, Winnipeg. During the same interval 49 of these reconstructions required reoperation and 6 additional cases were referred for secondary repair from other institutions. The authors reviewed these 55 cases to determine the reasons for reoperation and the cumulative results of secondary repair.

Secondary arterial repair was performed in 11.5% of cases of occlusive disease and in 1.2% of cases of aneurysmal disease. The overall frequency of reoperation was 6.7%. The mean interval between primary and secondary operation was 31.5 months. Perioperative failure, false aneurysm, graft infection, progression of disease and late technical problems were the major reasons for reoperation. Of the secondary repairs the results in 83.6% were satisfactory at 30 days. At 5 years, 57% of secondary repairs at risk remained satisfactory. The operative mortality for secondary arterial repair was 5.4%. The authors believe that continued aggressive management of failed primary aortoiliac reconstructions is justified.

Au cours d'une période de 19 ans, 729 reconstructions artérielles primaires pour anévrisme ou oblitération du système artériel aortoiliaque ont été effectuées au Health Sciences Centre de Winnipeg. Durant ce même intervalle, 49 de ces reconstructions ont exigé une réintervention et 6 autres cas ont été acheminés pour réparation secondaire d'autres institutions. Les auteurs ont étudié ces 55 cas dans le but de déterminer les raisons ayant entraîné une réintervention et les résultats cumulatifs des réparations secondaires.

Une réparation artérielle secondaire a été effectuée dans 11.5% des cas d'oblitération et dans 1.2% des cas d'anévrisme. La fréquence des réinterventions pour l'ensemble a été de 6.7%. L'intervalle moyen entre la première et la deuxième opération a été de 31.5 mois. Les principales causes d'une deuxième intervention ont été l'échec peropératoire, un faux anévrisme, l'infection du greffon, l'évolution de la maladie et certains problèmes techniques tardifs. Du nombre de réparations secondaires, des résultats satisfaisants à 30 jours ont été obtenus dans 83.6% des cas. Cinquante-sept pourcent des réparations artérielles secondaires à risque élevé sont demeurées satisfaisantes après 5 ans. La mortalité opératoire a été de 5.4%. Les auteurs croient que le maintien d'un traitement agressif dans les échecs des reconstructions aortoiliaques primaires est justifié.

The patency rate of aortoiliac and aortofemoral reconstructive procedures varies between 62% and 90% over 10 years.[1-7] Early and late complications leading to reoperation are uncommon in this form of surgery, but when they do occur corrective procedures can be challenging.

Between Jan. 1, 1958 and Oct. 31, 1976, 729 primary arterial reconstructions for aneurysmal or occlusive disease of the aortoiliac arterial system were performed at the Health Sciences Centre, Winnipeg. During the same period 49 patients required reoperation. Six additional patients were referred for secondary repair from other institutions. Seventy-nine operations were performed in these 55 patients (Table I). We have reviewed these secondary arterial reconstructions to examine the causes of failure leading to reoperation and to determine the cumulative results of secondary repair.

We define secondary repair as reoperation because of failure of a primary arterial reconstruction; perioperative occlusion was included. Early reoperation for hemorrhage, other than that resulting from infection, is excluded from the definition.

Seventeen patients required more than one reoperation. However, all reoperations related to the same primary reconstruction were considered as one statistical event.

There were 46 men and 9 women. The mean age was 59.9 years (range, 36 to 79 years). Duration of follow-up ranged from 3 months to 9 years (mean, 3 years). Three patients with successful secondary repairs were lost to follow-up at 37, 37 and 33.5 months.

Occurrence of Failure of Primary Operation

Vascular complications requiring reoperation occurred following 45 (11.5%) of 391 operations for occlusive disease and after only 4 (1.2%) of 338 operations for aneurysmal disease. The overall incidence of reoperation was 6.7%. The number of reoperations was related to the type of primary procedure (Table II). Secondary procedures were required in 3.5% of all aortic bifurcation grafts and in 9.2% of cases in which aortic bifurcation grafts were introduced for the management of occlusive disease. Of patients who underwent unilateral prosthetic procedures, 18.3% required reoperation. One would expect the risk of failure of bifurcation grafts to be twice that of unilateral grafts. How-

Table I—Secondary Arterial Repairs

No. of patients	No. of reoperations
38	1
13	2
3	3
1	6
55	79

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Table II—Frequency of Secondary Repair Related to Primary Operation

	No. primary operations	No. failed and reoperated	% reoperations
Aortoiliofemoral prosthesis	479	17	3.5
Occlusive disease	141	13	9.2
Aneurysm	338	4	1.2
Aortoiliac endarterectomy	43	6	13.9
Unilateral prosthesis	82	15	18.3
Unilateral endarterectomy	74	5	6.8
Unilateral vein graft	10	1	10
Cross-femoral graft (vein or prosthesis)	24	0	0
Axillofemoral graft	17	5	29.4
Total	729	49	6.7

Table III—Indications for Primary and Secondary Repair

Indication	Primary repair, no. of patients (and %)	Secondary repair, no. of patients (and %)
Claudication	30 (54.5)	14 (25.4)
Limb salvage	19 (34.6)	25 (45.4)
Aneurysm	6 (10.9)	—
False aneurysm	—	9 (16.4)
Graft infection	—	7 (12.7)
Total	55	55

ever, in patients with occlusive disease only 30.8% of the primary bifurcation graft procedures were performed for limb salvage compared with 46.7% of the primary unilateral procedures, suggesting that arteriosclerosis was more severe in the latter group. Reoperation was necessary in 13.9% of bilateral aortoiliac endarterectomies and in only 6.8% of unilateral iliac endarterectomies.

Symptoms attending failure of a primary vascular reconstruction were usually more severe than those indicating the need for initial repair. Of the 55 patients who later required reoperation, the indication for primary repair was claudication in 54.5% and limb salvage in 34.6% (Table III). Following failure of primary repair, these figures were 25.4% and 45.4% respectively. Graft infection and false aneurysm were the indications for secondary repair in the remaining patients.

Causes of Failure

Eight (14.5%) patients with perioperative occlusion required reoperation on the day of surgery. The higher proportion of immediate failures in the endarterectomy group probably reflects the higher degree of technical skill required for endarterectomy as compared with bypass procedures.

Progression of arteriosclerosis was responsible for 21 (38.2%) reoperations. Inadequate outflow from the deep femoral artery with concomitant chronic occlusion of the superficial femoral artery resulted in failure of 13 of 16 prosthetic procedures in this group. Only one patient had severe arteriosclerosis of the deep femoral artery and 12 had stenosis or occlusion at the origin of the deep femoral artery. These figures emphasize the importance of adequate management of the deep femoral artery at the primary reconstruction. In the remaining eight cases in this category failure occurred more than 3 years after reconstruction because of recurrent arteriosclerosis at the site of endarterectomy or the distal anastomosis. The 10 late technical failures (18.2% of the total) were in patients in whom none of the other identifiable causes of failure were apparent. Incomplete endarterectomy or inadequate initial anastomoses accounted for the late failures in this group.

There were seven graft infections (12.7%) (one of which was fatal) and two amputations. Nine patients required a secondary repair for a false aneurysm which was located in the groin in eight. Of the nine patients with a false aneurysm (16.4% of the total), five had associated aneurysmal disease. The higher frequency of false aneurysms in patients with aneurysmal disease suggests that the condition predisposes to false-aneurysm formation, but this awaits confirmation.

If immediate failures are excluded, the mean interval between primary and secondary operation was 31.5 months. Progression of disease necessitated a second operation an average of 31.6 months after the first. Graft infections presented an average of 9.1 months postoperatively. False aneurysm was a late complication developing an average of 56.2 months following surgery.

Operative Procedures

A variety of procedures were used for secondary operations.

False aneurysms in the groin are usually best managed by excision of the anastomotic site and insertion of a longer prosthesis (Fig. 1). In the presence of occlusion of the superficial femoral artery an end-to-end anastomosis to the divided end of the deep femoral artery is preferred. If the proximal aortic anastomosis is aneurysmal, a graft replacement is indicated (Fig. 2). Eight of nine patients were managed successfully by these methods.

Recurrent occlusion of an endarterectomized segment is best treated by a bypass graft. For unilateral iliac occlusion, a cross-femoral bypass graft may suffice.

Occlusion of one limb of a prosthesis is usually due to outflow obstruction. Where there has been recent occlusion of the prosthesis it may be possible to remove the thrombus by

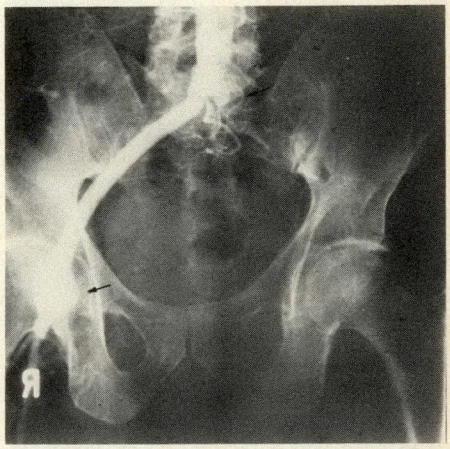

FIG. 1—Anastomotic false aneurysm, right groin, and occlusion, left prosthetic limb, due to anastomotic false aneurysm. Both treated by graft extension.

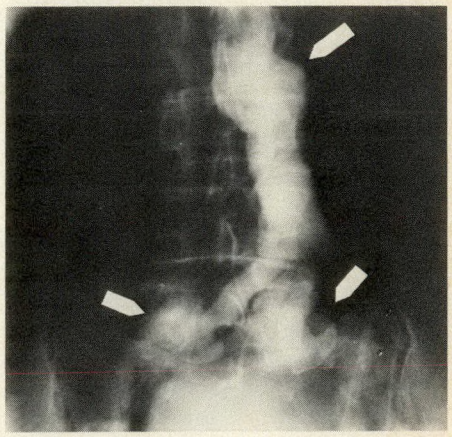

FIG. 2—Aortoiliac prosthetic graft, with false aneurysms at all three anastomoses.

way of the groin without exposing the graft in the abdomen.[8] A cross-femoral graft from the patent limb of the prosthesis may be the simplest reconstructive procedure (Fig. 3). It is most important to establish an adequate outflow to avoid reocclusion. If clot is present at the bifurcation of the graft, proximal control will be necessary, and thrombectomy of the occluded limb of the prosthesis may then be carried out (Fig. 4).

Graft infection usually necessitates removal of the graft and an amputation or an extra-anatomical reconstruction such as an obturator bypass (Fig. 5) or an axillofemoral bypass. Anastomotic stenosis requires patch-graft angioplasty or an extension of the prosthesis more distally to the site of an adequate outflow (Fig. 6). It cannot be overemphasized that the operation must be tailored to the individual patient.

Results

The evaluation of secondary repair demands careful analysis of the results because the indications for such procedures are variable. We define success as improvement in disabling claudication, limb salvage when the limb has been at risk, management of infected prostheses without loss of life or limb and repair of false aneurysms without incurring new vascular symptoms. Except in graft infections, patency of the repair parallels a successful result.

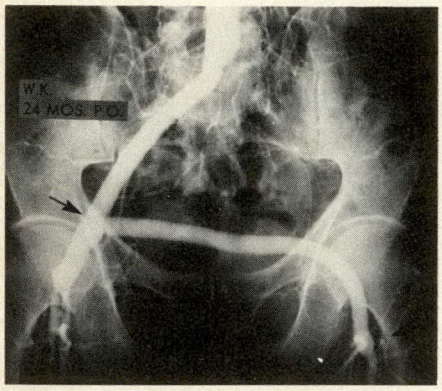

FIG. 3—Prosthetic limb occlusion treated by cross-femoral graft from patent limb to deep femoral artery.

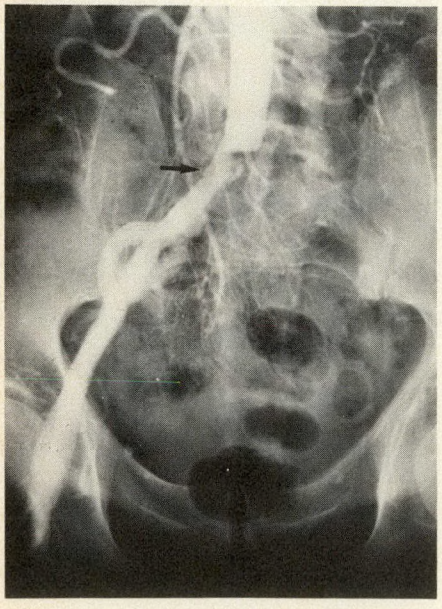

FIG. 4—Prosthetic limb occlusion with clot, extending into patent limb, requiring proximal control.

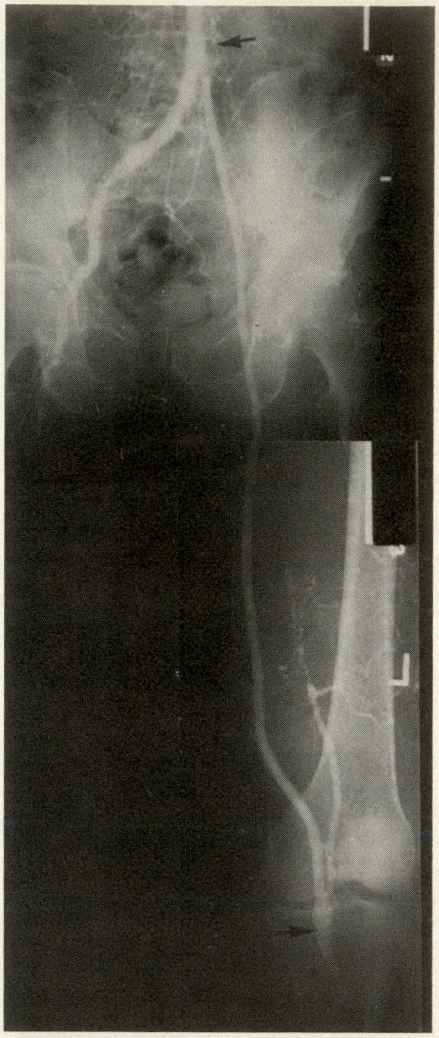

FIG. 5—Obturator vein bypass graft in groin for infection of prosthesis.

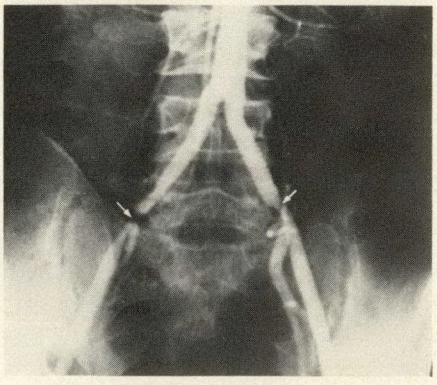

FIG. 6—Anastomotic iliac stenosis, requiring graft extension to common femoral arteries.

The average duration of follow-up in our cases of secondary repair was 3 years. We were interested in the ultimate result in patients, hence we considered more than one reoperation in an individual patient as a single statistical event. To analyse success we used the life-table method.[9]

Nine failures occurred within 30 days of operation. Our success rate at 30 days was 83.6%; at 2 years it had fallen to 62.2% and at 5 years to 57% (Fig. 7). There were three operative deaths, giving a surgical mortality of 5.4%. Two of the deaths were in patients with aortoenteric fistula and one followed unsuccessful repair of a ruptured iliac false aneurysm.

Discussion

All failed reconstructions do not necessarily lead to reoperation. Risk of reoperation has to be weighed against the expectation of technical success, the severity of symptoms and the possible mortality without operative intervention. Patients undergoing reoperation often have life or limb at risk. A patient may require several reoperations before a successful result is achieved.

Improvement in prosthetic materials, the use of synthetic sutures for anastomoses and definition of the stress forces on vascular anastomoses have reduced the frequency of false aneurysm to between 1.9% and 8%.[10-14] The frequency of false aneurysm among patients in our series was about 1.2%. With the evolution of perioperative management and vascular techniques, and possibly with the prophylactic use of antibiotics, the infection rate of prostheses varies between 1.5% and 6%.[15,16] Graft infection accounts for the highest morbidity and mortality, but aggressive surgical management can save most of these patients and their limbs as demonstrated by our experience. Progression of arteriosclerotic disease was the principal reason for failure of the primary operation.

There have been several reports on aortoiliac secondary repairs.[8,17-19] However, the long-term results of aortoiliac reoperations have not been well docu-

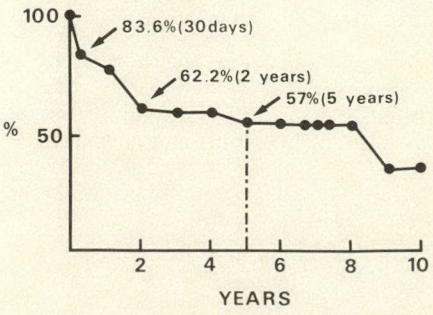

FIG. 7—Analysis of success of secondary repair of aortoiliac disease by life-table method.

mented. Continued aggressive management of failed primary aortoiliac reconstructions is indicated.

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Role of Doppler Ultrasonography in Determining the Hemodynamic Significance of Aortoiliac Disease

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Doppler ultrasound recordings from the common femoral artery were quantified by calculation of the pulsatility index (a number related to the maximum oscillatory energy of the wave). To demonstrate that the index permits detection of hemodynamically significant aortoiliac stenosis, studies were carried out that led to the following conclusions: (a) in patients with aortoiliac occlusive disease and normal distal vessels, the index correlates with the ankle pressure ratio (the ratio of systolic blood pressure at the ankle to brachial systolic blood pressure) ($r = 0.70$); (b) the index allows distinction of subjects with significant aortoiliac disease, demonstrated arteriographically, from normal subjects; and (c) in patients with pure aortoiliac occlusive disease (no evidence of distal disease on arteriography) there is a strong correlation between the index and the percentage improvement (i.e., increase) in the ankle pressure ratio following operation ($r = 0.80$). When the femoral pulsatility index was greater than 5, the ankle pressure ratio did not improve following operation, but when it was 4 or less, an objective improvement in ankle pressure ratio was demonstrated.

Les examens aux ultrasons de Doppler de l'artère fémorale commune ont été quantifiés par le calcul de l'index de pulsatilité (une valeur reliée au maximum d'énergie oscillatoire de l'onde). Pour démontrer que le calcul de l'index de pulsatilité fémorale permettait la détection d'une sténose aortoiliaque hémodynamiquement significative, des études ont été menées qui ont donné les conclusions suivantes: (a) chez les patients souffrant d'une maladie aortoiliaque occlusive et ayant des vaisseaux distaux normaux, l'index a montré une corrélation avec le rapport de pression de la cheville (le rapport de la pression systolique à la cheville et la tension artérielle brachiale systolique) ($r = 0.70$); (b) cet index permet de faire la distinction entre les sujets ayant une maladie aortoiliaque significative démontrée à l'artériographie, et les sujets normaux; et (c) chez les patients souffrant d'une maladie aortoiliaque occlusive pure (sans signe d'atteinte distale à l'artériographie), Il existe une forte corrélation entre l'index et le pourcentage d'amélioration (d'augmentation) du rapport de pression de la cheville après l'opération ($r = 0.80$). En présence d'un index de pulsatilité supérieur à 5, le rapport de pression de la cheville ne s'est pas amélioré après l'opération, mais quand l'index était de 4 ou moins, une amélioration objective du rapport de pression de la cheville a été démontrée.

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A successful vascular operation depends primarily on good clinical judgement combined with technical excellence. In aortoiliac surgery, in spite of careful preoperative clinical and arteriographic assessment and a technically successful procedure, some patients are unimproved following operation. The failure rate of aortoiliac reconstruction can be reduced by attention to certain technical considerations and perhaps by more precise objective assessment of the hemodynamic significance of aortoiliac stenosis.

The purpose of this study is to answer the question, Can noninvasive Doppler ultrasound recordings from the femoral artery determine if an aortoiliac stenosis is hemodynamically significant?

A New Doppler System

Before we could obtain quantitative information about the aortoiliac segment from femoral artery Doppler recordings, we had to overcome the inherent limitations of Doppler "flowmeters"[1-3] and solve the following problems: (a) to obtain meaningful directional Doppler signals: (b) to process the signals and produce a blood flow velocity wave free of artefacts; and (c) to quantify the Doppler wave. Our methods for accomplishing these objectives have been reported,[4,5] but will be briefly reviewed here in order to clarify the inherent limitations of currently available commercial Doppler "flowmeters".

Obtaining Meaningful Directional Doppler Signals

The normal blood flow velocity wave is triphasic with a forward flow, a reverse flow and usually a second forward flow component. Unless the Doppler system is able to separate clearly the directions of blood flow, the resultant waveform may be in error. Many commercial Doppler instruments have serious limitations in their direction-resolving ability. To overcome this problem, we have designed and constructed a heterodyne Doppler velocity meter which has almost perfect direction-resolving capabilities (Kassam M, Johnston KW, Cobbold RSC: Unpublished data, 1978).

Processing the Doppler Signals and Producing a Blood Flow Velocity Wave Free of Artefacts

Since our aim is to obtain quantitative information from the Doppler waveform, it is essential to obtain one that is free of errors and artefacts. Current commercial instruments use a zero crossing detector to process the Doppler signals, but unfortunately this method produces artefactual waveforms in many situations.[1-3] We have overcome this problem by designing a relatively inexpensive real-time frequency analyser which displays the Doppler waveform on an oscilloscope or on recording paper.[4]

Quantifying the Doppler Waveform

At present there is only one way to quantify the Doppler waveform accurately and that is by calculating the pulsatility index (a number that is proportional to the maximum oscillatory energy of the wave).[6-9] It would be ideal to calibrate the Doppler waveform and thus be able to measure absolute velocity, but at present this is not possible with any degree of accuracy.[6] The theoretical basis for the calculation of the pulsatility index and its in-vitro and in-vivo validation are beyond the scope of this paper;[5] suffice it to say that the pulsatility index can be calculated easily from the maximum instantaneous velocity wave by using a pencil and ruler.

Methods and Patients

In this study the hemodynamic significance of aortoiliac disease was determined from Doppler ultrasound velocity recordings taken from the femoral artery using our new Doppler system and a real-time frequency analyser and display system. The pulsatility index was calculated and was used to quantify the wave. Normally, the pulsatility index is high. Distal to an arterial stenosis the waveform is dampened (i.e., the peak is delayed and flattened and reverse flow is absent) and the pulsatility index is reduced.

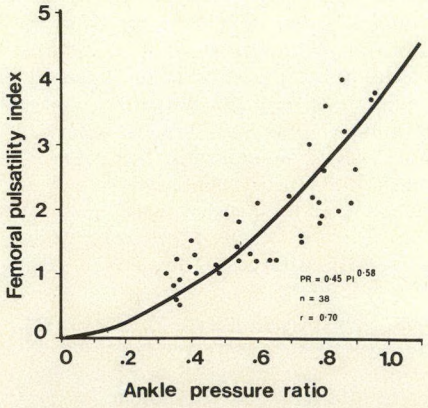

FIG. 1—Relation between femoral pulsatility index and ankle systolic pressure ratio (ratio of systolic blood pressure at ankle to brachial systolic blood pressure) in patients with aortoiliac occlusive disease and normal distal vessels.

Doppler ultrasound velocity recordings were made from the common femoral artery and the femoral pulsatility index was calculated from these recordings. In order to demonstrate that the femoral pulsatility index was actually a hemodynamic measurement and to determine whether it could be used to estimate the severity of aortoiliac disease, femoral pulsatility index was compared with: (a) the measurement of ankle pressure ratio (i.e., the ratio of systolic blood pressure at the ankle to brachial systolic pressure), (b) arteriograms graded according to the severity of the stenosis in the aortoiliac segment, and (c) the amount of improvement in the ankle pressure ratio following operation.

Results

Correlation between Femoral Pulsatility Index and Systolic Blood Pressure Ratio at the Ankle

Only patients with pure aortoiliac occlusive disease (i.e., no evidence of distal disease on arteriography) were studied; hence it is reasonable to assume that systolic blood pressure measured at the ankle was directly related to femoral artery blood pressure. Accordingly it was to be predicted that the femoral pulsatility index would also be related to systolic blood pressure ratio at the ankle. As illustrated in Fig. 1, for 38 points, ankle pressure ratio and femoral pulsatility index were related by a power equation of the form $y = ax^b$ with a correlation coefficient of 0.70.

Relation between Femoral Pulsatility Index and Arteriographic Grades in the Aortoiliac Segment

Although arteriography does not provide a hemodynamic measurement, the above relation is important to establish. When arteriography was used as a baseline for comparison, in 155 limbs femoral pulsatility index appeared to be as discriminating (Fig. 2). It distinguished subjects with clinically and arteriographically significant lesions from the normal group.

Relation between Femoral Pulsatility Index and the Objective Improvement Following Operation

Arteriography has serious limitations when used for determining the significance of lesions in the aortoiliac segment. Therefore in order to determine whether the measurement of femoral pulsatility index can detect and quantify the hemodynamic significance of an aortoiliac lesion, a third relation-

ship was assessed—that between the femoral pulsatility index and the results of operation as measured objectively by the increase in the pressure ratio following operation. Forty-six limbs of patients with pure aortoiliac occlusive disease were studied. Preoperatively, the femoral pulsatility index was measured and the ankle pressure ratio calculated. The ankle pressure ratio was remeasured postoperatively and the percentage improvement in the pressure ratio was calculated (Fig. 3). As predicted, when the preoperative femoral pulsatility index was high, the ankle pressure ratio did not improve. On the other hand, when the femoral pulsatility index was low, the pressure ratio did improve. It is apparent that the relation between femoral pulsatility index and percentage improvement in ankle pressure ratio, as expressed in Fig. 3, is an inverse function. Hence, if the inverse of the femoral pulsatility index is plotted against the percentage improvement in the pressure ratio, a linear relation results as illustrated in Fig. 4. For 46 limbs, we found a linear relation between inverse femoral pulsatility index and percentage improvement in the pressure ratio. The correlation coefficient was 0.80.

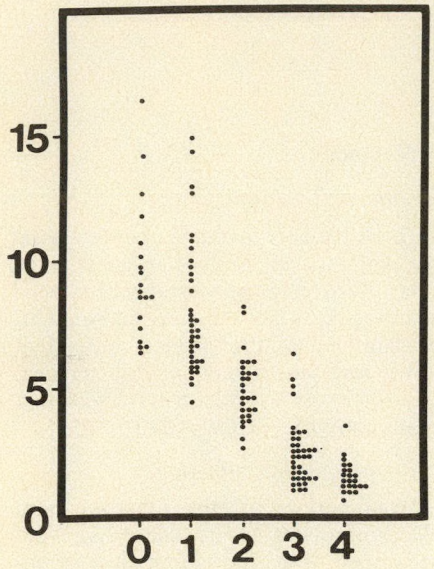

FIG. 2—Femoral pulsatility index plotted against corresponding arteriographic grade of aortoiliac segment. Grade 0 = normal subjects; grade 1 = patients with intimal irregularity only; grade 2 = patients with less than 50% stenosis; grade 3 = patients with greater than 50% stenosis; grade 4 = patients with complete arterial occlusion.

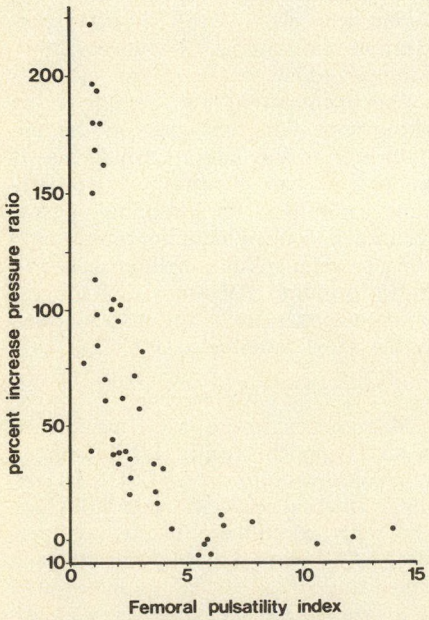

FIG. 3—Relation between femoral pulsatility index and percentage improvement (increase) in ankle pressure ratio achieved by operation. Only patients with aortoiliac disease and normal distal vessels were included.

Summary and Conclusions

We have demonstrated that the pulsatility index calculated from Doppler ultrasound recordings from the femoral artery is a quantitative measure of the hemodynamic significance of arterial occlusive disease in the aortoiliac segment. When the femoral pulsatility index is less than 4, a hemodynamically significant lesion is present in the aortoiliac segment and operative repair produces an objective improvement. When the femoral pulsatility index is greater than 5, no hemodynamically significant lesion is present in the aortoiliac segment and operation does not produce an objective hemodynamic improvement.

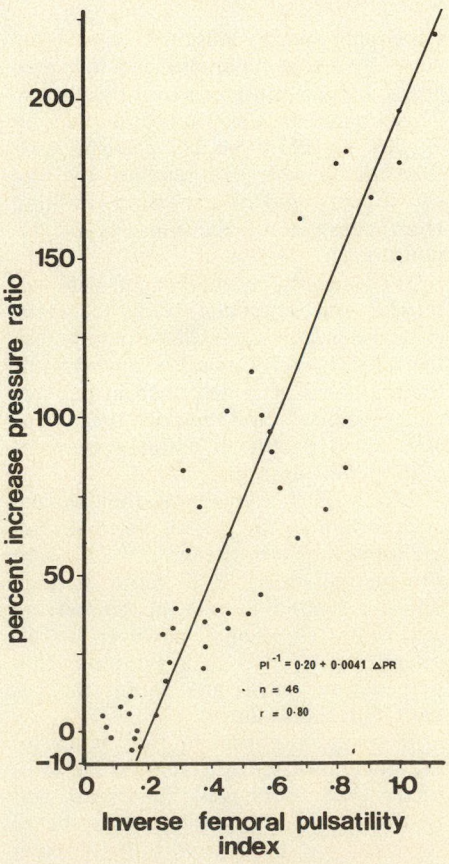

FIG. 4—There is linear relation between inverse of femoral pulsatility index and percentage improvement in ankle pressure.

The technical assistance of Mrs. B. Hansen, RN is acknowledged.

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Oropharyngeal Dysphagia in Patients with Oculopharyngeal Muscular Dystrophy

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Sixteen patients with an established diagnosis of oculopharyngeal muscular dystrophy underwent clinical, radiologic and manometric assessment. Secondary pharyngo-oral and pharyngonasal regurgitations are usually associated with this condition and chronic aspiration with consequent bronchorrhea is common. Such patients may present with marked oropharyngeal dysphagia.

Cineradiologic findings correlated well with the manometric results. The pharynx showed very weak contractions of longer duration than those observed in normal subjects. The proximal esophageal sphincter had a normal resting and closing pressure; however, relaxation and coordination of the sphincter were substantially different from those in a control group.

Eleven patients underwent cricopharyngeal myotomy. All had notable improvement of their symptoms. Surgery on the sphincter results in a substantial decrease in its resting pressure; pharyngeal contraction remains unaltered.

Seize patients porteurs d'une dystrophie oculopharyngée ont été évalués. Ils ont eu un examen clinique, radiologique ainsi qu'une étude de la fonction oesophagienne. Ces patients présentent une symptomatologie typique qui est d'apparition tardive. Une dysphagie oropharyngée souvent sévère est observée. Secondairement, des régurgitations pharyngo-orales et pharyngonasales surviennent. Des épisodes répétés d'aspiration entraînent une bronchorrhée importante.

La radiologie et la manométrie s'accordent: le pharynx montre des contractions faibles et prolongées. Le sphincter pharyngo-oesophagien présente une pression de repos et une pression de contraction comparables au normal. Le relâchement et la coordination du sphincter avec la contraction du pharynx varient cependant de façon significative d'avec les normaux.

Onze patients ont été traités par une myotomie du sphincter pharyngo-oesophagien. Tous ont été très améliorés par cette intervention. Les effets observés de la chirurgie sur la fonction du sphincter sont une diminution marquée de la pression de repos dans celui-ci. La fonction du pharynx demeure identique.

Oculopharyngeal muscular dystrophy is a syndrome characterized by progressive palpebral ptosis and dysphagia. This condition was first described by Taylor[1] in 1915; all his patients with this disease who had reached the age of 50 years died of starvation resulting from paralysis of the muscles of deglutition.

Subsequently a number of case reports[2-4] and a genetic study[5] revealed that this syndrome afflicts mainly patients of French-Canadian ancestry although it has been described in patients of Bohemian[6] and Jewish origin[2] as well as in people of Latin American[7] and Italian[8] descent.

Most publications on the subject concentrate on the genetic and neurologic aspects of the disease.[1,3,4,9] Late and progressive ptosis is a more striking clinical sign than the accompanying dysphagia. Dysphagia, however, is frequently mentioned as a symptom that precedes the ptosis and causes the patient much discomfort.[10-13]

It is our intention in this paper to: (a) document more precisely the oropharyngeal, esophageal, laryngeal and tracheobronchial symptoms presented by a group of patients with this disease, (b) assess the pharyngeal dysfunction through radiologic and manometric studies, and (c) evaluate the results of treatment.

Methods

Clinical Evaluation

In 16 patients (average age, 63 years) the diagnosis of oculopharyngeal muscular dystrophy was established by a neurologist (A.B.). All were subsequently examined at the surgical outpatient clinic and underwent a full medical assessment by a gastroenterologist and a surgeon (J.L., R.C., A.D.).

Radiologic Investigation

Examination of the pharynx and recording of the act of swallowing were performed with the patient in a standing or sitting position. Initially, the cineradiographic technique was used in the frontal and lateral projections at a frame rate of 30 per second. The patient was instructed to hold a mouthful of concentrated liquid barium (Micropaque 95%, Nicholas Laboratories Ltd., Slough, UK) (28 g in 30 mL water) until directed to swallow. The same procedure was repeated after the patient was given 5 mL of paste preparation (Microtrast, Nicholas Laboratories Ltd.).

The examination was completed by taking spot film exposures in the anteroposterior and lateral projections. If the patient had a history of troublesome aspiration, the examination was performed with cineradiography only using a water-soluble medium (Gastrografin, Squibb). All the radiologic examinations were reviewed and analysed by the same radiologist (H-P.L.).

Manometric Study

Manometric studies were performed in all 16 patients using a triple-lumen esophageal motility tube (USCI #1100, USCI International, Murray Hill, NJ). The body of the esophagus was perfused at a rate of 1.9 mL/min for each lumen and the proximal sphincter area at a rate of 7.6 mL/min for each lumen. Recording was done on a four-channel physiograph (model 7754A, Hewlett-Packard Co., Palo Alto, CA). All tracings were analysed according to fixed criteria and the statistical

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method used for interpretation was Student's *t*-test for paired values.

Treatment

Four patients were given an anticholinesterase medication and two were treated by dilatation using mercury bougies.

Eleven patients underwent cricopharyngeal myotomy. The indications for surgery were severe dysphagia with regular pharyngo-oral and pharyngonasal regurgitations as well as frequent episodes of tracheal aspiration. Surgery was performed under general anesthesia and using a left cervical approach. When the esophagus was isolated, a no. 42 mercury bougie was passed through the upper esophageal sphincter (UES) into the cervical esophagus. A 5-cm myotomy including the UES and distal hypopharynx was carried out. The mucosa was dissected from the muscular layer over approximately 40% of the circumference and the muscular layer was then fixed to the thyroid capsule.

Results

Clinical Findings

The clinical symptoms are set forth in detail in Tables I and II.

Generally, patients present complaining of marked oropharyngeal dysphagia of long duration. Solids and eventually liquids cause dysphagia, which is exacerbated by anxiety and by drinking cold liquids. Oropharyngeal and nasal regurgitations were experienced by nearly all patients. Consequently, alimentation time is longer and weight loss may follow. Odynophagia was noted and many patients reported a burning sensation in the pharynx on swallowing.

Most of the patients in this series had voice modification. Concomitantly with the dysphagia, episodes of airway aspiration supervene. This happens after every swallowing action in the more severe cases. During sleep, pooling of saliva in the hypopharynx and larynx causes the patient to aspirate the secretion and a severe bronchorrhea results. These symptoms were observed in all 16 patients during their manometric evaluation.

Radiologic Findings

The radiologic findings are presented in Table III. The pharynx showed a weak or nonexistent contraction against the UES which relaxed incompletely or late in the majority of cases. The esophageal lumen at the UES level remained concentrically diminished in

Table III—Radiologic Findings in 16 Patients with Oculopharyngeal Muscular Dystrophy

Finding	No. of patients
Pharynx	
Weak or absent contractions	14
Hypopharyngeal stasis	14
Nasal regurgitation	3
Upper esophageal sphincter (UES)	
Cricopharyngeus impression	
Small	8
Marked	4
Absent	4
Lumen diameter	
Diminished	10
Adequate	4
Complete obstruction	2
Relaxation	
Incomplete or late	12
Absent	4
Laryngeal aspiration	9
Aspiration pneumonitis on lung roentgenography	2

Table II—Laryngeal, Tracheobronchial and Pulmonary Symptoms

		Aspiration			Bronchorrhea			
Patient no.	Voice change	While eating	While sleeping	Pneumonias	While sleeping	During motility study	After surgery*	Systemic disease
1	+	++	++	0	++	++	++	+
2	+	++	++	0	++	++	+	0
3	+	++	++	+	++	++	++	0
4	+	++	++	+	++	++	++	+
5	+	++	++	0	++	++	+	0
6	0	++	++	+	++	++	++	+
7	+	+	+	0	++	+	++	0
8	+	++	++	+	++	++	++	+
9	+	++	++	0	++	++	++	0
10	+	++	++	0	++	++	++	0
11	+	++	++	0	++	++	++	0
12	+	+	+	0	0	+	—	0
13	+	+	+	0	++	+	—	0
14	0	+	+	0	0	+	—	0
15	+	+	+	0	0	+	—	+
16	+	+	+	0	++	+	—	0
Total	14	16	16	4	13	16	11	5

*11 patients.
+ = mild; ++ = severe; 0 = absent.

Table I—Oropharyngeal Symptoms

		Symptoms									
		Dysphagia				Odynophagia		Regurgitation			
Patient no.	Age, yr	Solids	Liquids	Increased with cold	Increased with anxiety	Severe	Burning sensation in pharynx on swallowing	Pharyngo-nasal	Pharyngo-oral	Alimentation time, min*	Weight loss, kg†
1	76	++	++	+	+	0	0	++	++	—	0
2	61	++	++	+	+	0	0	++	++	75	0
3	64	++	++	+	+	0	0	++	++	30	18
4	68	++	+	+	+	0	0	0	++	35	9
5	61	++	0	+	+	0	0	++	++	45	0
6	74	++	+	+	+	0	+	++	0	60	0
7	52	++	+	+	+	0	+	++	++	45	0
8	74	++	++	+	+	0	+	++	++	60	0
9	66	++	+	+	+	++	0	++	++	35	18
10	69	+	+	0	+	0	0	++	++	35	13.5
11	50	++	++	0	+	0	0	++	++	30	6.75
12	57	+	0	0	0	0	0	++	0	45	13.5
13	61	+	0	0	0	0	0	+	0	45	0
14	62	+	0	0	+	0	0	0	0	20	0
15	61	+	0	+	+	0	0	0	0	45	0
16	56	+	0	0	0	0	0	+	0	45	0

*Average, 45 min.
†Average, 13.0 kg.
+ = mild; ++ = severe; 0 = absent.

response to swallowing in eight patients. Consequently, hypopharyngeal and laryngeal pooling induced aspiration in more than half the group. Repeated swallowing was necessary to empty the pharynx of its content.

Motility Studies

Table IV summarizes the significant findings of pharyngeal and proximal sphincter evaluation. The detailed study of esophageal function will be reported separately.

The pharynx was uniformly very weak so that its contraction time was significantly longer than in a control group (Fig. 1). The UES, while registering resting and contracting pressures comparable to those found in a normal group, showed a significant number of inadequate and incoordinated relaxations. The swallowing pattern was that of weak and repeated pharyngeal contractions attempting to relax the upper sphincter (Fig. 2).

Evaluation of Treatment

The four patients for whom anticholinesterase treatment was prescribed had had early dysphagia; they were clinically improved by the medication. Of the two patients treated by dilatation, one was 50% better while the other obtained no relief and subsequently underwent a cricopharyngeal myotomy.

Eleven patients underwent UES myotomy. Clinical and manometric effects of the operation are summarized in Table V. All experienced marked improvement of their symptoms. Eight patients reported that swallowing was "more than 100% better". One patient declared it was 75% better and two patients admitted it was 50% better.

After surgery all patients ate faster and stopped regurgitating either nasally or orally during meals. Four out of five patients who had lost weight regained it in the months following surgery.

All patients who underwent the operation experienced fewer episodes of aspiration and much less nocturnal accumulation of secretions; only one complained of having to get up at night as often as before to relieve his bronchorrhea.

The two patients admitted with pneumonia showed a normal postoperative evolution of the disease with significant improvement of their condition.

Postoperative complications occurred in two cases. In one patient who had a cholecystectomy as well as UES myotomy, postoperative respiratory insufficiency occurred, necessitating tracheostomy, long-term respiratory support and intravenous hyperalimentation. In the other patient a retropharyngeal hematoma developed and then resolved spontaneously. There were no deaths.

Table IV—Significant Findings Resulting from Evaluation of the Pharynx and UES in Patients with Oculopharyngeal Muscular Dystrophy

Finding	Control subjects	Patients with oculopharyngeal muscular dystrophy	P value
Pharynx			
Peak contraction, mm Hg	40.6 ± 1.8	10.4 ± 2.2	< 0.001
Contraction duration, s	0.37 ± 0.03	0.73 ± 0.07	< 0.001
UES			
Resting pressure, mm Hg	55.3 ± 4.1	54.7 ± 7.9	NS
Contraction pressure, mm Hg	81.2 ± 5.3	71.3 ± 7.3	NS
Relaxation, %	100	94.4 ± 2.7	< 0.02
Coordination, %	100	76.5 ± 9.5	< 0.01

NS = Not significant.

Table V—Results of Surgery

Patient no.	UES pressure before operation, mm Hg	UES pressure after operation, mm Hg	Clinical response	Length of follow-up, mo
1	69	45	Excellent	24
2	100	33	Excellent	14
3	54	58	Excellent	12
4	35	16	Excellent	8
5	34	29	Good	6
6	61	28	Excellent	5
7	56	17	Excellent	5
8	125	14	Good	4
9	30	22	Excellent	3
10	53	19	Good	1
11	—	—	Excellent	18
	61.7 ± 9.5*	28.1 ± 4.4*		

*P < 0.002.
Excellent = major improvement in all symptoms; good = persistence of one or more incapacitating symptoms.

Discussion

Oculopharyngeal muscular dystrophy is considered a rare disease. In certain areas, however, it can be observed quite frequently. Since the genetic basis was established by Barbeau,[5] a clear autosomal dominant transmission in a number of Quebec families has been described. Most of the cases reported elsewhere are also of French-Canadian origin.

Because of the rarity of the disease, relatively little is known of the clinical aspects and management of these patients. Attention has focused mainly on its genetic and neurologic aspects.

As early as 1915 Taylor[1] had mentioned that with the passage of time a degree of dysphagia develops of such severity that these patients cannot eat and die of starvation. This was frequently described by a number of our patients who remembered a parent dying of starvation, malnutrition or from clinically diagnosed "laryngeal or esophageal cancer".

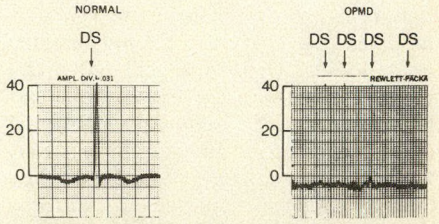

FIG. 1—Normal pharyngeal contraction generates peak pressure of 41 mm Hg. In patient with oculopharyngeal muscular dystrophy (OPMD), pharynx shows powerless contractions. These voluntary contractions must be repetitive since bolus cannot easily cross proximal sphincter area.

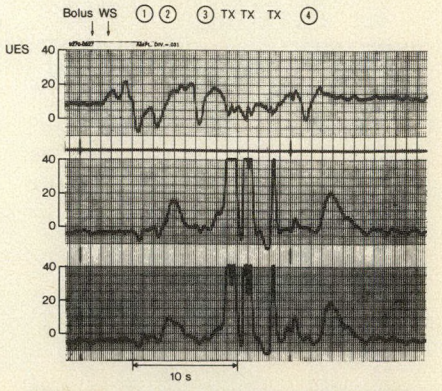

FIG. 2—Proximal manometric reading is in upper esophageal sphincter (UES) area. Adequate relaxation can be observed on swallowing but coughing from aspiration eventually results. Two readings in proximal esophagus show absent peristalsis in waves that follow sphincter closure.

Most of the patients in our series had seen a number of doctors and obtained little improvement from symptomatic management. After clinical, radiologic and manometric evaluation, we conceived the pattern of oropharyngeal dysphagia to be as follows: pharyngeal contractions are powerless against the normal resting pressure of the proximal esophageal sphincter and since an adequate pressure signal is essential for proper function of the UES, relaxation of the sphincter is late or incomplete. Oral and nasal regurgitation occur with repeated episodes of aspiration. These patients avoid eating with their families or in public.

Whether this malfunction of the UES is due to a disease or results from a weak signal secondary to a deficient pharyngeal contraction is still not clear. Present knowledge points to a primary pathologic condition of the muscle,[3,4,7-12] but the peripheral nervous system as well as neural transmission may be involved. Of interest is the clinical observation by one of us (A.B.) that in the early phase of the disease dysphagia responds to anticholinesterase medication. This is contrary to the conclusions of most reports published to date on the use of edrophonium chloride (Tensilon, Roche). More studies are needed to evaluate the response to this medication. Two patients who ceased to respond to anticholinesterase treatment were submitted to esophageal dilatation by mercury bougies. This proved very helpful in one patient but brought about no change in the other.

Surgical treatment by cricopharyngeal myotomy, as reported by Montgomery and Lynch,[10] Peterman, Lillington and Jamplis,[11] Blakeley, Garety and Smith,[14] Bender[15] and Mills,[16] brought about clinical improvement in most of the reported cases. It is surprising to see such an improvement in patients with completely deficient pharyngeal contraction. The degree of improvement was impressive in our patients on whom surgery was performed. The only physiologic explanation for this is a lowering of the pressure barrier at the UES level in the presence of normal activity and propulsive force of the tongue, permitting an easier transit of food from the pharynx to the esophagus. The surgical treatment was restricted to patients with severe symptoms. Lesser degrees of dysphagia appear to be manageable by medication or dilatation.

A word of caution is in order concerning dilatation. At operation, in all patients with oropharyngeal muscular dystrophy, a tight and localized point of constriction was observed at the junction of the pharynx and the cervical esophagus. Even under anesthesia with the esophagus in hand, it may prove difficult to pass the bougie across the UES area. With such a resistance and the lateral dilatations of the pyriform sinuses, perforation could easily occur.

Even if surgery does not influence the underlying pathology of the disease, marked symptomatic improvement may result from a simple myotomy at the proximal sphincter level. Long-term results need to be assessed.

We thank Dr. Jacques Sylvestre and Dr. Gilles Beauchamp for constructive criticism and Miss Christine Holland for typing the manuscript.

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Critique of Item 20 (SESAP II)

Anemia is a common finding among postgastrectomy patients. The point at issue is whether the anemia is related to failure to absorb iron, to iron loss, or to the deficiency of extrinsic factors. Iron deficiency might result simply from inadequate intake or from inadequate absorption. Iron deficiency may also develop when relative or absolute achlorhydria is present, or when the ingested iron is diverted from the normal duodenal absorptive surface. Iron deficiency anemia would be expected in the presence of marginal ulceration and slow but chronic loss of blood. In either instance, the anemia would be microcytic and hypochromic. Anemia secondary to loss of the extrinsic factors B_{12} and folic acid is typically megaloblastic and therefore macrocytic and normochromic. Among the tests listed, the blood indices would be the most helpful. Commonly used methods for determining B_{12} absorption seem to be of little value after gastrectomy. If deficient B_{12} is suspected, studies of the level of serum B_{12} and red blood cell B_{12} are indicated.

D

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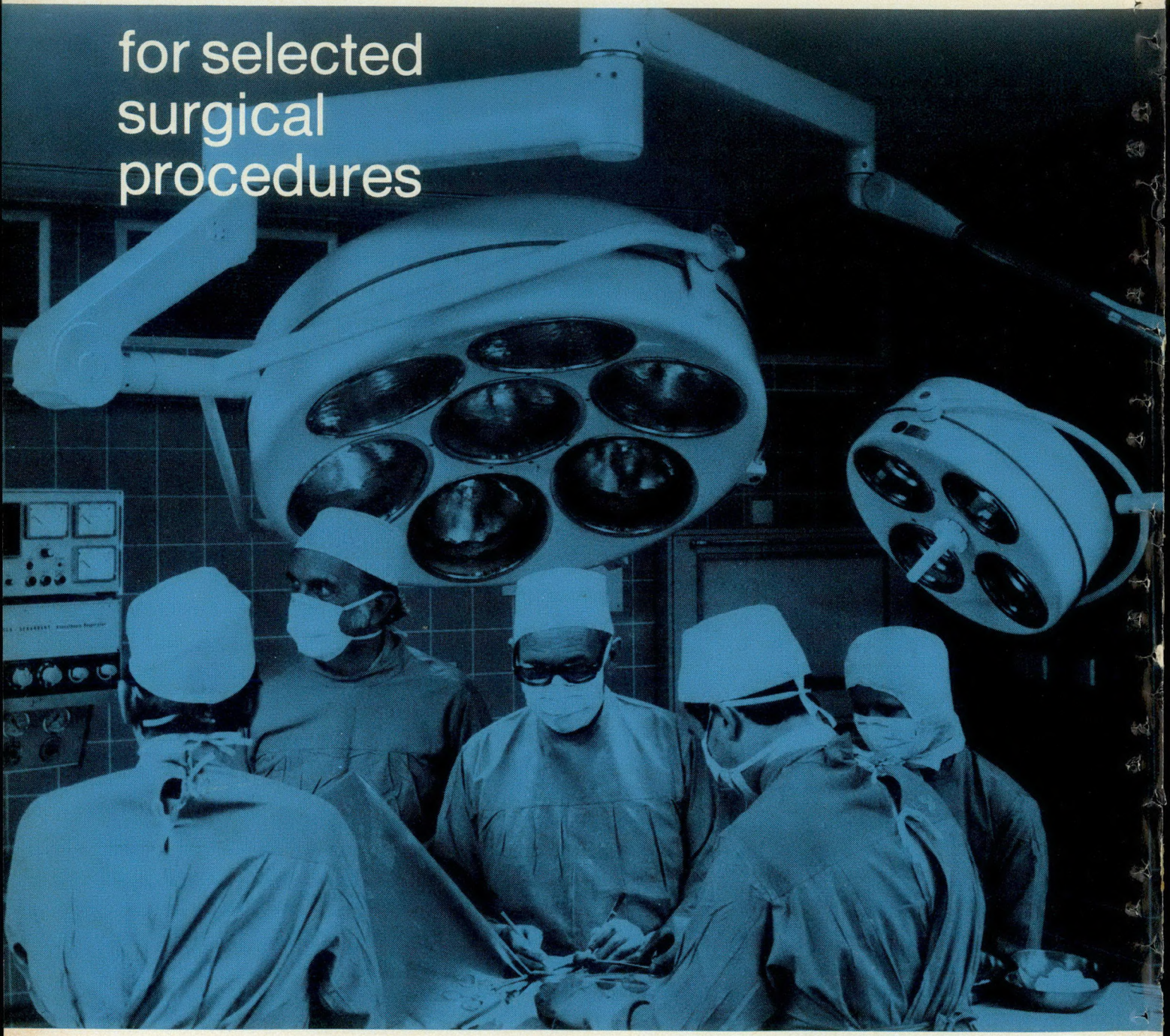
To lower
blood pressure
during
anesthesia

for selected
surgical
procedures



Nipride*

reduces excessive
blood loss

Nipride* (sodium nitroprusside)

for controlled hypotension during anesthesia

Rx Summary

'Nipride' is only to be used as an infusion with sterile 5% dextrose in water without preservatives. Not for direct injection.

Indications

'Nipride' is indicated for producing controlled hypotension during anesthesia to reduce bleeding in surgical procedures where deemed appropriate. Benefit-risk ratio should be carefully considered on an individual basis.

Contraindications

In the treatment of compensatory hypertension, e.g. arteriovenous shunt or coarctation of the aorta. It is also contraindicated in physically poor-risk patients (A.S.A. Risk 5), in patients with uncorrected anemia or hypovolemia or in those with known inadequate cerebral circulation. In patients with liver disease, severe renal disease, Leber's optic atrophy and disease states associated with vitamin B_{12} deficiency.

Warnings

'Nipride' is only to be used as an infusion with sterile 5% dextrose in water without preservatives. Not for direct injection. Infusion rates greater than 8 μg/kg/minute are virtually never required. If at this rate an adequate reduction in blood pressure is not obtained within 10 minutes, administration of 'Nipride' should be stopped.
Fatalities due to cyanide poisoning have occurred following sodium nitroprusside administration. One factor is common to all known cases, namely that large amounts of nitroprusside were infused at high rates. Since detoxification relies upon enzymatic action, the rare possibility of deficient or atypical enzymes occurring in humans should always be considered. Patients most apt to run into difficulties are those who are resistant to the hypotensive effect or those in whom maintenance at the selected blood pressure level is difficult or impossible.
Constant attention to the patient's dose-response characteristics is mandatory. If infusion rates are in excess of 8 μg/kg/minute determine the nature of the response (effective constant response at higher dose; tachyphylactic; resistant – none or less than expected). As soon as either tachyphylaxis or resistance is determined the infusion of 'Nipride' should be discontinued immediately. In abnormal responders it has been noted that metabolic acidosis may occur at higher doses.

Caution should be exercised in using 'Nipride' in patients with hypothyroidism or severe renal impairment.
Blood levels of thiocyanate should be determined if treatment is to be extended especially in patients with severe renal dysfunction. As long as blood thiocyanate levels do not exceed 10 mg/100 ml, it is probably safe to continue with the infusion. Peritoneal dialysis can be helpful if too high levels of thiocyanate are found.
Hypertensive patients are more sensitive to the intravenous effect of sodium nitroprusside than are normotensive subjects. Patients receiving concomitant antihypertensive medications (especially hydralazine or hexamethonium) are more sensitive to the hypotensive effect of sodium nitroprusside and the dosage of 'Nipride' should be adjusted downward accordingly.
The following Warnings apply to the use of 'Nipride' for controlled hypotension during anesthesia:

1. Extreme caution should be exercised in patients who are especially poor surgical risks (A.S.A. class 4 and 4E).
2. Tolerance to blood loss, anemia and hypovolemia may be diminished. If possible, preexisting anemia and hypovolemia should be corrected prior to employing controlled hypotension.
3. Hypotensive anesthetic techniques may alter pulmonary ventilation perfusion ratio. Patients intolerant of additional dead air space at ordinary oxygen partial pressure may benefit from higher oxygen partial pressure.
4. Resistance and tachyphylaxis occur more frequently in normotensive patients infused with sodium nitroprusside. Induction of deliberate hypotension in healthy young individuals may prove to be more difficult than in other segments of the population.
5. Upon discontinuance of the sodium nitroprusside infusion for the purpose of controlled hypotension during anesthesia a rebound hypertension has been observed on rare occasions.

Usage in pregnancy

The safety of 'Nipride' in women who are or who may become pregnant has not been established; hence, it should be given only when the potential benefits have been weighed against possible hazard to mother and fetus.

Usage in children

The safety of 'Nipride' in children has not been established. Clinical experience is limited.

Precautions

Adequate facilities, equipment and personnel should be available for frequent and vigilant monitoring of blood pressure. When the infusion is slowed or stopped, blood pressure usually begins to rise immediately and returns to pretreatment levels within one to ten minutes. It should be used with caution and initially in low doses in elderly patients, since they may be more sensitive to the hypotensive effects of the drug.
If, in the clinical situation, stress induced by pain or manipulation is reduced or eliminated during 'Nipride' infusion, the patient could experience a greater than expected reduction in blood pressure unless the rate of infusion is adjusted downward as required.
'Nipride' tends to deteriorate in the presence of light. Therefore, the infusion bottle should be wrapped with aluminum foil or other opaque material. Solutions of 'Nipride' should not be kept or used longer than four hours. 'Nipride' in aqueous solution yields the nitroprusside ion, which reacts with even minute quantities of a wide variety of organic and inorganic substances to form usually highly coloured reaction products (blue, green or dark red). If this occurs, the infusion should be replaced as quickly as possible.

Adverse reactions

Nausea, retching, emesis, diaphoresis, apprehension, headache, restlessness, agitation, muscle twitching, retrosternal discomfort and chest pain, palpitations, dizziness, faintness, weakness, rash, abdominal pain, confusion and somnolence have been noted with too rapid reduction in blood pressure. These symptoms rapidly disappeared with slowing of the rate of infusion or temporary discontinuation of infusion and did not reappear with continued slower rate of administration.
Irritation of the injection site may occur. Methemoglobinemia and one case of hypothyroidism following prolonged therapy have been reported.

Dosage and administration (for controlled hypotension)

Use of 'Nipride' in anesthetized normotensive patients undergoing deliberate hypotensive surgery must be restricted to carefully selected cases. There is a possibility of an abnormal response occurring in normotensive patients. In this event, the infusion of 'Nipride' should be discontinued immediately. (See Warnings).

The contents of a 50 mg 'Nipride' vial should be dissolved in 3 ml of sterile dextrose in water without preservatives. **No other diluent should be used.** Depending on the desired concentration, all of the prepared stock solution should be diluted in 500 or 1000 ml of 5 percent sterile dextrose in water and promptly wrapped in aluminum foil or other opaque material. Both stock solution and infusion solution should be freshly prepared and any unused portion discarded. The freshly prepared solution for infusion has a very faint brownish tint. If it is highly coloured, it should be discarded. (See Precautions). The solution should not be kept or used longer than four hours from initial reconstitution. The infusion fluid used for the administration of 'Nipride' should not be employed as a vehicle for simultaneous administration of any other drug.
'Nipride' dosage varies considerably from patient to patient, hence the need for individual titration. The infusion should be started at the lower dosage range, 0.5 μg/kg/minute and increased by 0.2 μg/kg/minute every 5 minutes until the desired reduction in blood pressure is obtained. The blood pressure usually starts to drop immediately or at least within a few minutes. Continuous monitoring of the blood pressure is necessary. Blood pressure should not be allowed to drop at too rapid a rate and systolic pressure should not be lowered below 60 mm Hg.
Infusion rates greater than 8 μg/kg/minute should rarely be used. The maximum recommended dose is 800 μg/minute.
'Nipride' should be administered by an infusion pump, micro-drip regulator or any similar device that will allow precise measurement of the flow rate. Avoid extravasation. The rate should be adjusted to maintain the desired hypotensive effect, as determined by frequent blood pressure determinations.
For the use of 'Nipride' in the treatment of hypertensive crises please refer to the Product Monograph.

Supply

'Nipride' is supplied in 5 ml amber-coloured vials containing the equivalent of 50 mg sodium nitroprusside for dilution with 5 percent sterile dextrose in water (available in packages of 10).

Product Monograph available on request.

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Cholestatic Jaundice During Total Parenteral Nutrition

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Because of the frequent occurrence of cholestasis in patients receiving total parenteral nutrition (TPN), the authors reviewed 32 cases in which the patient had been so supported for over 30 days. The indications for this form of management were complications of gastrointestinal surgery or inflammatory bowel disease.

The initial protocol for administering TPN provided a total of 45 Cal/kg (188 kJ/kg). Sixty percent of the energy requirement was supplied as Intralipid 10% (Pharmacia), 3 g/kg daily, and 40% as hypertonic dextrose. Amino acids were supplied by Travasol (Baxter Laboratories), 100 g or 2 g/kg of protein daily.

Twenty-four of the 32 patients treated according to this protocol showed elevated serum alkaline phosphatase values by 19 ± 2.9 days. An increase in the concentration of serum bilirubin was evident at 30 ± 1.5 days; in 19 of the 32 individuals the increase was progressive to above 2.5 mg/dL (43 μmol/L). Liver biopsy specimens from eight patients showed well-preserved hepatocytes, but bile-duct proliferation, periportal bile plugs and inflammatory infiltrates in portal areas.

The cholestasis was corrected and liver function returned to normal in all surviving patients when TPN was discontinued. Substantial reduction in the Intralipid component resulted in reversal of cholestasis in three patients.

The authors conclude that TPN supplies a high total and percentage of energy requirements in the form of lipid emulsion when combined with hypertonic dextrose and that a high protein intake (2 g/kg daily) will induce progressive cholestatic jaundice in a high percentage of patients if administered for more than 30 days.

A cause de l'apparition fréquente d'une cholostase chez les patients recevant une alimentation parentérale complète (APC) les auteurs ont étudié 32 cas où les patients ont été maintenus de cette façon pendant plus de 30 jours. Les indications de ce mode de traitement ont été les complications de la chirurgie gastrointestinale ou une maladie inflammatoire de l'intestin.

Le protocole original d'APC assurait un total de 45 Cal/kg (188 kJ/kg). Soixante pourcent des besoins énergétiques ont été assurés par de l'Intralipid 10% (Pharmacia), 3 g/kg par jour, et 40% sous forme de dextrose hypertonique. Les acides aminés ont été procurés par le Travasol (des Laboratoires Baxter), 100 g ou 2 g/kg de protéine quotidiennement.

Vingt-quatre des 32 patients traités selon ce protocole ont présenté une augmentation de la phosphatase alcaline sérique à compter du jour 19 ± 2.9. Une augmentation de la concentration sérique de bilirubine a été observée au jour 30 ± 1.5; chez 19 des 32 sujets, l'augmentation a été progressive jusqu'à plus de 2.5 mg/dL (43 μmol/L). Chez huit patients, une biopsie du foie a révélé une bonne conservation des hépatocytes, mais aussi une prolifération du canal biliaire, des bouchons biliaires péri-portes et des infiltrats inflammatoires de la région porte.

La cholostase s'est corrigée et la fonction hépatique est revenue à la normale chez tous les patients qui ont survécu, lorsque l'APC a été interrompue. Une réduction substantielle de la partie Intralipid a amené une inversion de la cholostase chez trois patients.

Les auteurs concluent que l'APC procure un total élevé et un fort pourcentage des besoins énergétiques sous la forme d'une émulsion de lipides quand elle est associée à une solution hypertonique de dextrose et qu'un apport protéinique élevé (2 g/kg par jour) provoque progressivement un ictère cholostatique chez un fort pourcentage des patients lorsqu'il est administré pendant plus de 30 jours.

Progressive cholestatic jaundice may develop in adult patients receiving total parenteral nutrition (TPN). Since 1975 more than 150 patients under our care have been supported with TPN. In 37 of them this form of management was continued for over 30 days but we omit from this review five cases in which the course of the illness was complicated by severe sepsis and repeated operations. In the remaining 32, enterocutaneous fistulas and inflammatory bowel disease were the commonest indications for instituting TPN (Table I). Cholestatic jaundice developed in 19 patients and the serum alkaline phosphatase concentration was elevated in 24.

We have examined the records of these patients with particular attention to the composition of the solutions administered, the monitoring of various clinical and laboratory values and the effect of TPN on hepatic function.

Composition of Solutions

Parenteral nutrition was initiated using a mixture comprising 1500 mL of Intralipid 10% (Pharmacia, Dorval, PQ) (3 g/kg), 1100 mL of Travasol (Baxter Laboratories of Canada Ltd., Malton, Ont.) and 400 mL of 50% dextrose. The total nonprotein energy supply was 2300 Cal (9.63×10^3 kJ) (45 Cal/kg [188 kJ/kg]). Solutions were generally administered through centrally placed catheters, but through peripheral veins for short periods in some patients. Because of the development of jaundice in a few patients,

Table I—Underlying Conditions of 32 Patients Who Received TPN for Longer than 30 Days During 1976 and 1977

Condition	No. of patients
Inflammatory bowel disease	10
Esophageal disease	3
Duodenal fistula	5
Intestinal fistula	5
Colonic fistula	8
Other	4
Total	35*

*More than one condition was present in some patients.

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20% dextrose or a protein hydrolysate (Amigen 5% or Amigen 800 [Baxter Laboratories]) was substituted as the energy or protein source.

The major components and additives of the TPN solution are shown in Table II. Folic acid (10 mg), vitamin B_{12} (100 μg) and phytonadione (10 mg) were given intramuscularly once a week. Zinc sulfate and other trace metals were given if the course of TPN extended beyond 3 weeks.

Monitoring

Patients receiving TPN had close monitoring of pulse rate, temperature and fluid balance. Values of serum electrolytes, blood urea nitrogen and creatinine, hemoglobin, and leukocyte count and differential were determined twice weekly; values of serum alkaline phosphatase, glutamic oxaloacetic transaminase (SGOT), bilirubin (total and indirect), cholesterol, triglycerides and proteins and the prothrombin time were measured weekly. The bromsulfalein test was performed in three patients before the start of TPN.

Oral feeding was withheld in most patients. Access to water was permitted for those able to take fluids. Two patients were able to take a fluid diet, and one patient was advanced to full diet while on TPN in order to observe the effect on cholestasis.

Table II—Major Components and Additives of TPN Solution

Travasol (Baxter Laboratories), mL	1050
Intralipid 10% (Pharmacia), mL	1500
Dextrose 50%, mL	450
Protein, g	105
Nitrogen, g	17.5
Nonprotein energy, Cal	2650
Additives	
MVI (Arlington Laboratories), mL	10
Calcium gluconate, meq/d	4.7–9.4
Magnesium sulfate, meq/d	4.0–8.0
Vitamin K, mg/wk	20
Vitamin B_{12}, μg/wk	100
Folic acid, mg/wk	10

Liver Function during TPN

Table III sets forth, for the 32 patients studied, the composition of the TPN mixture infused, the duration of TPN when elevation of serum bilirubin first became apparent, and the peak

Table III—32 Patients on TPN Classified According to the Presence of: Progressive Cholestasis (19), Minimal Changes (5), or No Change in Liver Function (8)

Patient no.	Sex	Age, yr	Diagnosis	Composition of TPN solution, mL			Serum bilirubin			Serum alkaline phosphatase			SGOT peak value, IU	Duration of therapy, d
								Days of TPN				Days of TPN		
				Travasol	Intralipid 10%	Dextrose 50%	Peak value, mg/dL	Elevated at day	Peak at day	Base value, IU	Peak value, IU	Elevated at day		
1	M	45	Crohn's disease (ileum)	1050	1500	450	8.8	24	38	73	750	—	—	35
2	F	34	Crohn's disease (colon)	1600	2000	400	9.6	20	37	158	735	—	230	39
3	F	64	Ovarian carcinoma, rectovaginal fistula	1050	1500	450	11.2	33	48	77	349	28	107	116
4	M	66	Esophageal necrosis	1050	1500	450	3.4	25	32	46	420	—	170	60
5	F	26	Crohn's disease	1600	2000	400	4.7	30	60	—	700	24	—	52
6	M	37	Crohn's disease, gastric outlet obstruction	1200	2000	600	4.5	27	40	68	655	15	152	52
7	F	58	Perforation of esophagus	1100	1500	400	4.0	38	—	—	1150	10	58	62
8	F	69	Duodenal fistula, pancreatitis	1050	1500	450	4.6	30	37	—	520	20	50	41
9	M	61	Pancreatitis	1050	1620	450	24.5	—	—	—	400	—	—	31
10	M	35	Crohn's disease (ileum)	1150	1500	450	13.2	31	46	—	800	10	200	49
11	M	73	Postgastrectomy	1100	1500	450	4.9	30	51	91	1800	10	200	45
12	F	62	Small-bowel fistula	1100	1500	400	6.4	42	67	—	480	15	85	64
13	F	38	Perforated gastric ulcer	1050	1500	450	4.0	35	45	50	722	—	—	42
14	F	66	Ulcerative colitis	1050	1500	450	3.6	36	52	65	1000	24	90	46
15	M	52	Diverticulitis	1500	200	500	6.2	32	60	120	750	20	210	109
16	M	64	Subphrenic abscess	1100*	1500	400	3.6	25	31	44	313	40	85	42
17	F	61	Crohn's disease	1700	2000	300	9.8	30	54	—	758	20	202	64
18	M	28	Appendectomy, fistula	1100	1500	400	3.0	63	—	—	767	—	—	60
19	M	40	Duodenal fistula	1000	1000	—	2.5	26	28	30	—	—	—	33
20	F	78	Irradiation for carcinoma of esophagus	1000	1500	400	1.3	28	—	—	—	—	30	—
21	F	50	Colonic carcinoma	1050	1500	450	1.3	24	—	—	580	24	29	80
22	F	52	Crohn's disease	1100	1500	400	1.6	45	50	—	275	—	52	—
23	M	73	Abdominal wall sepsis, fistula	1100	1500	400	1.3	27	—	—	—	—	106	—
24	M	61	Hypernephroma, mesenteric thrombosis	1400	1500	600	1.4	30	34	39	203	—	38	56
25	M	17	Crohn's disease	1500	—	1500	N	—	—	—	N	—	N	35
26	F	22	Crohn's disease (rectovaginal fistula)	1500†	1500	400	N	—	—	—	340	10	N	38
27	M	50	Small-bowel fistula	1500†	2000	600	N	—	—	—	N	—	N	54
28	F	18	Crohn's disease, total colectomy	1100	1500	400	N	—	—	—	—	—	N	38
29	M	70	Small-bowel fistula, necrotizing fasciitis	1100	1500	400	N	—	—	—	506	30	N	49
30	M	45	Duodenal fistula	1400	2000	600	N	—	—	—	N	—	N	77
31	M	64	Bladder carcinoma, bowel obstruction	750	1500	750	N	—	—	—	—	—	—	—
32	F	54	Pancreatitis	750	1500	—	1.0	—	—	—	449	—	N	38

*Freamine (McGaw Laboratories, Santa Ana, CA).
†Amigen 800 (Baxter Laboratories).
N = normal.

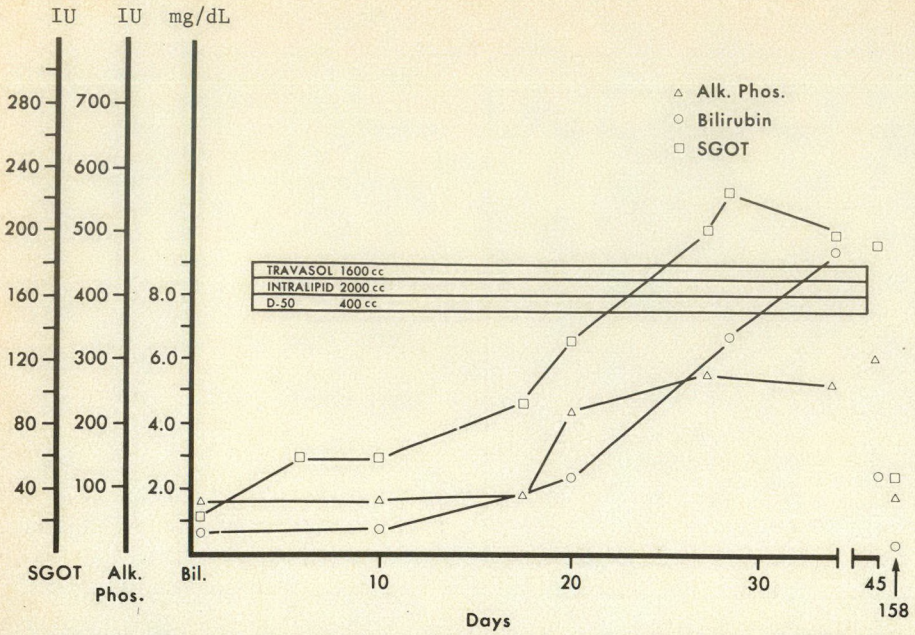

FIG. 1—Case 1. Values of serum glutamic oxaloacetic transaminase (SGOT, IU), alkaline phosphatase (Alk. Phos., IU) and bilirubin (Bil., mg/dL) during this patient's hospital course (days).

bilirubin and alkaline phosphatase concentrations reached.

The patients were divided into three groups—those demonstrating progressive elevation of serum bilirubin and alkaline phosphatase (19 patients), those with bilirubin values between 1.0 and 2.5 mg/dL (17.1 and 42.7 μmol/L) associated with elevated serum alkaline phosphatase values (5), and those who maintained normal serum bilirubin concentrations (8). Two of the last-named group had elevated serum alkaline phosphatase concentrations.

All patients who eventually exhibited progressive cholestasis had normal serum bilirubin values when TPN was started. In three individuals tested, the bromsulfalein test also gave a normal result.

The earliest time at which the serum bilirubin concentration became elevated was on day 20 after starting TPN. By day 42, 18 of 32 patients were jaundiced. One individual received treatment with TPN for 63 days before

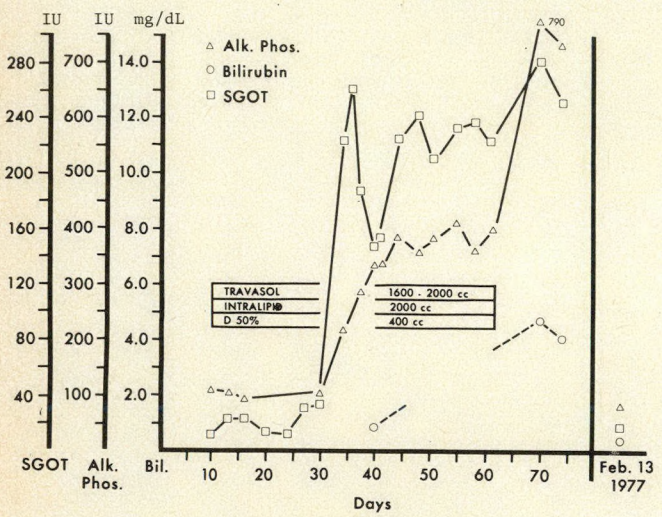

FIG. 2—Case 2. Values of SGOT, serum alkaline phosphatase and bilirubin during hospitalization.

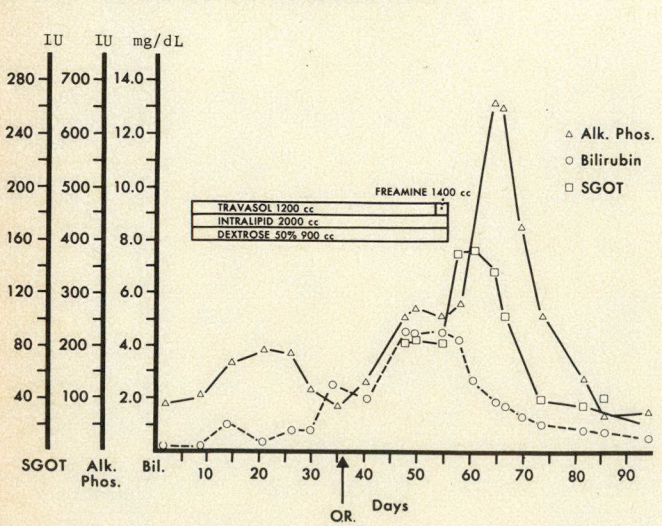

FIG. 3—Case 3. Values of SGOT, serum alkaline phosphatase and bilirubin during hospitalization.

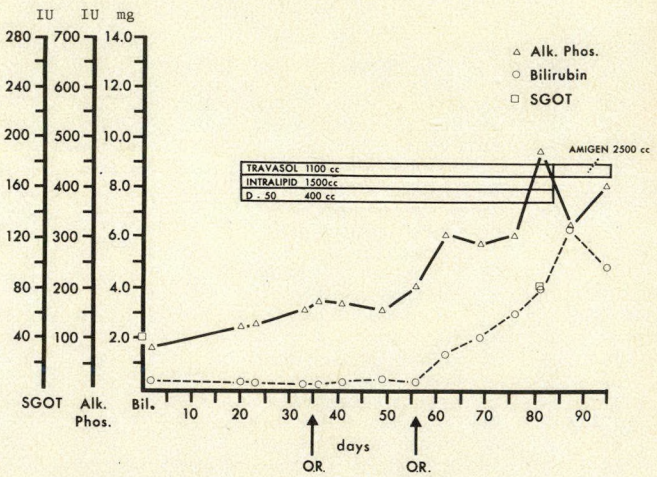

FIG. 4—Case 4. Values of SGOT, serum alkaline phosphatase and bilirubin during hospitalization.

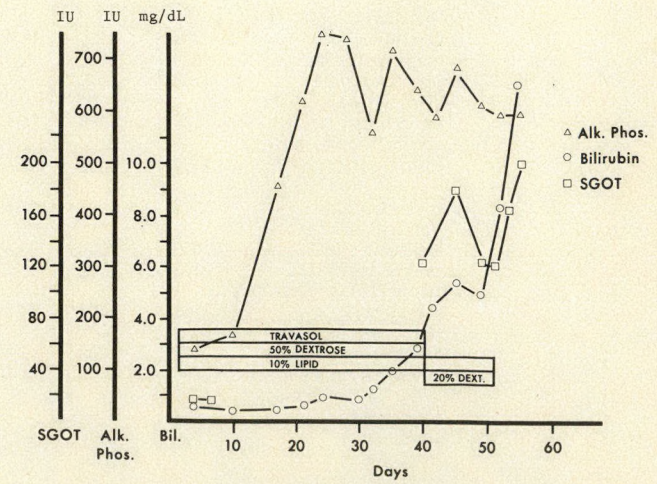

FIG. 5—Case 5. Values of SGOT, serum alkaline phosphatase and bilirubin during hospitalization.

elevation of the serum bilirubin value was noted.

Elevation of serum alkaline phosphatase was apparent before elevation in serum bilirubin; the average time at which it was first noted was on day 19 ± 2.9 days. Peak values of 748 ± 89 IU were reached. Moderate elevation of the SGOT concentration developed and stabilized at 100 to 200 IU (normal, to 37 IU). The prothrombin time and serum albumin value were normal or improved while the patient received TPN.

The course of bilirubin, alkaline phosphatase and SGOT values in six patients is illustrated by the cases reported below (Figs. 1 to 7). Generally the first abnormality to appear is a progressive rise in the serum alkaline phosphatase value, followed by an increase in SGOT and bilirubin concentrations. The bilirubinemia is largely direct-reacting. Withdrawal of TPN resulted in prompt reversal of these trends in most patients, although "overshoot" and slow recovery were noted in four individuals (Figs. 2 to 5). The results of all liver function tests showed a return to normal in all surviving patients. Three deaths occurred in the group of jaundiced patients and two of these individuals were still jaundiced at the time of death. Deaths were due to cardiorespiratory complications or to an advanced malignant condition and did not appear to be related to cholestasis.

Case Reports

Case 1.—A diagnosis of Crohn's disease with predominantly colonic involvement had been made in a 34-year-old woman (patient 2, Table III) 2 years before admission and she was taking sulfasalazine (Salazopyrin, Pharmacia) and prednisone 20 mg/d. Exacerbation of her disease had developed and she was daily passing 10 to 20 liquid stools containing blood. She was admitted for a period of intestinal rest. This patient had a slightly cushingoid appearance and was mildly obese (weight, 58 kg). Her temperature was normal and her pulse rate was 90 beats/min. She was allowed clear fluids by mouth up to 1000 mL/d. TPN was instituted; the solution provided 1600 mL of Travasol and 2000 mL of Intralipid 10% per day (3 g/kg of protein and 3.4 g/kg of fat daily). Total intake was 2800 Cal (11.72 × 10^3 kJ) daily or 50 Cal (209 kJ)/kg. The patient was managed on a medical service apart from the surgical parenteral nutrition program and it is our belief that the protein and fat intake and total energy intake for a 58-kg patient, requiring maintenance only, was in excess of the requirements. The effects on her liver function are shown in Fig. 1. No manifestations of sepsis appeared during her illness. Her tachycardia (between 90 and 100 beats/min) persisted throughout her hospitalization. Leukocyte and differential counts were normal. Her gastrointestinal symptoms were much relieved when she was discharged on the 45th hospital day, although her SGOT and serum alkaline phosphatase and bilirubin values were still elevated. When she returned 5 months later for hemorrhoidectomy, all indices of liver function were within normal limits.

Case 2.—A 26-year-old woman (patient 5, Table III) had Crohn's disease of the terminal ileum and cecum and complained of persistent obstructive symptoms. She was admitted for intestinal rest. She was taking prednisone 50 mg/d and Salazopyrin 0.5 g six times daily. The same TPN protocol was observed as for the patient in case 1 for 52 days with similar effects upon liver function (Fig. 2). Her pulse rate fluctuated between 90 and 110 beats/min. Throughout her hospitalization she remained afebrile, and the leukocyte and differential counts were normal. She was ambulatory and symptomatically greatly improved. On admission she weighed 51 kg so that calculated amounts of Travasol and Intralipid 10% and her total energy supply were clearly excessive. After 75 days in hospital her symptoms were considerably relieved and her weight had increased to 67 kg. Results of tests for liver function were still abnormal when she was discharged. She was kept under surveillance as an outpatient and indices of liver function showed improvement. Approximately 150 days later she was readmitted for intestinal resection because of increasing obstruction. Liver function was normal at that time.

Case 3.—A 37-year-old man (patient 6, Table III) was transferred to Vancouver General Hospital because of recent perforation of a stomal ulcer at a gastroenterostomy site; the operation had been performed for obstruction of the duodenum caused by Crohn's disease. Gastric outlet obstruction persisted with daily loss of large volumes of fluid. On admission he weighed 53 kg, his temperature was 38°C and his pulse rate 100 beats/min; the leukocyte and differential counts were normal. Initially he was treated by nasogastric decompression and parenteral feeding. Calculated amounts of Travasol and Intralipid 10% administered were more modest than in cases 1 and 2 but were still excessive. On this regimen his weight increased to 60 kg and his strength and mobility greatly improved. However, the SGOT value showed a mild increase and the serum bilirubin concentration was elevated above 2 mg/dL (34.2 μmol/L) by hospital day 35 (Fig. 3). A repeat gastrojejunostomy was performed on day 36 to permit gastric drainage. Postoperatively he continued to show an upward trend of serum bilirubin, alkaline phosphatase and SGOT values. TPN was discontinued on hospital day 55, and after a short interval and overshoot of serum alkaline phosphatase concentration, his liver function returned to normal. Intravenous cholangiography at this time showed normal-sized extrahepatic ducts.

Case 4.—This 62-year-old woman (patient 12, Table III) originally underwent laparotomy for a pelvic mass. She was found to have ovarian metastases from a previous primary growth of the colon. As there was no evidence of spread elsewhere, the ovarian tumour was extirpated. A small-bowel fistula developed on the 10th postoperative day so TPN

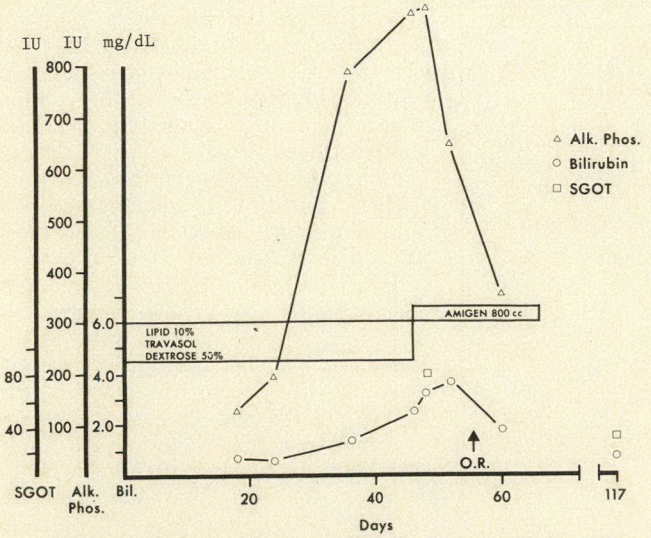

FIG. 6—Case 6. Values of SGOT, serum alkaline phosphatase and bilirubin during hospitalization.

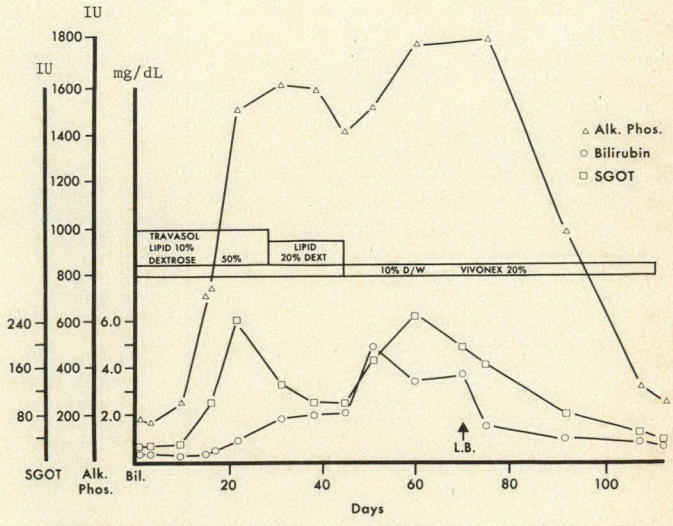

FIG. 7—Case 7. Values of SGOT, serum alkaline phosphatase and bilirubin during hospitalization.

was instituted. Initially there was persistent tachycardia and leukocytosis but these manifestations of sepsis regressed. After 40 days of TPN, however, the fistula had not closed, so a small-bowel resection was performed. TPN was continued and an increase in concentrations of serum bilirubin and alkaline phosphatase was detected (Fig. 4). After 60 days of TPN the regimen was changed to Amigen with a partial reversal of cholestasis. The patient was discharged after 95 days in hospital. She returned 3 months later with evidence of further intra-abdominal neoplasia; her condition deteriorated progressively and she died. At the time of death, liver function was normal.

Case 5.—A 35-year-old man (patient 10, Table III) had recurrent Crohn's disease of the ileum and left colon following previous resection of the terminal ileum and right colon. He had severe perianal complications with abscesses and fistulas. Following evacuation of a perianal abscess TPN was instituted to ensure intestinal rest and to improve his nutritional status prior to further surgery. Serum alkaline phosphatase concentration increased early and rapidly after the institution of TPN (Fig. 5). The serum bilirubin value was elevated after 38 days of TPN. Resection of the left colon and rectum was performed on day 24 of TPN. At operation, calculi were found in the gallbladder, which was removed. An operative cholangiogram showed a normal extrahepatic biliary tree without evidence of obstruction. Following surgery he exhibited no manifestations of bacterial infection. His pulse rate never rose above 100 beats/min, he was afebrile and the band cells were never in excess of 10%. He received no medications commonly recognized as causing cholestasis. Because of progressive cholestasis, Travasol was deleted from his program on about day 40. He was supported on dextrose and lipid alone for 10 days but cholestasis progressed nevertheless. During hospitalization he gained 5.4 kg and was discharged on about hospital day 55, still icteric and with an elevated alkaline phosphatase concentration but feeling well and eating a full diet. On follow-up within 30 days of discharge, serum bilirubin, alkaline phosphatase and SGOT values had all returned to normal.

Case 6.—Cholestasis developed in a 66-year-old woman (patient 14, Table III) who was receiving TPN and intestinal rest for severe ulcerative colitis. Because of progressive cholestasis (Fig. 6) her nutritional support was changed from lipid, dextrose and Travasol to Amigen 800 on day 50 of her TPN program. Amigen 800 supplies energy requirements as fructose and as a small quantity of ethanol. Cholestasis was reversed promptly on this regimen. Colectomy was performed on day 57. Liver function tests 117 days after TPN was instituted revealed normal serum bilirubin and SGOT values.

Case 7.—Six months before admission, this 73-year-old man (patient 11, Table III) had had a total gastrectomy for adenocarcinoma of the stomach with a Roux-en-Y esophagojejunostomy. Partial obstruction appeared to have developed at the anastomotic site. Weight loss ensued and he was readmitted for intravenous feeding and investigation. Early in the course of TPN, rapid elevation of alkaline phosphatase and SGOT concentrations was noted (Fig. 7). The patient had no abdominal pain and was afebrile with a pulse rate of 80 beats/min. Leukocyte count was normal. He had received no icterogenic drugs. He was allowed clear fluids and took up to 1000 mL/d. Elevation of serum alkaline phosphatase values was suspected to be caused by recurrent tumour. Because of cholestasis, Travasol was deleted on day 23 of TPN. On lipid and 20% dextrose alone the patient remained jaundiced with greatly elevated serum alkaline phosphatase values. All parenteral feeding was discontinued on day 40 and he was supported on a mixture of 10% dextrose and water, Vivonex (Eaton Laboratories) and other fluids. A liver biopsy showed periportal inflammation and bile-duct proliferation. After discontinuance of TPN the results of all liver function tests returned to normal. At the same time the patient's nutritional status was deteriorating. Terminally, pneumonia and ureteral obstruction developed. Autopsy showed recurrent tumour in the retroperitoneal tissues obstructing the ureter. No hepatic metastases were present. The extrahepatic biliary tree was patent and of normal calibre.

Table IV—Evidence for Bacterial Sepsis in 19 Cases of Progressive Cholestasis

	No. of patients
Febrile (over 37°C orally) for more than 5 of first 30 days on TPN	0
Pulse rate over 90 beats/min for more than 5 of first 30 days	5
Total leukocyte count over 12.0 × 10^9/L in first 30 days	5
Band forms over 20% in first 30 days	2
Positive blood culture	2
Severe sepsis:	
Temperature over 38°C	
Pulse rate over 120 beats/min	0
Leukocytes over 20.0 × 10^9/L, or	
Band forms over 30%	

Table V—Operation Prior to Onset of Progressive Cholestasis

	No. of patients
No operation prior to elevation of serum bilirubin concentration	7
Operation (no halothane) prior to elevation of serum bilirubin concentration	2
Operation with halothane anesthesia	10

Table VI—Prior Use of Drugs in Cases of Progressive Cholestasis

Drug	No. of patients
Phenothiazines	0
Androgenic steroids	0
Erythromycin	0
Chloral hydrate	2
Barbiturates	2
Flurazepam HCl	3
Sulfasalazine (Salazopyrin)	1
Steroids	2
Antibiotics	
Chloramphenicol	2
Gentamycin	4
Ampicillin	2
Clindamycin	2
Cephalothin	3
Cloxacillin	3
Tobramycin	1
Digoxin	2

Other Causes of Cholestasis

A relationship of the course of cholestasis to coexisting sepsis, prior operation and anesthesia or to medication seemed unlikely (Tables IV to VI). Six patients did not have an anesthetic or operation. In three individuals their operation was performed 1 month before the onset of jaundice. None received any medication commonly associated with cholestasis. None of the 32 patients suffered from severe bacterial sepsis, defined as pyrexia over 38°C, pulse rate over 120 beats/min, leukocyte count over 20 × 10^9/L or band forms in excess of 30% (Table IV).

The absence of a relation to bacterial sepsis is further illustrated by the case of a 66-year old man (patient 4, Table III) who underwent resection of the thoracic esophagus as a result of strangulation of a paraesophageal hernia with mediastinitis. This was reconstructed with left colon. Postoperatively a leak developed from the proximal coloesophageal anastomosis so TPN was begun. On the TPN regimen serum alkaline phosphatase and bilirubin concentrations became elevated (Fig. 8a). Travasol and dextrose were continued but the lipid was reduced to 1000 mL weekly to avoid deficiency of essential fatty acids. On markedly reduced lipid intake serum bilirubin and alkaline phosphatase values returned to normal. His temperature and pulse rate remained normal throughout, except on one occasion (Fig. 8b). Although the percentage of band cells in the differential leukocyte count was increased initially, it was below 10% throughout the period in which cholestasis was evident.

Patency of the biliary system was demonstrated by cholangiography, B-scanning, or at autopsy in seven of the jaundiced patients. Eight others were operated on before or during their course of TPN and the liver and biliary system were found to be normal (Table VII). No operative or radiologic evaluation of the bile ducts was made in four patients, but their liver function returned to normal and remained so after TPN was discontinued.

Liver Biopsy

Liver biopsy specimens were obtained from eight patients and demonstrated a consistent lesion typified by portal areas expanded by inflammatory cell infiltrates and bile-duct proliferation. Bile plugs were present in periportal canaliculi. The liver cells were well preserved (Figs. 9 to 11).

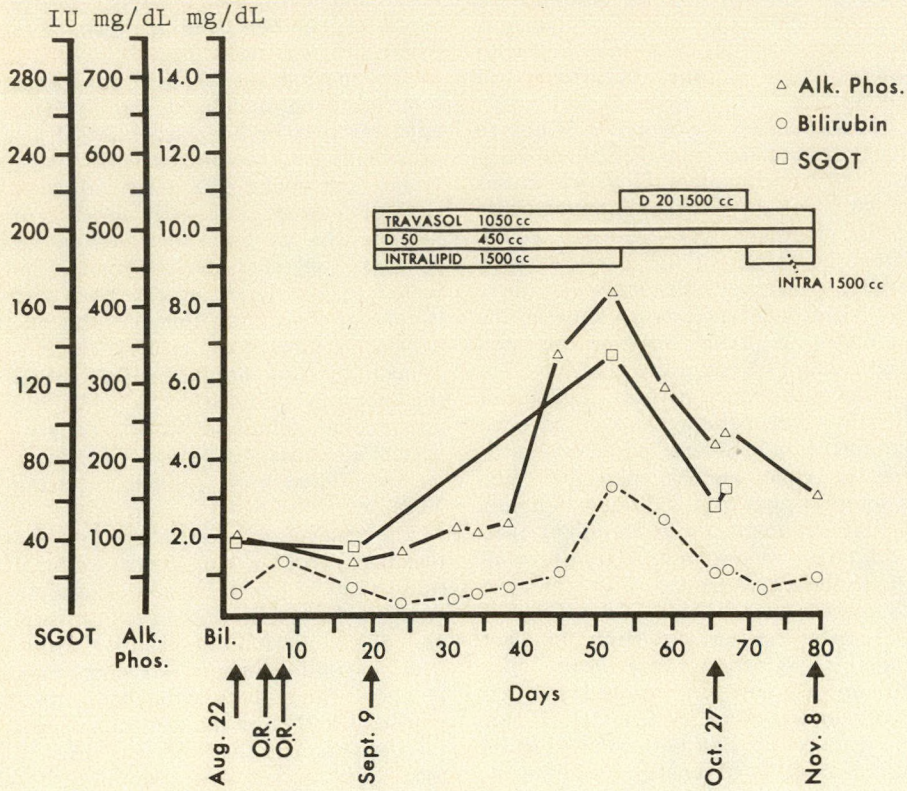

Fig. 8a

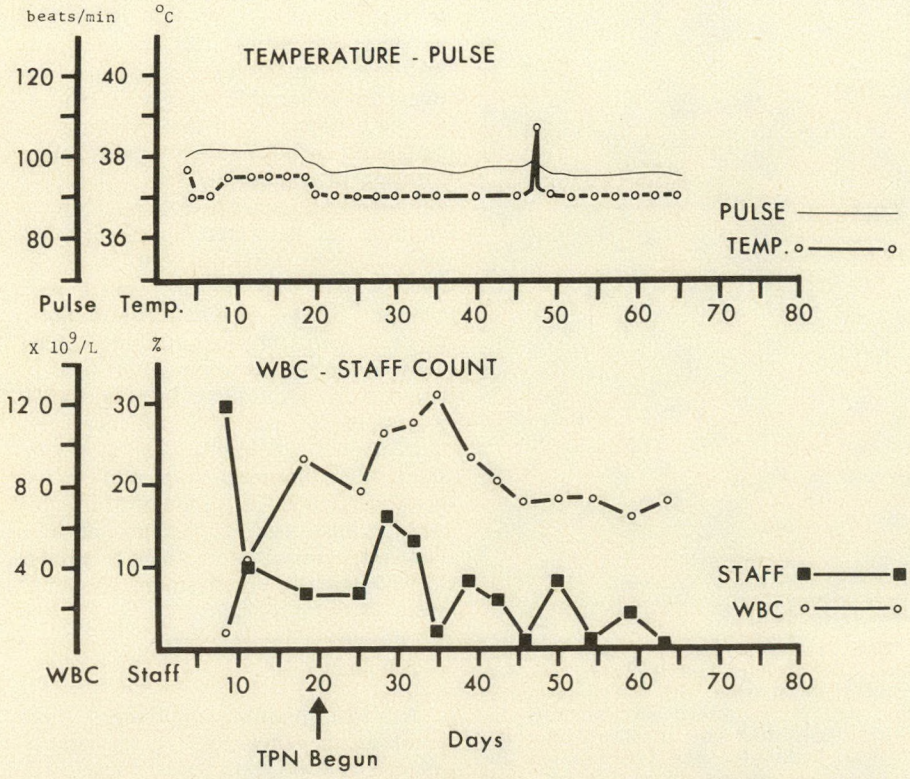

Fig. 8b

FIG. 8—Absence of relation between cholestasis and bacterial sepsis. (a) Values of SGOT, serum alkaline phosphatase and bilirubin. (b) Pulse rate, temperature, leukocyte count and band cells during hospital course of 66-year-old man who received TPN when leak developed at anastomosis after resection of thoracic esophagus.

Discussion

The development of abnormalities of liver function has not been detected by close observation of adults who have been maintained on long-term parenteral nutrition.[1] Furthermore, it has usually been possible to ascribe hyperbilirubinemia in surgical patients receiving parenteral nutrition to sepsis, drugs, tissue trauma, resolving hematomas, anesthetic agents, hemolysis, hypoxia, shock, or extrahepatic ductal obstruction. Because these septic and metabolic insults have been identified in many of our patients, one might question whether the cholestatic jaundice we report here was related to TPN.

The early phase of our patients' illness often involved major trauma, operative procedures and bacterial sepsis. The cholestasis seen later bore no relation to the earlier catabolic illness. In contrast, cholestasis appeared to develop when patients were in a phase of rapid anabolism without manifestations of sepsis. Although some patients did demonstrate moderate tachycardia (pulse rate, 90 to 100 beats/min) and leukocytosis for extended periods, cholestasis supervened on an unchanging pattern of pulse rate and leukocyte count.

Two patients with Crohn's disease were receiving TPN to ensure a period of intestinal rest and to improve their nutritional status. No operation was performed and the only medications prescribed were prednisone and sulfasalazine (Salazopyrin, Pharmacia). Neither patient was febrile and the pulse rate was elevated only minimally throughout. Both individuals demonstrated progressive elevation of serum alkaline phosphatase and SGOT concentrations and later a direct hyperbilirubinemia (Figs. 1 and 2).

Biochemical evidence of cholestasis appeared consistently within 2 to 3 weeks of starting TPN, which strongly suggests an association.

Table VII—Patency of Biliary System in 19 Cases of Progressive Cholestasis on TPN

	No. of patients
Liver and gallbladder described as normal at operation	8
Intravenous cholangiogram normal	2
T tube in place, cholangiogram normal. No obstruction found at autopsy	1
No obstruction found at autopsy	1
B scan showed normal ducts and gallbladder	1
Operative cholangiogram showed patent ducts	1
Sinogram to common bile duct normal	1
No information on biliary system	4

Although halothane was administered to 10 of the 19 patients in the progressively jaundiced group, 2 of the 10 patients were given the general anesthetic more than 30 days before the onset of cholestasis. Moreover, the pathologic features were not similar to those seen in previously described cases of halothane hepatitis. Therefore to infer that this agent contributed to the disturbed liver function would be to presume an extraordinary incidence of halothane hepatitis.[1]

Because there was no anemia, morphologic abnormalities of erythrocytes, or indirect-reacting hyperbilirubinemia, hemolysis cannot have been a factor contributing to the occurrence of cholestasis.

If the cholestatic jaundice is due to the TPN regimen, it is difficult to identify the component of TPN that causes it. None of the routine additives (minerals, vitamins, trace elements) would, either by reason of their deficiency or excess, be responsible. However, there are identifiable differences between the composition of the solution we used and other TPN solutions that have not caused disturbance of liver function or histology when employed over extended periods. For long-term parenteral feeding Jeejeebhoy and his colleagues[2] used a solution supplying 25% of nonprotein energy requirements as Intralipid 10% and 65% as dextrose. Only three of their patients received Travasol as a source of amino acid, and no change was noted in measurements of liver function in these individuals. The amount of nitrogen supplied in their program was more modest than in ours (13 g/d or 1 g/kg). Our TPN program supplied 60% of energy requirements as lipid, 40% as dextrose and 18 g of nitrogen daily.

It is possible that reducing the lipid contribution radically, supplying only 1000 mL weekly to prevent essential fatty acid deficiency, resulted in reversal of cholestasis in the two cases where this was tried (Fig. 8).

The mechanism of this cholestasis remains to be elucidated, but it seems apparent that lipid/dextrose ratios approximating 3:2 combined with a high amino acid intake of 2 g/kg will cause cholestatic jaundice in 50% to 75% of patients who are given the solutions for 30 days. Suggested mechanisms are defective hydroxylation of bile acids and intrahepatic accumulation of lithocolic acid,[3] or a direct toxic effect of a component of the amino acid solution (methionine).[4] Antioxidants added to amino acid solutions have been suggested as causative agents of changes in liver function in patients receiving TPN.[5]

The absence of oral intake and the resulting absence of gastroduodenal stimulation of the water and electrolyte components of bile flow have been suggested as contributory factors.[6] However, two individuals in our series took a clear fluid diet throughout their course of TPN and this did not prevent the development of cholestasis (Figs. 1 and 2). Full diet was introduced for one patient (patient 1, Table III) and failed to reverse the course of hyperbilirubinemia.

Abnormalities of liver function and histology that have developed in patients on other TPN regimens should not be confused with the condition encountered in the patients in this series. Infusion of a solution that will supply all nonprotein energy requirements as dextrose, as described by Grant,[5] will lead to acute fatty infiltration of the liver which may be associated with elevated SGOT, serum alkaline phosphatase and serum bilirubin values. This lesion is preventable or can be reversed by addition of Intralipid 10% to supply 20% to 40% of energy requirements.[7] Cholestatic jaundice subsiding after discontinuation of TPN has been described in premature infants[8] and the histologic appearance of liver biopsy specimens from them is similar to what was observed among the adult cases in our program.

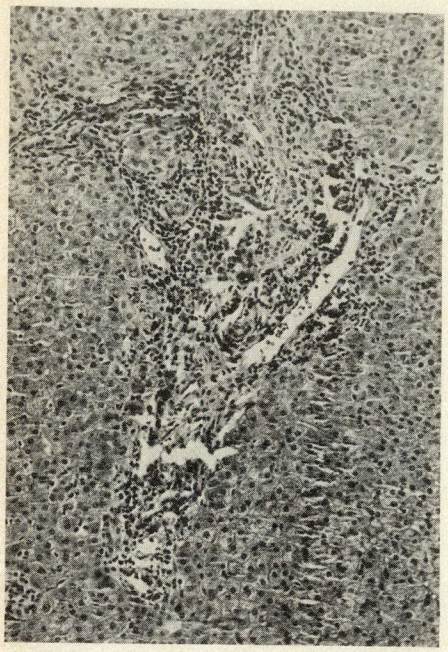

FIG. 9—Gastric outlet obstruction (patient 13, Table III). Expanded portal triad shows mixed inflammatory infiltrate, including numerous polymorphonuclear leukocytes, moderate numbers of eosinophils and lymphocytes, and proliferation of bile ducts (hematoxylin and eosin, reduced by 50% from ×160).

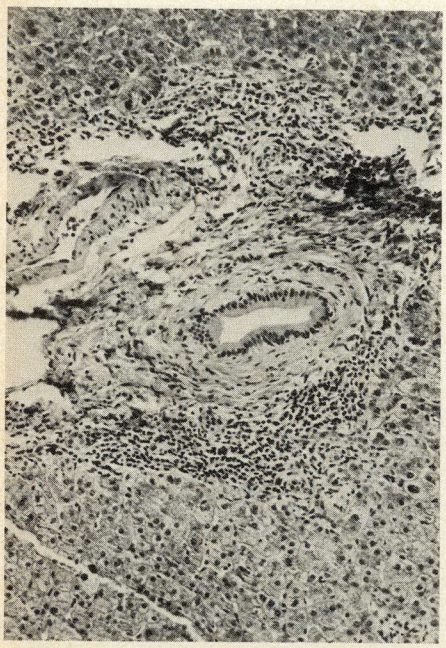

FIG. 10—Same patient as in Fig. 9. Larger portal zone with interlobular ductal proliferation with associated mixed inflammation around margin of portal area. Limiting plate is intact (hematoxylin and eosin, reduced by 50% from ×400).

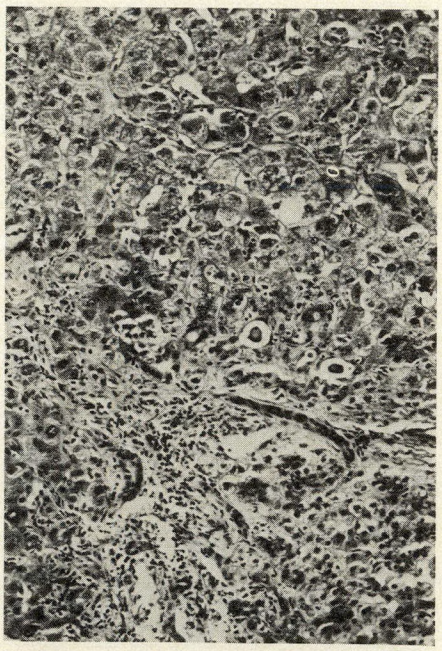

FIG. 11—Pancreatitis, T tube in common bile duct (patient 9, Table III). Expanded portal triad with ductal proliferation and heavy mixed inflammatory infiltrate consisting chiefly of polymorphonuclear leukocytes and lymphocytes. Inflammation extends into adjacent liver parenchyma but there is no piecemeal necrosis. Cholestasis is severe, bile thrombi being most prominent in periportal zone. Within lobule hepatocytes show degeneration (hematoxylin and eosin, reduced by 50% from ×400).

Summary

A TPN mixture supplying a lipid emulsion in a dose of 3 g/kg, supplemented by 900 Cal (3.8×10^3 kJ) as 50% dextrose and with a protein intake of 2 g/kg led to development of progressive cholestasis in 19 of 32 patients receiving long-term TPN. Elevated serum alkaline phosphatase concentra-

tions appeared consistently around day 20, and by day 42 jaundice was apparent in 18 of the 32 patients. Serum proteins and prothrombin time were not appreciably affected, and serum bilirubin, serum alkaline phosphatase and SGOT values returned to normal when TPN was discontinued.

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Antibiotics in Surgery of the Colon

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In a randomized prospective study of patients undergoing elective colonic surgery the postoperative wound infection rate was 13% (early, 10%) in patients receiving systemic cephaloridine perioperatively and 12% (early, 7.3%) in those given oral neomycin and erythromycin base preoperatively. Wound infections were more frequent in patients with severe lymphopenia or hypoalbuminemia preoperatively, but the potential degree of wound contamination was the main determinant of postoperative infection.

Dans une étude prospective randomisée chez des patients subissant une opération non urgente du côlon, le taux d'infection postopératoire a été de 13% (10% pour les infections précoces) chez les patients recevant un traitement peropératoire à la céphaloridine systémique, et de 12% (7.3% pour les infections précoces) chez ceux qui ont reçu de la néomycine et de l'érythromycine par voie orale dans la période préopératoire. Les infections de la plaie ont été plus fréquentes chez les patients ayant une lymphopénie ou une hypoalbuminémie sévères avant l'opération, mais le potentiel de contamination de la plaie a été le principal déterminant des infections postopératoires.

From the department of surgery, Queen Elizabeth Hospital of Montreal Centre, Montreal, PQ

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The determinants of bacterial surgical infection are well known:[1] (a) contamination by an inoculum of bacteria, (b) lodgement of bacteria in a favourable local environment, and (c) bacterial propagation unhindered by host resistance. Recent studies have attempted to describe finite dimensions for these determinants, which may permit their manipulation to minimize the risk of postoperative infection. Thus Robson, Krisek and Heggers[2] have designated quantitatively the critical extent of bacterial contamination normally associated with bacterial wound infection. MacLean and his colleagues[3,4] have demonstrated that impaired nutrition may be an important determinant of diminished host resistance associated with surgical sepsis. Burke,[5] Polk and Lopez-Mayor[6] and Waterman and Kastan[7] have shown that the timing and dosage of antibiotics are critical to their successful use in preventing lodgement in potentially contaminated, contaminated and dirty wounds. Controversy remains, however, as to the optimal route and antibacterial spectrum of antibiotics indicated in surgery of the colon. Polk[8] administered perioperatively a systemic antibiotic that was effective mainly against aerobic bacteria. Nichols and associates[9] preferred preoperative administration of an enteral antibiotic combination effective against both aerobic bacteria and the main colon anaerobes.

Starting in November 1975 a prospective randomized study of patients undergoing elective colonic surgery was undertaken at the Queen Elizabeth Hospital of Montreal Centre to compare these two modes of antibiotic prophylaxis and to examine the determinants of wound sepsis in these patients.

Patients and Methods

Patients undergoing elective surgery of the colon were randomly assigned to two groups. All patients received a standardized mechanical bowel preparation as indicated in Table I. Group 1 patients received cephaloridine, 2 g intravenously or intramuscularly, 2 hours preoperatively and again 5 hours

Table I—Mechanical Bowel Preparation

Preoperative day	Procedure
3	1 tab bisacodyl (Dulcolax) at 1800 h
2	Low-residue diet Magnesium citrate, 56.7 g, at 1000, 1400 and 1800 h Saline enemas to clear at 1800 h
1	Clear fluids only, orally Magnesium citrate, 56.7 g, at 1000 h Saline enema at 1400 h

later. Group 2 patients received neomycin and erythromycin base, 1 g of each orally, on the final preoperative day at 1300, 1400 and 1800 hours. At operation smears were obtained for culture from the open colon and from the subcutaneous tissues of the wound before closure; the degree of wound contamination was noted. Wounds were inspected for signs of infection on the fifth and seventh postoperative days and thereafter as required. Wounds showing tenderness, erythema, or induration were closely observed to resolution or discharge of pus. Wounds that discharged pus were regarded as infected (early wound infection) and the discharge was cultured. A follow-up report was requested from each surgeon on wound infections not diagnosed until after the patient left hospital but within the first month after operation (late wound infection). Patient records were reviewed to ascertain lymphocyte counts and serum albumin concentrations determined preoperatively and prior to any transfusion of blood or blood products. Concentrations were defined for severe hypoproteinemia and lymphocytopenia according to criteria suggested by Blackburn and associates[10] and Lee and colleagues.[11] Patients who underwent surgery on a segment of colon previously defunctioned by proximal colostomy were excluded from the study. The age of the patients, the duration of preoperative hospitalization, the identity of the operating surgeon, diagnosis and the type of operation performed and its duration "from skin to skin" were noted. A risk index of postoperative wound infection for each procedure was calculated as recommended by Davidson, Clark and Smith.[12] Statistical analysis was performed where indicated by the χ^2 test and by Student's *t*-test.

Results

Seventy-nine patients were included in the study; 38 were allocated to group 1 and 41 to group 2. A comparison of the groups reveals that they were reasonably well matched with respect to age and risk index (Table II). The groups were also matched with respect to the number of cases and frequency of wound infections for each operating surgeon. When wounds were classified according to the potential degree of contamination,[13] 5 of 13 contaminated or dirty wounds became infected, while in 5 of 66 clean-contaminated wounds infection developed ($P < 0.002$). A similar preponderance of infections in contaminated and dirty cases was seen within each group.

The overall rate of wound infection was 12.6% and of early wound infection, 8.8%. There were no significant differences in the frequency of wound infections between group 1 and group 2 (Table III). Anaerobic bacteria were cultured from 2 of 15 specimens taken from the colon in group 1 and from 4 of 17 such specimens from group 2; anaerobes were isolated from one infected wound in each group.

Table IV shows the relation between postoperative wound infections and host resistance as indicated by absolute peripheral lymphocyte counts and serum albumin concentrations measured before operation. The mean lymphocyte count before operation in the patients who had sepsis after operation, $1.095 \pm 0.498 \times 10^9$/L, was significantly lower than the $1.683 \pm 0.706 \times 10^9$/L in those without postoperative sepsis ($P < 0.03$).

Discussion

This study confirms that, of the established determinants of wound infection, the degree of wound contamination is the pre-eminent factor. This appears to be true whether one assesses the potential degree of contamination by classification of wounds,[13,14] as in the present study, or the actual degree of wound contamination as determined by culture of the subcutaneous tissues after the fascia is closed.[12,15] Effective aseptic technique and antisepsis to prevent contamination should therefore remain the primary approach to minimizing the frequency of wound infection.

Table II—Comparison of Patient Groups

Factor	Group 1	Group 2
Age, yr		
< 60	13	11
60-80	20	25
>80	5	5
Risk index	27.9	28.7
Diagnosis and operative site, no. of wound infections/no. of cases		
Carcinoma	2/25	3/28
Inflammation	3/13	2/13
Operation in true pelvis	2/24	1/17
Operation outside true pelvis	3/14	4/24

Table III—Incidence of Wound Infections

Wound	No. of wound infections/total no. of cases: Group 1 (n = 38)	Group 2 (n = 41)	Total wound infections (and %)
A. Clean-contaminated wounds	3/31	2/35	5 (7.6)
B. Contaminated and dirty wounds	2/7	3/6	5 (38.6)
C. Total wound infections	5/38	5/41	10 (12.6)
D. Early wound infections	4/38	3/41	7 (8.8)

The difference between A and B is statistically significant ($P < 0.002$).
Differences between groups 1 and 2 are not statistically significant.

Table IV—Host Resistance and Wound Infections

Laboratory measurement	No. of wound infections/total no. of cases	P value
Lymphocytes, X 10^9/L		
< 1.0	2/6	
> 1.0	3/24	> 0.05
Serum albumin concentration, g/L		
< 22.5	3/6	
> 22.5	0/23	< 0.005

Antibiotic therapy is, however, an important adjunct in patients at risk of sepsis. Polk[8] has demonstrated consistently the diminished frequency of surgical infection brought about by administration of systemic cephaloridine perioperatively, but others[16,17] have expressed dissatisfaction with this regimen, and have attributed its failures to its inability to deal with the bowel anaerobes. Since the completion of the present study Clarke and colleagues[18] have shown convincingly that oral administration of neomycin and erythromycin before operation reduces the frequency of septic complications of colon operations.

Our investigation showed no difference in frequency of wound infection when systemic cephaloridine and orally administered neomycin–erythromycin were compared. The cephaloridine regimen employed was slightly different from that used in Polk's original study, in keeping with Waterman's recommendations[7] and Polk's subsequent practice. We did not include a no-antibiotic group because we believed that the excellent studies of Polk and Lopez-Mayor[6] and Washington and associates[19] had already clearly demonstrated the advantage of the use of antibiotic regimens in colon surgery. The wound infection rates in both our groups were somewhat higher than those reported by Polk and Lopez-Mayor[6] and Clarke and colleagues.[18] However, neither of these groups specifically mentioned the inclusion of late wound infections diagnosed up to 1 month postoperatively. Their total wound infection rates were approximately the same as the early wound infection rates found in our study.

Our data do not explain why the differences in route of administration and spectrum of the antibiotics used in the two treatment groups were not associated with different infection rates. Moore, Cato and Holdeman[20] noted that the redox potential of the colon, which is the primary site of action of the neomycin–erythromycin combination, is –250 mV, in contrast to that of +120 mV of the normal wound, which is the primary site of action of cephaloridine. Stone, Kolb and Geheber[21] indicated that in normal tissues elimination of the aerobic partner of the usual aerobe–anaerobe symbiosis automatically increases redox potential of the environment so that it becomes hostile to anaerobes. Thus, antibiotics acting on the wound and effective primarily against aerobes may afford adequate prophylactic therapy. In the colon the low redox potential allows anaerobes to thrive even when aerobic bacteria have been eliminated; hence for preoperative bowel preparation an antibiotic combination effective against anaerobic as well as aerobic bacteria is required.

The association we discovered between lymphocytopenia, hypoproteinemia and postoperative infection has not previously been reported. It is, however, in keeping with the established close correlation between peripheral lymphocyte counts and cell-mediated immunity (CMI)[11] and the observed interaction of impaired CMI, impaired nutrition and postoperative sepsis.[22,23] Lee and coworkers[11] noted a close relation between lymphocytopenia and anergy to 2,4-dinitrochlorobenzene skin testing in cancer patients; Pietsch and Meakins[22] were able to identify surgical patients at increased risk of sepsis by preoperative anergy; and Law, Dudrick and Abdou[23] as well as Spanier and associates[4] have related diminished immunocompetence in surgical patients to impaired surgical nutrition and hypoproteinemia. Since the number of patients in the present report in whom lymphocytopenia and hypoproteinemia were studied is small, further investigation is required to corroborate these findings.

Conclusions

The determinants of wound sepsis have been examined in a prospective randomized study of patients undergoing elective colonic surgery. Two modes of antibiotic prophylaxis, differing in route and antibacterial spectrum, were compared.

1. The potential degree of wound contamination remains the dominant determinant of postoperative wound sepsis.

2. Preoperative bowel preparation with oral neomycin and erythromycin base is as effective in prophylaxis as the systemic administration of cephaloridine perioperatively.

3. Preoperative lymphocyte counts and serum albumin concentrations may be useful guides to the role of host resistance in permitting postoperative sepsis.

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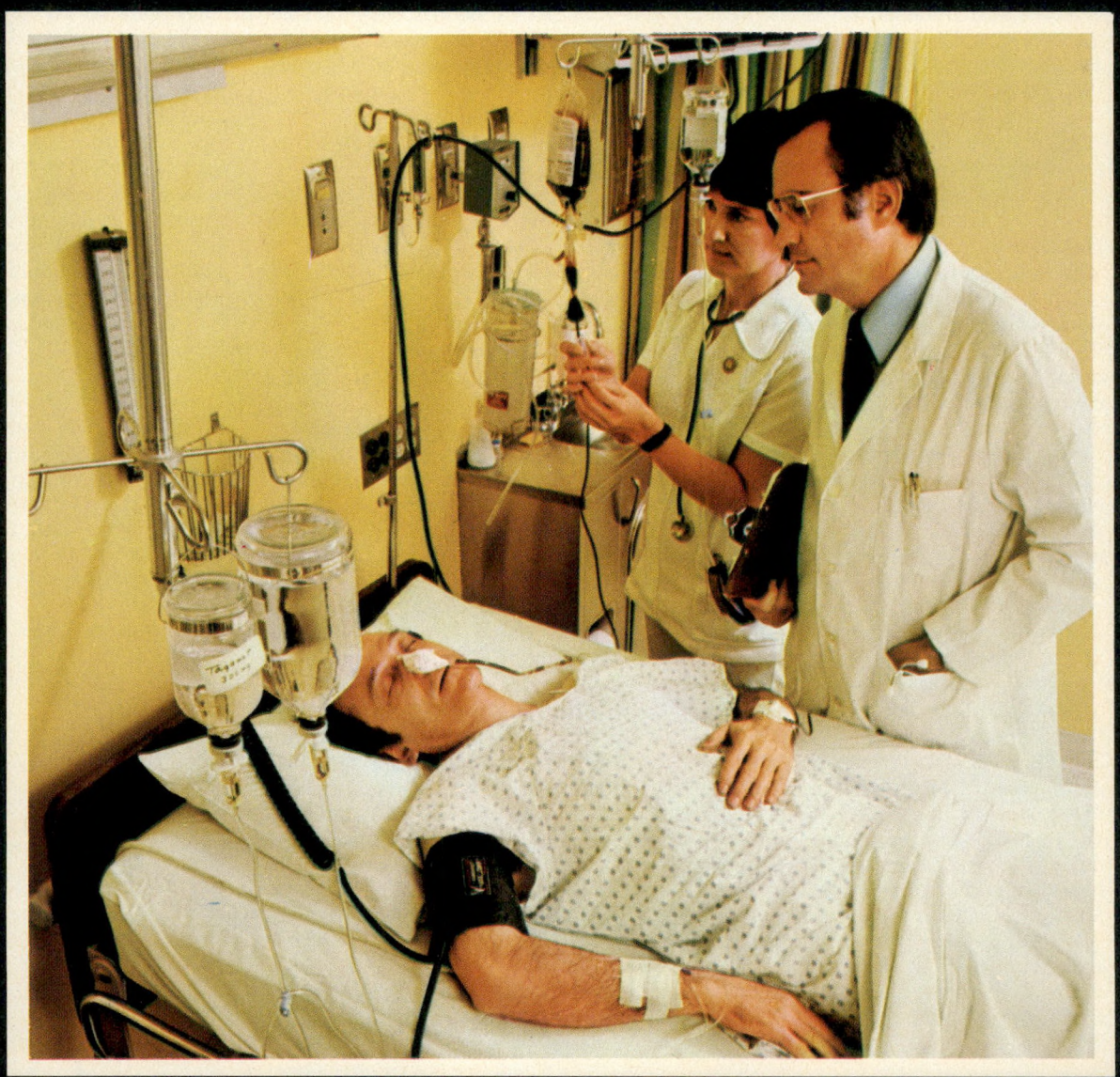
To control upper gastrointestinal bleeding due to stress ulcer, hemorrhagic gastritis, stress gastritis, bleeding gastric erosions, duodenal and gastric ulcers...



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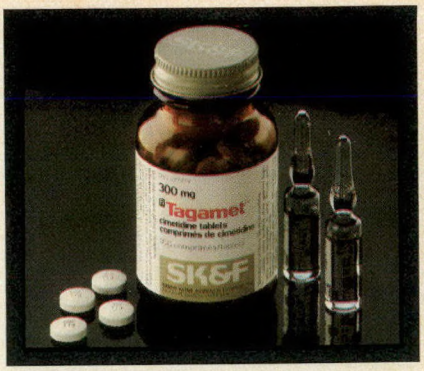

The 'Tagamet' effect

The precise mechanism by which 'Tagamet' controls upper g.i. bleeding is not understood, although several theories exist, of which these seem the most likely.

Significantly Inhibits Gastric Acid Secretion,

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May Decrease Gastric Mucosal Blood Flow

due to inhibition of acid secretion, allowing the body's hemostatic mechanism to control bleeding.

May Prevent Further Damage to the Mucosa

by acid through blockade of histamine H_2 receptors, thereby encouraging healing of the mucosal injury.

65 patients in whom other non-surgical measures had failed, or for whom surgical intervention was considered impossible or unduly hazardous, were evaluated; the results are reported in the adjacent table.[1]

	Complete Success	Partial Success	Complete & Partial Success	Failure
Heavy	65%	15%	80%	20%
Moderate	52%	22%	74%	26%
Subacute/recurrent	45%	25%	70%	30%

1. Data on file, SK&F Medical Department

The H_2 Receptor Antagonist–A major clinical advance for uncontrolled g.i. bleeding

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BOOK REVIEWS

INFECTION IN THE FEMALE. William J. Ledger. 240 pp. Illust. Lea & Febiger, Philadelphia; The Macmillan Company of Canada Limited, Toronto, 1977. Price not stated. ISBN 0-8121-0560-5.

This monograph offers a well-organized approach to its subject. The first half deals mostly with bacteriology and is up-to-date. It includes a description of the latest information on etiologic agents such as mycoplasma and *Bacteroides fragilis*. The problems associated with specimen collections are detailed, and specific reference is made to anaerobic and aerobic infections. Ledger has also provided the reader with an excellent discussion on urinary specimens and their collection.

The second half of the book deals with clinical problems. Separate chapters are included on community and hospital-acquired gynecologic and obstetric infections. The investigation and treatment of postpartum infections is specifically dealt with. The author has not considered the use of IgM testing and gamma globulin therapy in rubella contacts. However, there is a good chart on what to do for the woman exposed to rubella during pregnancy and how to interpret rubella antibody titres. Included also is an excellent chart on vaccination during pregnancy and the effects of certain diseases such as measles, mumps, thyroid, polio, cholera, plague and rabies on mother and child.

While postoperative management of the gynecologic patient is carefully discussed, the description of some of the common office gynecologic problems is less than adequate. One of the most vexing problems for the office practitioner is treatment of the patient with a persistent vaginal discharge; unfortunately a discussion of this subject is not included. Candidal and trichomonal infections are only discussed in generalities. A more detailed account of how to handle acute herpes genitalis would have been welcome. This problem is mentioned in several areas of the book, but it is not all brought together in one place. What should the physician do when he or she sees the vesicles? How do you make the patient comfortable and what bath solutions can be recommended?

This book offers a good, although at times superficial, review of the subject; for this limited purpose, it can be recommended.

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LYMPHEDEMA. Supplement to "Lymphology". Edited by Leo Clodius. 192 pp. Illust. Georg Thieme Verlag, Stuttgart; Stratton Intercontinental Medical Book Corporation, New York, 1977. Price not stated. ISBN 3-13-544901-7.

Lymphedema is a concise readable text; its value far exceeds its modest format. For years clinicians of all specialties have

continued on page 366

Hypothermic Coronary Perfusion for Myocardial Protection During Aortocoronary Bypass

MANT HARAPHONGSE, MD, FRCP[C], R. LEIGHTON FISK, MD, FRCS[C], RICHARD E. ROSSALL, MD, FRCP[C], CARLOS A.E. BASUALDO, MD, FRCP[C], ROBERT S. FRASER, MD, FRCP[C], ELLIOTT T. GELFAND, MD, FRCS[C] AND JOHN C. CALLAGHAN, MD, FRCS[C]

Numerous methods have been used in an attempt to prevent myocardial injury that results from the interruption of aortic flow during cardiac operations. The authors describe a relatively simple means of inducing cardioplegia during coronary bypass surgery by coronary perfusion with cold lactated Ringer's solution through the aortic root. When the results following the employment of hypothermic coronary perfusion for intraoperative cardioplegia were compared with those obtained without its use, the procedure was found to confer a degree of intraoperative myocardial protection and appeared to lead to a decrease in intraoperative myocardial infarction, subendocardial ischemia and intraoperative mortality.

Plusieurs méthodes ont été utilisées dans l'intention de prévenir les lésions myocardiques qui résultent de l'interruption du débit aortique durant une opération du coeur. On décrit un moyen relativement simple de provoquer une cardioplégie par perfusion coronarienne d'une solution de Ringer refroidie dans le tronc aortique; celui-ci a été utilisé au University of Alberta Hospital pour les interventions de pontage coronarien.

Comparativement aux résultats antérieurs, la perfusion coronarienne hypothermique employée pour provoquer une cardioplégie durant l'opération a conféré un degré de protection myocardique et semble avoir entraîné une diminution des infarctus myocardiques durant l'opération, de l'ischémie sous-endocardique et de la mortalité peropératoire.

From the departments of medicine and surgery, University of Alberta Hospital, Edmonton, Alta.

Presented in part at the annual meeting of the Canadian Cardiovascular Society, Edmonton, Alta., Oct. 18-23, 1976

Reprint requests to: Dr. M. Haraphongse, Director, Hemodynamic laboratory, University Hospital, Edmonton, Alta. T6G 2B7

Anoxic cardiac arrest is necessary for the adequate performance of cardiac surgery. It has been very useful in aortocoronary bypass surgery (ACBS) because it provides a dry, immobile operative field which is necessary for an accurate anastomosis. To avoid anoxic injury to an already ischemic myocardium is one of the most important goals in ACBS. Many methods have been used in an attempt to minimize the myocardial damage that results from the interruption of aortic flow during cardiac operations. A relatively simple means of inducing cardioplegia by coronary perfusion with cold lactated Ringer's solution through the aortic root has been used at the University of Alberta Hospital, Edmonton, for both valve replacement and coronary bypass surgery. The results appear to be better following this procedure and the incidence of myocardial injury and intraoperative mortality have been reduced.

Patients and Method

Between May 1, 1975 and Apr. 30, 1976, 159 patients had ACBS with aortic occlusion and myocardial hypothermia induced by perfusion with cold lactated Ringer's solution. A reversed saphenous vein was used for the graft on each occasion. Cannulation for extracorporeal circulation was carried out in a standard manner using transatrial vena caval catheters and arterial return from the extracorporeal circuit to the ascending aorta. A left atrial, left ventricular or pulmonary arterial vent catheter was placed. In most instances both the distal and the proximal anastomoses were done during a single aortic occlusion. Hypothermic cardioplegia was induced by perfusion with 5% glucose and lactated Ringer's solution, to which was added potassium chloride (40 mmol/L) and sodium bicarbonate (44.6 mmol/L). This solution at 5°C was introduced into the aortic root after the start of cardiopulmonary bypass. Once the patient was on total bypass, an aortic cross-clamp was placed and 500 to 700 mL of solution was introduced into the aorta proximal to the clamp through a small catheter placed through a purse-string suture in the aorta. Once the desired amount of solution had been introduced, the cannula was withdrawn and the purse-string suture tightened. This site could later be used for an aortic vent or aortotomy for proximal coronary graft anastomosis. Cardiac arrest occurred after 200 mL of cold solution was injected. Additional hypothermic solution was placed initially in the pericardial well around the heart, but usually was aspirated before dissection of the vessels. If the period of aortic cross-clamping needed to complete the procedure

was long, additional cold solution was introduced through the aortic root and into the pericardial well. Upon release of the aortic cross-clamp and re-establishment of coronary arterial flow, rewarming of the heart took place within minutes.

Results

There were six operative deaths. No patient died in the operating room. Three patients died of myocardial infarction postoperatively. Two patients were doing well after the operation but were found dead in the washroom, one on day 6 and the other on day 9 after operation, probably owing to cardiac arrhythmias. One death was attributed to septicemia.

Six percent of the patients experienced subendocardial ischemia which was diagnosed if symmetrical T-wave inversion was noted on the electrocardiogram within the first 24 hours following surgery. Eight percent of the patients had postoperative myocardial infarction which was diagnosed if new Q waves appeared. Supraventricular and ventricular arrythmias developed in 19% and 2% of patients, respectively. Ten percent of the patients had heart failure postoperatively.

We compared the results of ACBS under hypothermic coronary perfusion for myocardial protection (group 1) with the results obtained from 185 patients who had similar preoperative characteristics (Table I) and who had undergone ACBS without hypothermia between Jan. 1, 1974 and Apr. 30, 1975 (group 2). The incidence of subendocardial ischemia, postoperative myocardial infarction and intraoperative mortality was significantly reduced in group 1 patients (Table II).

Postoperative serum concentrations of creatine phosphokinase, glutamic oxaloacetic transaminase and lactic dehydrogenase (CPK, SGOT and LDH) were analysed (Fig. 1) in all patients with a normal postoperative course. The values increased with the prolongation of anoxic arrest extended beyond 60 minutes in group 1 and 40 minutes in group 2. Maximal values of enzymes in the patients with hypothermia were significantly lower than in normothermic patients who had been exposed to the same durations of anoxia.

Discussion

A motionless heart and a dry opera-

Table I—Preoperative Characteristics in Hypothermic (Group 1) and Normothermic (Group 2) Patients

Characteristic	No. of patients (and %) Group 1 (n = 159)	Group 2 (n = 185)
Mean age, yr	54	52
Men	140 (88)	149 (80)
Angina alone	105 (66)	160 (87)
Angina + previous myocardial infarction	49 (31)	75 (41)
Angina + previous myocardial infarction + heart failure	2 (1)	2 (1)
Angina + heart failure	3 (3)	—
Heart failure alone	—	2 (1)
Elevated left ventricular end-diastolic pressure	78 (49)	95 (51)
New York Heart Association functional class		
II	19 (12)	17 (9)
III	121 (76)	133 (72)
IV	19 (12)	35 (19)
Extent of arterial disease		
1 artery	15 (9)	25 (13)
2 arteries	66 (42)	81 (44)
3 arteries	78 (49)	79 (43)

Table II—Cardiac Complications in Hypothermic (Group 1) and Normothermic (Group 2) Patients

Complication	No. of patients (and %) Group 1 (n = 159)	Group 2 (n = 185)	P value
Detected by electrocardiography			
Subendocardial ischemia	9 (6)	29 (16)	< 0.005
Myocardial infarction	12 (8)	35 (19)	< 0.005
Arrhythmias			
Supraventricular	31 (19)	34 (18)	
Ventricular	3 (2)	8 (4)	
Nonfatal			
Low cardiac output	—	1 (0.5)	
Low cardiac output + myocardial infarction	—	3 (2)	
Heart failure	16 (10)	9 (5)	
Fatal	6 (3.6)	14 (8)	
Intraoperative	—	5 (3)	< 0.05
Perioperative			
Myocardial infarction	3 (2)	5 (3)	
Sudden death	2 (1)	—	
Low cardiac output + myocardial infarction	—	1 (0.5)	
Septicemia	1 (0.6)	1 (0.5)	
Embolism			
Pulmonary	—	1 (0.5)	
Cerebral	—	1 (0.5)	

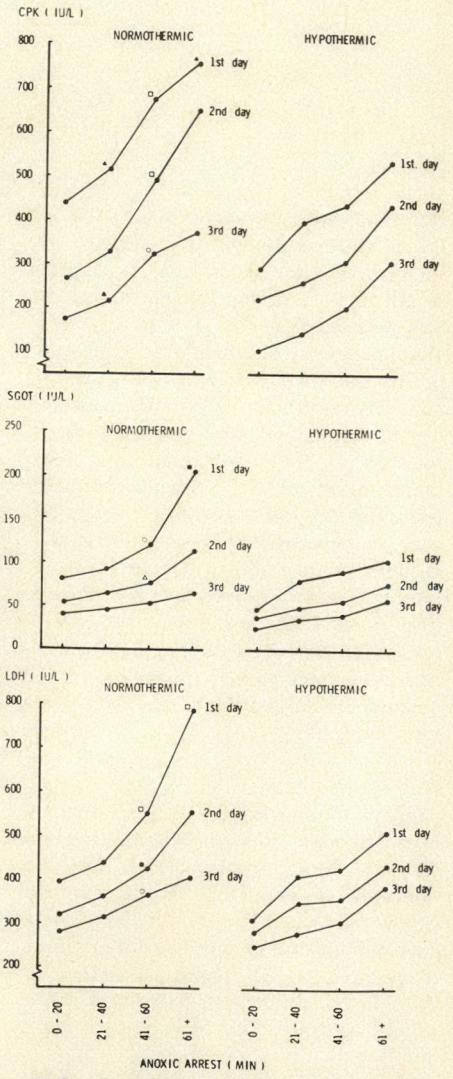

FIG. 1—Mean serum enzyme values following surgery in patients with normal postoperative course. Values of enzymes in patients with hypothermia were significantly lower than in normothermic patients who had been exposed to same duration of anoxia (▲ = P < 0.05, △ = P < 0.025, ■ = P < 0.01, ○ = P < 0.005 and □ = P < 0.001). CPK = creatine phosphokinase, SGOT = serum glutamic oxaloacetic transaminase, LDH = lactic dehydrogenase.

tive field permit a rapid and precise anastomosis in ACBS. Cardiac arrest reduces metabolic requirements of the heart,[1] thereby prolonging myocardial tolerance to ischemia. Improved methods for cardioplegia and myocardial protection during cardiac arrest have been developed recently. Early techniques of cardioplegia using potassium citrate or acetylcholine were abandoned because they produced severe, sometimes irreversible, myocardial damage.[2] Iced saline (slush)[3] for topical hypothermia was introduced both to protect the myocardium and to provide a quiescent heart. The popularity of this technique declined because atrial fibrillation, epicardial reaction and phrenic nerve paralysis were associated with its use.[4]

Although coronary artery perfusion[5] gained wide acceptance for valvular surgery,[6] it, too, appeared to be associated with a number of complications.[7-9] Bloodwell and associates[10] popularized the technique of normothermic anoxic arrest. Ischemic cardiac arrest under normothermic anoxic conditions is a safe method for open-heart correction of congenital defects, valve replacement[10] and ACBS.[11] It has been shown that normothermic anoxic arrest is moderately well tolerated for 30 minutes.[12,13] Beyond that time biochemical changes,[14] subendocardial hemorrhage[15] and generalized myocardial damage are progressive and probably irreversible.[13] Topical cardiac hypothermia extended the safe period of ischemic arrest.[16] Various methods of producing myocardial hypothermia topically are in use,[17,18] but have been associated with a number of problems. Homogeneous reduction of myocardial temperature cannot be achieved rapidly by surface cooling of the heart particularly when severe left ventricular hypertrophy is present. Irrigation of the pericardial well requires the management of cold fluid supply and drainage. Blood is lost from the circulation to the wash solution in variable amounts. The use of selective cardiac hypothermia induced by perfusion of the coronary arteries with cold lactated Ringer's solution through the aortic root[19,20] avoids many disadvantages of topically induced hypothermia. This method produces rapid cardioplegia and better myocardial preservation.[13]

Iyengar and associates[15] related normothermic ischemic arrest directly to the production of subendocardial hemorrhagic necrosis. This damage has been attributed to stasis, sludging and thrombosis in the myocardial microcirculation.[21] Deterioration of myocardial function and myocardial infarction following ACBS have been observed despite the presence of a patent graft.[22,23] Hypothermic coronary perfusion for intraoperative cardioplegia in ACBS has significantly reduced the incidence of subendocardial ischemia and myocardial infarction in our series as assessed by electrocardiographic change.

Hypothermia has the advantage of conferring considerable protection on the myocardium by reducing the metabolic rate[24] and extending the safe period of ischemic arrest.[16] The functional recovery of the heart following the termination of arrest is related to the concentration of ATP and creatine phosphate in the myocardium at the end of the period of arrest.[25] Hypothermic coronary perfusion for intraoperative cardioplegia provides rapid cardiac arrest and uniform cooling of the heart. Thus, the myocardium sustains minimal hypoxia. Under these conditions the concentration of cellular high-energy phosphates is maintained and complete recovery is possible.[25,26]

The patients in the two groups had ACBS performed in two successive periods of time. Greater surgical experience, better selection of patients and more extensive revascularization may have been contributing factors in producing more favourable results in group 1. Nevertheless, the changes in serum enzyme values following operation indicated that more effective myocardial protection during aortic cross-clamping was provided in patients with hypothermic coronary perfusion than in patients operated on under normothermic conditions. Hypothermic coronary perfusion appeared to result in a decrease in the number of myocardial complications and intraoperative mortality.

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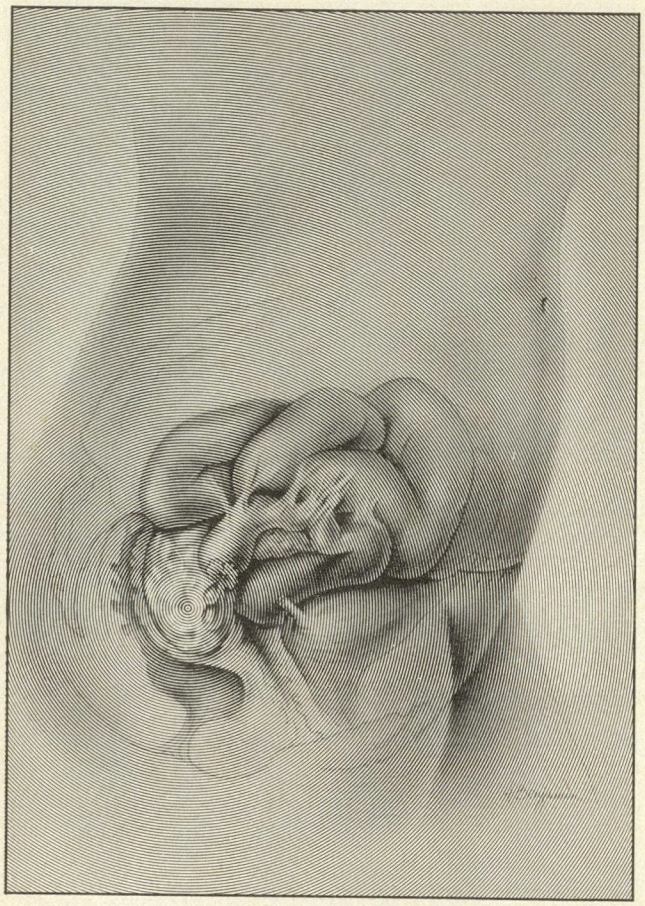
an urgent problem
postoperative anaerobic

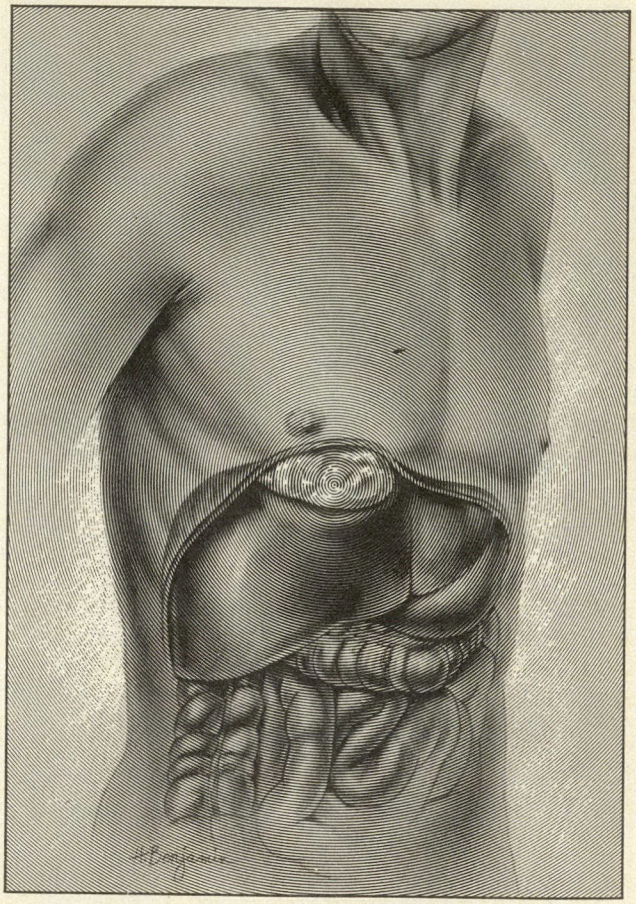
in gynecological infections



"...clindamycin is an important antibiotic in the therapy of such [gynecological] infections."

Swenson, R.M., et al. (1974). Obstet. & Gynecol., *44*:699.

in abdominal infections



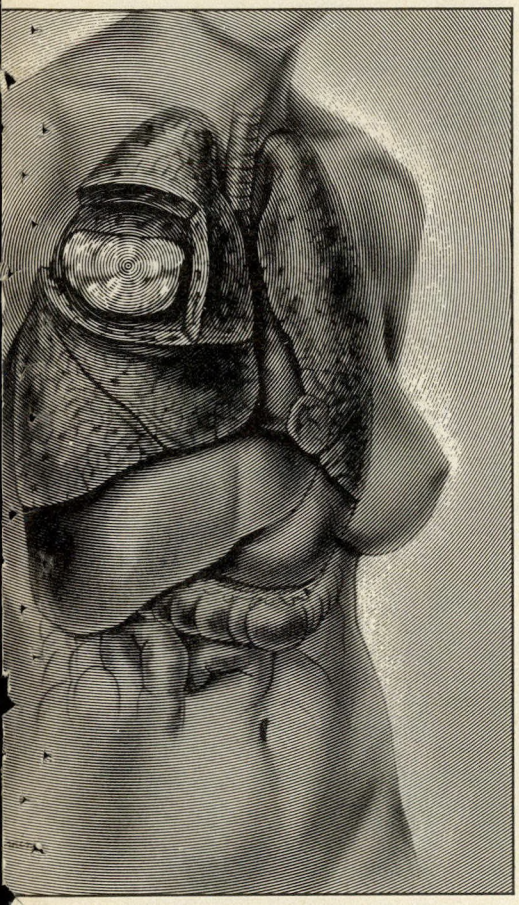
This study suggests "...clindamycin is an excellent and relatively safe antibiotic for treatment of [abdominal] infection caused by anaerobes when combined with surgery (when indicated) or other antibiotics active against aerobic gram-negative bacilli, if present."

Levison, M.E., et al. (Mar., 1974). Antimicrob. Agents & Chemother., p. 276-280.

an accepted solution
Dalacin C Phosphate S.S.

infections

in pulmonary anaerobic infections



...clindamycin has been reported to be the most active antimicrobial agent tested in vitro against anaerobic bacteria; [in the pulmonary tract] concentrations of 3.1 μg/ml or less inhibited 96% of strains tested..."

Fass, R.J., et al. (1973). Annals Intern. Med., *78*:853.

Indications: Dalacin C Phosphate (clindamycin phosphate injection N.F.) Dalacin C Phosphate Sterile Solution is indicated for the treatment of infections where the oral route is not indicated or feasible.

Clindamycin phosphate is indicated in the treatment of serious infections due to sensitive anaerobic bacteria, such as Bacteroides species, peptostreptococcus, anaerobic streptococci, Clostridium species and micro-aerophilic streptococci.

Clindamycin phosphate is also indicated in serious infections due to sensitive Gram-positive organisms staphylococci (including penicillinase-producing staphylococci), streptococci and pneumococci when the patient is intolerant of, or the organism resistant to, other appropriate antibiotics.

Contraindications: The use of Dalacin C Phosphate is contraindicated in patients previously found to be hypersensitive to this compound, the parent compound, clindamycin, or clindamycin palmitate. Although cross-sensitisation with Lincocin (lincomycin) has not been demonstrated, it is recommended that Dalacin C Phosphate not be used in patients who have demonstrated lincomycin sensitivity. Until further clinical experience is obtained, Dalacin C Phosphate is not indicated in the newborn (infants below 30 days of age), or in pregnant women.

Warnings: Some cases of severe and persistent diarrhoea have been reported during or after therapy with Dalacin C Phosphate. This diarrhoea has been occasionally associated with blood and mucus in the stools and has at times resulted in acute colitis. When endoscopy has been performed, some of these cases have shown pseudomembrane formation.

If significant diarrhoea occurs during therapy, this drug should be discontinued or, if necessary, continued only with close observation. Significant diarrhoea occurring up to several weeks post-therapy should be managed as if antibiotic-associated.

If colitis is suspected, endoscopy is recommended. Mild cases showing minimal mucosal changes may respond to simple drug discontinuance. Moderate to severe cases, including those showing ulceration or pseudomembrane formation, should be managed with fluid, electrolyte, and protein supplementation as indicated. Corticoid retention enemas and systemic corticoids may be of help in persistent cases. Anticholinergics and antiperistaltic agents may worsen the condition. Other causes of colitis should be considered.

Precautions: Dalacin C Phosphate, like any drug, should be prescribed with caution in atopic individuals.

The use of antibiotics occasionally results in over-growth of nonsusceptible organisms – particularly yeasts. Should superinfections occur, appropriate measures should be taken as dictated by the clinical situation.

Since abnormalities of liver function tests have been noted occasionally in animals and man, periodic liver function tests should be performed during prolonged therapy. Blood counts should also be monitored during extended therapy.

As with all antibiotics, perform culture and sensitivity studies in conjunction with drug therapy.

Clindamycin phosphate may be used in anuretic patients and patients with impaired liver function. The serum half-life of clindamycin phosphate in patients with markedly reduced renal function is greater than that of the half-life of the compound in normal patients. The dose of clindamycin phosphate should, therefore, be appropriately decreased. Haemodialysis and peritoneal dialysis are not effective means of removing the compound from the blood. Periodic serum levels of clindamycin should be determined in patients with severe renal insufficiency.

Adverse Reactions: *Local.*

(a) *Intramuscular Injections:* Of 404 patients treated with clindamycin phosphate intramuscularly (with a solution containing 150 mg/ml), six (1.5%) demonstrated local reactions as follows: Two complained of pain at the injection site, two demonstrated induration at the injection site and two developed sterile abscesses.

(b) *Intravenous Infusion:* Of 192 patients treated with clindamycin phosphate by intravenous infusion, 14 (7.3%) demonstrated local reactions. Eleven patients developed superficial thrombophlebitis and one patient developed both superficial and deep thrombophlebitis. The majority of these cases developed in conjunction with the use of indwelling IV catheters and it is difficult to know how much the drug contributed to the irritation. Two patients developed localised erythema, swelling and pain at the site of the infusion.

Systemic Side Effects: Twenty-eight patients of 596 treated with clindamycin phosphate by either the intramuscular or intravenous routes developed systemic side effects as follows:

	Number of Patients		*Number of Patients*
Rash	7	Hypotension	1
Urticaria	1	Hypertension	1
Pruritis	1	Shortness of Breath	1
Fever, Leucocytosis	1	Superinfection*	4
Nausea, with or without vomiting	1	Cardiac arrest**	1
Diarrhoea (See also under "Warnings")	4	Bad or bitter taste in mouth	5

*Superinfection is a complication of antibiotic therapy in general and is not necessarily a true side effect of clindamycin phosphate.

**Due to underlying myocarditis in this patient.

Clinical and Laboratory Findings: Patients treated during clinical trials of clindamycin phosphate were followed with clinical laboratory tests, including complete haematology, urinalysis and liver and kidney function tests. Some of these tests were abnormal initially and returned to normal during therapy with clindamycin phosphate, while others were normal initially and became abnormal during therapy. Overall evaluation of clinical laboratory values in these patients does not indicate that clindamycin phosphate therapy has a toxic effect on the haematopoietic, hepatic or renal systems. Transient elevations of serum transaminases have occurred in some patients, but other liver function tests (alkaline phosphatase, serum bilirubin) have not shown any tendency to increase and there have been no clinical signs of drug-induced hepatic toxicity.

Symptoms and Treatment of Oversoage: No cases of overdosage have been reported. No specific antidote is known. Doses as high as 1200 mg every six hours (4800 mg/day) by infusion for five days have been given without adverse effect.

DOSAGE AND ADMINISTRATION

Adults

Intramuscular Injection: 600 mg/day in two equal doses.

Moderately severe infections: 600 to 1200 mg/day in two or three equal doses.

Severe infections: 1200 to 2400 mg/day in two, three or four equal doses. Intramuscular injections of more than 600 mg into a single site are not recommended.

Intravenous Administration: Dalacin C Phosphate must be diluted prior to IV administration to a dilution of 300 mg in 50 ml of diluent (6 mg/ml) or more, and infused in not less than 10 minutes. Administration of more than 1200 mg in a single one-hour infusion is not recommended. Dalacin C Phosphate should not be injected intravenously undiluted as a bolus.

Moderately severe infections: 900 to 1800 mg/day by continuous drip or in two or three equal doses, each infused over 20 minutes or longer.

Severe infections: 1800 to 2700 mg/day by continuous drip or in three or four equal doses, each infused over 20 minutes or longer. In life-threatening infections, doses of 2700 to 4800 mg/day by continuous drip or in three or four equal doses each infused over 20 minutes or longer may be given.

Children: (Over one month of age)

Intramuscular Injection: 10 to 15 mg/kg/day in two, three or four equal doses.

Moderately severe infections: 15 to 20 mg/kg/day in three or four equal doses.

Severe infections: 20 to 30 mg/kg/day in three or four equal doses.

Intravenous Administration:

Moderately severe infections: 15 to 25 mg/kg/day by continuous drip or in three or four equal doses, each infused over 20 minutes or longer. In severe infections, it is recommended that children be given not less than 300 mg/day regardless of body weight. (Dilute Dalacin C Phosphate Sterile Solution in the same manner as for adults.)

AVAILABILITY:

Dalacin C Phosphate Sterile Solution – Each ml contains clindamycin phosphate equivalent to clindamycin base 150 mg in 2 ml ampoules.

Product Monograph available upon request.

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Importance of a Fifth Parathyroid Gland in the Surgical Treatment of Hyperparathyroidism

JOHN A. PALMER, MD, FRCS[C], FACS* AND FRANK R. SUTTON, MD†

Of 365 patients surgically treated for hyperparathyroidism at the University of Toronto hospitals, 3 had hypercalcemia due to an abnormal and ectopic fifth parathyroid gland.

Autopsy studies have shown that a fifth gland may be present in 3% to 5% of patients with hyperparathyroidism.

The possibility of an abnormal fifth gland as the cause of primary hyperparathyroidism should be considered when four glands of normal size and histology have been found in the neck, and such a gland should be sought in all patients with the diffuse hyperplasia of secondary hyperparathyroidism. The fifth gland is usually in the lower neck or upper mediastinum, frequently within the thymus. If present, it can usually be recognized and excised.

Sur 365 patients ayant reçu un traitement chirurgical pour hyperparathyroïdie aux hôpitaux de l'Université de Toronto, 3 avaient une hypercalcémie due à une cinquième glande parathyroïde anormale et ectopique.

Des études des résultats d'autopsie ont montré qu'une cinquième glande peut être présente chez 3% à 5% des patients souffrant d'hyperparathyroïdie.

La possibilité d'une cinquième glande anormale causant une hyperparathyroïdie primaire devrait être envisagée quand quatre glandes de grosseur et d'histologie normales sont retrouvées dans le cou, et une telle glande devrait être recherchée chez tous les patients présentant l'hyperplasie diffuse caractéristique de l'hyperparathyroïdie secondaire. La cinquième glande est habituellement retrouvée dans la partie inférieure du cou ou au dessus du médiastin, fréquemment à l'intérieur du thymus. Lorsqu'elle est présente, elle peut habituellement être identifiée et excisée.

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In 1925 Mandl[1] successfully excised a parathyroid adenoma that had caused osteitis fibrosa cystica. For many years thereafter the identification and removal of a single adenoma was considered to be the optimal treatment for hyperparathyroidism. However, as experience increased it was realized that abnormalities of more than one gland occurred in approximately 15% of patients,[2] in the form of either diffuse hyperplasia or multiple adenomas, and it was considered advisable to identify four parathyroid glands and to remove those that were abnormal on visual examination or hypercellular on biopsy. In a further attempt to reduce the incidence of persistent or recurrent hypercalcemia, Paloyan and colleagues[3] recommended subtotal parathyroidectomy for all patients with hyperparathyroidism. We do not believe that this is necessary for patients with a single adenoma provided the remaining glands are normal in size and on biopsy, but we agree that subtotal parathyroidectomy is advisable for patients with an abnormality of two or more glands.

This form of treatment has given excellent long-term results. However, approximately 5% of patients remain hypercalcemic postoperatively. The usual reason for persistent hypercalcemia is failure either to find an adenoma or to recognize and properly manage an abnormality of more than one gland.[4] A hyperfunctioning fifth gland unrecognized at operation may, on occasion, be responsible for an unsatisfactory result. In a University of Toronto hospital study of 365 patients, 3 patients with primary hyperparathyroidism, whose cases are reported herein, had a fifth gland that was of critical importance in surgical management. A fourth patient with secondary hyperparathyroidism associated with chronic renal failure requiring dialysis, had persistent hypercalcemia following radical subtotal parathyroidectomy and is awaiting exploration for a fifth gland in the mediastinum.

Case Reports

Case 1.—A 50-year-old woman had recurrent renal calculi and hypercalcemia. The serum concentrations of calcium varied from 3.12 to 3.42 mmol/L (12.5 to 13.7 mg/dL) and of phosphate from 0.613 to 0.839 mmol/L (1.9 to 2.6 mg/dL). A diagnosis of primary hyperparathyroidism was made.

At operation, four parathyroid glands of normal size were indentified and examination of frozen sections of each revealed no abnormality. The left upper gland, the largest of the four, was removed and on subsequent examination of paraffin sections was described as hyperplastic. Serum calcium concentrations remained unchanged after operation.

It was assumed that this patient had diffuse hyperplasia of all four glands, despite their relatively normal size, and that subtotal parathyroidectomy should have been done at the original operation.

On re-exploration of the neck 10 months later, the right lobe of the thyroid gland and the right upper and lower parathyroid glands were removed; from the remaining normal-sized left lower parathyroid gland a biopsy only was taken. Postoperatively the serum calcium concentration increased to 3.74 mmol/L (15 mg/dL).

Five months later the mediastinum was explored through a sternal-splitting incision. An adenoma measuring 3 × 3 cm was found in the left inferior pole of the thymus and removed. Serum calcium concentrations have since remained within normal range (2.24 to 2.32 mmol/L [9.0 to 9.3 mg/dL]). Thus in this patient three glands were removed from the neck, a fourth gland was biopsied and an adenoma of a fifth gland was removed from the mediastinum.

Case 2.—A 38-year-old woman had recurrent upper abdominal pain associated with diarrhea. On investigation she was found to have recurrent subacute pancreatic calcification, mild nephrocalcinosis and hypercalcemia (2.87 to 3.37 mmol/L [11.5 to 13.5 mg/dL]). There was no history of alcohol ingestion and her biliary system was normal.

Primary hyperparathyroidism with associated pancreatic and renal calcinosis was diagnosed. Venography and sampling of multiple veins in the neck and mediastinum for parathormone (PTH) revealed values in the high-normal range without a gradient in either the neck or mediastinal veins.[5,6]

On exploratory surgery of the neck four parathyroid glands were found in their usual positions; they appeared normal in size and colour. Subtotal parathyroidectomy was done, removing three glands; a biopsy was taken from the right lower gland and the remnant was marked with a silver clip. On examination of frozen sections the glands were considered normal. At this stage we decided that the diagnosis of hyperparathyroidism was

probably in error, so the operation was terminated. Postoperatively serum calcium concentrations remained elevated.

Further assessment included repeat venography and radioimmunoassay for PTH; as before there was no PTH gradient in any vein. The concentration of urinary cyclic AMP was elevated to 8.7 μmol/24 h. There was no evidence of other causes of hypercalcemia and the cortisone suppression test gave a negative result. We concluded that the diagnosis of primary hyperparathyroidism was correct and that the condition was caused by an adenoma of a fifth gland, probably in the mediastinum.

Five months later the previous neck incision was reopened. The recurrent laryngeal nerves were identified and the tissues inferior to the thyroid were dissected to allow examination of the thymus and surrounding tissues. An abnormality was noted at the inferior aspect of the right lobe of the thymus; the gland could not safely be mobilized into the neck. A short sternotomy to the third interspace allowed excision of a parathyroid adenoma, measuring 2 × 1.2 × 1 cm, situated within the thymus. Serum calcium values have remained normal since operation.

Case 3.—A 75-year-old woman with a 20-year history of recurrent renal calculi was found to have serum concentrations of calcium ranging from 2.87 to 3.24 mmol/L (11.5 to 13.0 mg/dL) and of phosphate ranging from 0.517 to 0.904 mmol/L (1.6 to 2.8 mg/dL). Primary hyperparathyroidism was diagnosed. Venography and radioimmunoassay for PTH were not considered necessary.

At operation four parathyroid glands of normal size were found in their usual positions. Biopsy specimens of all four glands were considered to be normal histologically although there was a possibility that the right lower gland was mildly hypercellular. We now believe that normal-sized glands, even if hyperplastic, will not produce serum calcium concentrations of 2.87 mmol/L (11.5 mg/dL) or higher. Therefore we decided to search for a fifth gland.

The fibrofatty tissues inferior to the thyroid lobes and the thymus were displayed and an adenoma measuring 1.5 × 2 cm was identified in the midportion of the right lobe of the thymus. The adenoma and the right lobe of the thymus were removed through the cervical incision; quick section confirmed the diagnosis of a parathyroid adenoma. Because of the possibility of diffuse hyperplasia, we decided to do a subtotal parathyroidectomy. Hence, both right glands, the left upper gland and the mediastinal adenoma were all removed; a biopsy of the left lower gland was done so that only a remnant of this gland remained.

Discussion

Autopsy studies, in which the neck is carefully examined for parathyroid glands and their presence and number are proved by microscopic examination, have shown that more than four parathyroid glands may be present.

In a detailed study of 428 cases, Gilmour[7] found six parathyroid glands in 2 cases (a frequency of 0.5%), five in 25 cases (6%), four in 374 cases (87%), three in 26 cases (6.1%) and only two glands in 1 case (0.2%).

Vail and Coller[8] in a similar autopsy study found five glands in 10 of 202 cases. None had more than five glands and all glands appeared normal on both gross and histologic examination.

Alveryd[9] in 352 autopsies found five glands in 13 cases (3.7%), four glands in 319 cases (90.6%), three glands in 18 cases (5.1%) and two glands in 2 cases (0.6%).

It is difficult to evaluate the reported occurrence of fewer than four glands because it is doubtful whether all glands were identified.

A fifth parathyroid gland is believed to be of surgical importance but its presence has been difficult to verify. By the time the presence of a fifth gland is suspected, the patient usually has had a number of operations because of persistent hypercalcemia and often the number of glands has not been verified by biopsy and microscopic examination. In the past surgeons have been reluctant to do biopsies of parathyroid glands because of the possibility of interference with the blood supply. This need not be of concern, although if a subtotal parathyroidectomy is done, the surgeon must take care to preserve the vascular pedicle of the remnant.[10]

The clinical importance of the fifth gland in our patients is obvious because it was proved to be the cause of their hyperparathyroidism.

We conclude that the possibility of a fifth gland should be considered in all patients with primary and secondary hyperparathyroidism. If present, the fifth gland is usually located in the lower neck or upper mediastinum, in particular within the thymus gland. In Alveryd's study,[9] 10 of the 13 fifth glands were in the lower neck and 3 of these were within the thymus.

A search for a possible fifth gland is recommended in patients with diffuse hyperplasia, particularly if it is associated with chronic renal disease. A fifth gland can be assumed to be present in approximately 3% to 5% of patients. If present in patients with secondary hyperparathyroidism this gland will also be hyperplastic, and if it is not excised surgical treatment will be unsuccessful. It is possible that this factor is of greater importance than the current controversy over the relative merits of subtotal parathyroidectomy and total parathyroidectomy with autotransplantation.

A possible fifth gland should also be sought in patients with primary hyperparathyroidism when four glands have been identified but appear to be of normal size. There is a correlation between the size of an adenoma and the serum calcium value; in general, patients with serum calcium values above 2.87 mmol/L (11.5 mg/dL) will have an adenoma measuring 1.5 cm in diameter, or larger. If such values are due to diffuse hyperplasia, the glands will appear enlarged. Thus, as in case 3, the possibility of a fifth gland in the upper mediastinum or elsewhere should be considered if the four glands in the neck are normal or only slightly enlarged.

The role of venography and selective radioimmunoassay for PTH in the diagnosis of a fifth gland has not been clarified (Murray TM: Personal communication, 1977). These methods are of questionable value in measuring concentrations of PTH in the large veins of the mediastinum. Of interest is the patient in our case 2 who had normal PTH values in the neck and mediastinum without gradients and who subsequently was found to have a fifth gland in the mediastinum. Failure to demonstrate a localizing gradient in PTH concentrations in the neck (provided the blood sampling from the neck veins has been meticulous and complete) suggests that the hyperfunctioning gland is ectopic and is probably in the mediastinum.

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Aspiration and Gastroesophageal Reflux

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Gastroesophageal reflux is the commonest esophageal cause of chronic intermittent aspiration. The authors investigated 1000 consecutive patients with reflux with reference to their medical history, and by barium esophagography, esophageal manometry and pH studies. In patients with respiratory complications, chest roentgenography and pulmonary function tests were also performed.

Of the total number, 279 patients aspirated either by coughing and choking during swallowing or as a result of night reflux; of these, 159 had associated respiratory symptoms, which included cough, voice change, recurrent respiratory infection, bronchiectasis and asthma.

Of the patients with aspiration, 120 had surgical correction of reflux because conservative management failed. This form of reflux control improved the symptoms of cough and voice change and the condition of patients with recurrent infections or bronchiectasis, but alleviated the symptoms in only 8 of 28 asthmatic persons.

Le reflux gastro-oesophagien est la cause d'origine oesophagienne la plus fréquente d'aspiration intermittente chronique. Les auteurs ont étudié 1000 patients consécutifs souffrant de reflux, pour leur anamnèse et par oesophagographie au barium, manométrie oesophagienne et études du pH. Chez les patients ayant des complications respiratoires, une radiographie pulmonaire et des tests de la fonction pulmonaire ont aussi été effectués.

Du total, 279 patients aspiraient soit par accès de toux, soit en s'étouffant durant la déglutition, ou encore comme résultat du reflux durant le sommeil; de ceux-ci, 159 présentaient des symptômes respiratoires associés, incluant toux, changements de la voix, infections respiratoires récidivantes, bronchiectasie et asthme.

Des patients souffrant d'aspiration, 120 ont subit une correction chirurgicale après échec d'un traitement conservateur du reflux. Cette forme de contrôle du reflux a permis d'améliorer la toux, les changements de voix et l'état des patients souffrant d'infections récidivantes ou de bronchiectasie, mais n'a soulagé les symptômes que de 8 personnes asthmatiques sur 28.

Aspiration of food or gastric content into the respiratory tract can occur as an acute condition or as an intermittent, chronic phenomenon. Acute aspiration is usually secondary to diminished consciousness such as occurs with anesthesia, cerebral injury, or inebriation.[1,2] Chronic aspiration is most commonly caused by esophageal disease, and gastroesophageal reflux, the most common esophageal disorder, is most frequently responsible.

The reported frequency of hiatal hernia in patients with chronic aspiration varies between 1.3%[3] and 45%.[4] The frequency of aspiration in patients with reflux has not been adequately documented. Previous reports have indicated the potential severity of lung damage from aspiration and also the effectiveness of surgery in controlling reflux.[5,6] The present study documents the frequency of reflux aspiration and the development of respiratory symptoms.

Patients and Methods

We investigated 1000 consecutive patients with gastroesophageal reflux who were admitted for a variety of reasons, including the investigation of chest pain and the assessment of the severity of reflux symptoms. In all patients a history of the esophageal and respiratory complaints was obtained and barium esophagography, esophageal manometry and pH studies were carried out. In patients with symptoms of asthma or respiratory infection chest roentgenography and pulmonary function tests were also performed. The radiologic studies were done by several different radiologists and were not standardized in technique.

The history provided the most important diagnostic information. Besides documenting symptoms of reflux, we paid particular attention to symptomatic aspiration. Aspiration can occur at night, when gastroesophageal reflux to the pharynx spills forward to the larynx and results in coughing and choking. Aspiration may also occur during the day when food sticks at the cricopharyngeus; forward spillage of food to the vocal cords results in choking.

The patient's history was also used to determine the frequency of aspiration and to indicate the type of aspirate (of oral or gastric content). The aspirate was considered to be of oral content when aspiration was associated with pharyngoesophageal dysphagia in which coughing and choking with swallowing allow aspiration of food and saliva. The aspirate was considered to be of gastric content when aspiration occurred with night reflux; in these circumstances gastric content spills into the tracheobronchial tree and the aspirate may contain food, gastric secretion and duodenal content. Frequency of aspiration was categorized as mild (less than once per week), moderate (more than once per week, but less than once per day) and severe (at least once per day).

In the respiratory history attention was paid to cough and voice change and to symptoms of recurrent respiratory infection, chronic bronchitis, bronchiectasis and asthma.

Barium esophagography confirmed the presence of a hiatal hernia or gastroesophageal reflux in all patients included in the study. Reflux can be demonstrated radiologically, but in the conscious patient tracheal aspiration of reflux barium is rare and was not seen in this study. During deglutition barium may spill into the tracheobronchial tree owing to pharyngoesophageal obstruction. This is an intermittent phenomenon and is difficult to demonstrate radiologically.

Esophageal manometric and pH studies were performed in the same unit on all patients to exclude other

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esophageal motor disorders and to identify reflux. Such studies may occasionally be of value in the investigation of aspiration. They may demonstrate an abrupt decrease in pH in the body of the esophagus owing to reflux. At the time of reflux the patient may cough and choke and consequently aspirate, but, since this type of aspiration is intermittent, the phenomenon cannot be reliably reproduced. When it does occur it is in the conscious patient and may be altered by the presence of tubes in the esophagus. This finding was recognized only late in the study and its frequency cannot be documented.

Results

The frequency of reflux and aspiration as well as of pharyngoesophageal dysphagia and aspiration is shown in Table I.

Respiratory problems were associated with aspiration in 159 patients: 90 of the 279 patients with aspiration had chronic cough or voice change, or both, as the only symptoms; 27 patients had recurrent respiratory infection, 2 had bronchiectasis and 40 patients were asthmatic.

No relation could be found between the frequency or quality of the aspirate and the development of respiratory symptoms. In patients who had pharyngoesophageal dysphagia and aspiration combined with night reflux and aspiration, respiratory symptoms occurred more frequently.

Surgical Correction of Reflux

Of the 279 patients with aspiration 120 were treated surgically for control of reflux. Surgery was indicated when medical management failed and severe esophageal symptoms persisted. Seven (5.8%) of the 120 patients had recurrent hiatus hernia demonstrated radiologically and 4 of these required further surgical correction. Following surgery all four patients had persistent pharyngoesophageal dysphagia and required a cricopharyngeal myotomy. Follow-up ranged from 3 to 5 years (average, 3.6 years).

Of the 90 patients with cough or voice change, or both, 31 patients whose only symptom was cough at the time of aspiration were treated surgically. All became asymptomatic. Of 46 patients with chronic cough or voice change who underwent surgery, 44 were greatly improved. One patient had a persistent cough, but his spasms of coughing were fewer and less severe. One other patient, whose cough was not severe, was unimproved.

In the group of 27 patients with intermittent respiratory tract infection 13 underwent surgery and none have had recurrent infections since the operation.

The two patients with bronchiectasis were markedly improved following surgical control of aspiration. In both, less sputum was produced and the condition has been well controlled with conservative therapy.

In the group of 40 patients with asthma 28 were treated surgically. Four showed marked improvement, 4 moderate improvement, 9 slight improvement and 11 were not improved.

Table I—Aspiration Associated with Gastroesophageal Reflux in 1000 Patients

	No. of patients
Reflux to throat and aspiration	115
Pharyngoesophageal dysphagia and aspiration	54
Combined reflux and dysphagia and aspiration	110
Total no. of patients with aspiration	279

Discussion

Aspiration of esophageal or gastric content into the lungs has frequently been shown to be associated with secondary respiratory infection, but the frequency and severity of respiratory symptoms have not been documented.[5,6]

In evaluating esophageal disease, the history alone provides an accurate diagnosis in 80% of patients.[7] Roentgenography, manometry, pH studies and acid perfusion measurements increase the diagnostic accuracy and allow clear distinction between the types of esophageal disorder.[8] For the diagnosis of aspiration a history of night reflux or of pharyngoesophageal dysphagia, resulting in coughing and choking on food and saliva, must be obtained.

The quality, frequency and quantity of the aspirate, together with the response of the lungs to the aspiration, are variables that are difficult to assess. While the circumstances of aspiration indicate the type of material aspirated, they do not provide an evaluation of the gastric content, which may be acidic from gastric secretions or alkaline from duodenogastric bile reflux. Both bile and acid present in the stomach have been shown experimentally to produce severe damage to the lung when aspirated.[9,10] Pharyngoesophageal dysphagia and aspiration of solid particles may produce bronchial obstruction.[11,12] It is not possible to evaluate all of the factors from history alone and, in particular, the quantity of material aspirated at any one time cannot be determined.

In this study we have documented the presence of respiratory complications attributable to aspiration. To establish the relationship it is necessary first to control the aspiration and then to evaluate the resolution of the respiratory problems. In 120 patients with aspiration the reflux was corrected surgically and the condition of the patients evaluated at follow-up. Cough or voice change were effectively corrected in 44 of 46 patients, indicating that this syndrome responds well to surgical correction. However, other causes of cough must first be excluded. The cough due to aspiration is secondary to laryngeal irritation and is often severe; it tends to be unproductive and minor inflammation of the vocal cords may be present.

Recurrent respiratory infections were also effectively controlled by surgical correction of reflux. Only two patients with bronchiectasis were included in the series and, although both were improved, no conclusions can be drawn.

The association of asthma with aspiration is well recognized.[13] In our experience surgical correction of aspiration does not always confer benefit in this condition. Also, chest discomfort associated with reflux is often described as causing dyspnea, although some patients do recognize that this feeling of tightness differs from that induced by exercise. Chest discomfort causing dyspnea in the asthmatic person is very difficult to distinguish from that due to bronchospasm, so that the patient may mistake relief of the discomfort by correction of reflux for improvement of the asthma. Only 8 of 28 patients with asthma were notably improved by surgery and none were totally relieved of their symptoms. In some the symptomatic relief may have been secondary to control of the chest tightness associated with heartburn and may not have been related to any change in respiratory function.

It seems that asthma is irritated by aspiration but is not caused by it. In some patients a major association can be demonstrated between episodes of aspiration and subsequent bronchospasm. The group of patients treated surgically were reviewed to see if this association could be substantiated. Of 20 asthmatic patients who showed no improvement or only slight improvement following reflux correction only 1 described a clear association between reflux and asthmatic episodes. In contrast all eight patients who were greatly improved described such an association. In asthmatic patients with reflux the decision to operate should be based on the need to control the symptoms attributable to reflux. The patient should be told that there may be a relation between the reflux and the asthma, but that improvement in the asthma after operation is unpredictable.

Summary

Chronic intermittent aspiration is an important source of secondary respiratory disease. Aspiration was present in 279 of 1000 consecutive patients with gastroesophageal reflux; in 159 of them respiratory disease developed. One hundred and twenty patients with aspiration were treated by surgical correction of reflux, which was effective in alleviating chronic cough and voice change, recurrent respiratory infections and bronchiectasis but less effective in treating asthma. In patients with asthma the history must indicate a relation between bronchospasm and episodes of aspiration for effective relief to be expected. Aspiration does not produce asthma, it merely aggravates the symptoms.

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The Anterior Interosseous Nerve Syndrome

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A review of the literature pertaining to the anterior interosseous nerve (AIN) syndrome revealed that the diagnostic criteria for this syndrome need to be defined.

The authors describe the etiology of the AIN syndrome and use two cases of their own and 52 cases reported in the English literature to draw up a definition of the diagnostic criteria. The recommended criteria are: (a) demonstrable weakness of muscles innervated by the anterior interosseous nerve; (b) electromyographic findings of marked denervation potentials and decreased or absent voluntary motor unit potentials of these muscles; (c) operative evidence of entrapment of, or injury to, the anterior interosseous nerve; and (d) improved power in the muscles and reversal of the electromyographic changes on follow-up after operation.

Une revue de la littérature consacrée au syndrome du nerf interosseux antérieur (NIA) a révélé que les critères de diagnostic de ce syndrome doivent être définis.

Les auteurs décrivent l'étiologie du syndrome du NIA, et emploient deux de leurs propres cas et 52 cas décrits dans la littérature de langue anglaise pour arriver à une définition des critères de diagnostic. Les critères recommandés sont: (a) une faiblesse démontrée des muscles innervés par le nerf interosseux antérieur; (b) des résultats électromyographiques de potentiels de dénervation marqués et une diminution ou l'absence de potentiels d'unité motrice de ces muscles; (c) à l'opération, des signe de coincement ou de blessure du nerf interosseux antérieur; et (d) une amélioration de la puissance musculaire et une inversion des changements électromyographiques en post-observation.

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The anterior interosseous nerve (AIN) syndrome is characterized by functional impairment of those muscles supplied by this nerve, namely the flexor pollicis longus, the radial aspect of the flexor digitorum profundus and the pronator quadratus.[1] Its terminal branches mediate sensation from the radiocarpal, intercarpal, carpometacarpal and distal radioulnar joints.[2]

Anatomy and Etiology

The anterior interosseous nerve arises from the posterior portion of the median nerve as its largest branch and runs as a separate bundle within that nerve for approximately 2.5 cm.[3] The exit from the median nerve is 2 to 6 cm below the medial epicondyle or 5 to 8 cm distal to the lateral epicondyle of the humerus.

Injury to the anterior interosseous nerve is rare because of its well-protected course. However, it is vulnerable at several points.

Fibrous Arch of the Pronator Teres Muscle

In 30 dissected limbs, Spinner and Schreiber[4] found that the anterior interosseous nerve passed through a connective tissue arch (Fig. 1), usually composed of loose areolar tissue, arising from the deep head of the pronator teres muscle. In seven limbs this arch consisted of tough fibrous tissue. Com-

pression of the nerve by a fibrous arch or band or, alternatively, by a tendinous insertion of the deep head of the pronator teres muscle may result in the AIN syndrome.

Close Proximity to the Ulna

Spinner and Schreiber[4] also pointed out that when a fibrous arch or band is present, the nerve is tightly held against the ulna (Fig. 2). They cited six cases in children of supracondylar fracture resulting in the AIN syndrome. They suggested that the mechanism is traction applied by the proximal fragment of the humerus to cause a tethering action of a fibrous arch or band at the level of the pronator teres muscle.

Compression of the Anterior Interosseous Artery

Near its origin the anterior interosseous nerve is crossed by anterior interosseous vessels (Fig. 3). It has been postulated that thrombosis of these vessels can result in the AIN syndrome.[4,5]

Tendinous Origin of Flexor Digitorum Superficialis

Approximately 4 cm distal to its origin the anterior interosseous nerve gives off a motor branch to the flexor pollicis longus muscle (Fig. 4). At this point it is crossed by the flexor digitorum superficialis to the long finger. A tendinous origin of this muscle has been implicated in producing the AIN syndrome.[6-8]

Close Proximity to the Radius

Warren[9] has drawn attention to the close proximity of the anterior interosseous nerve to the radius more distally in the forearm (Fig. 5). He cited two cases of forearm fracture associated with the AIN syndrome. Direct trauma, traction, or formation of a hematoma at this site could account for the palsy.

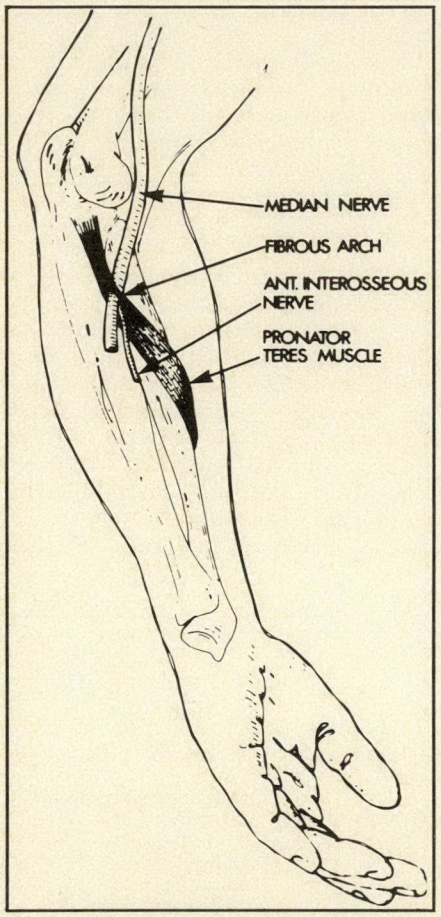

FIG. 1—Fibrous arch of pronator teres muscle over anterior interosseous nerve.

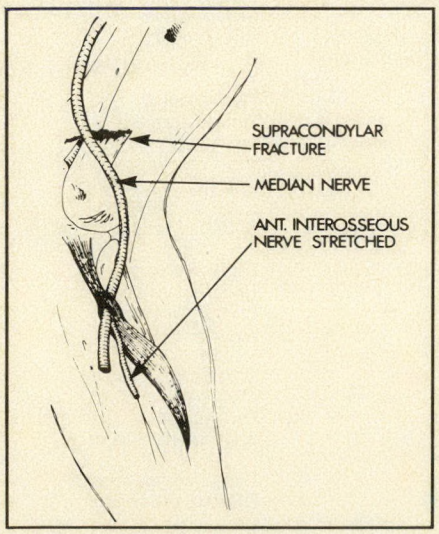

FIG. 2—Close proximity of anterior interosseous nerve to ulna.

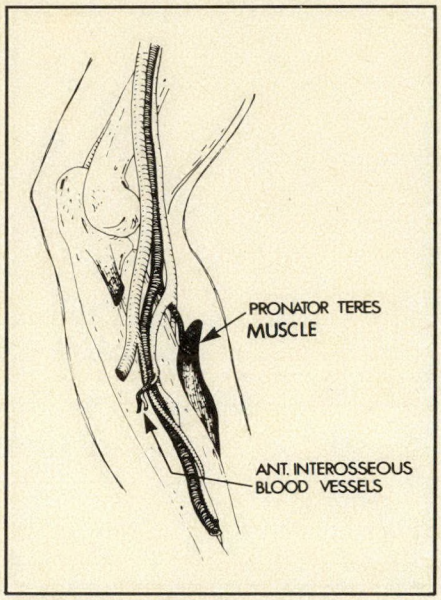

FIG. 3—Anterior interosseous artery causing compression of anterior interosseous nerve.

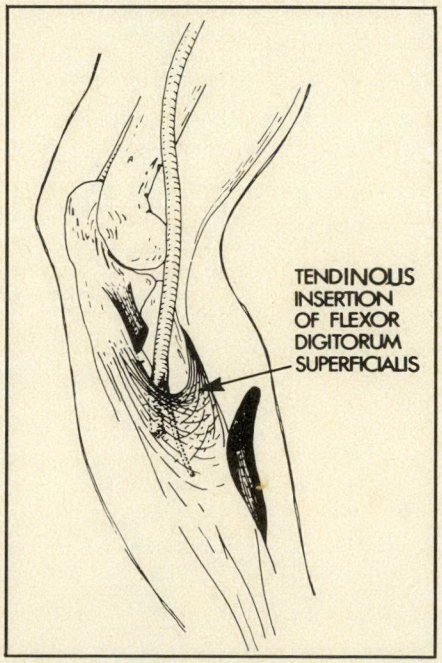

FIG. 4—Tendinous origin of flexor digitorum superficialis muscle affecting anterior interosseous nerve.

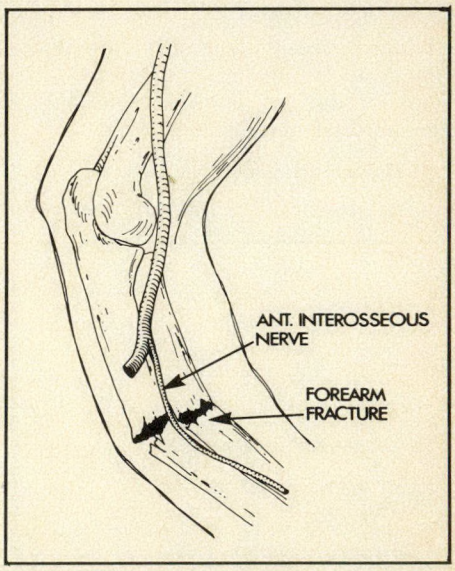

FIG. 5—Close proximity of anterior interosseous nerve to radius and injury to nerve caused by fracture of forearm.

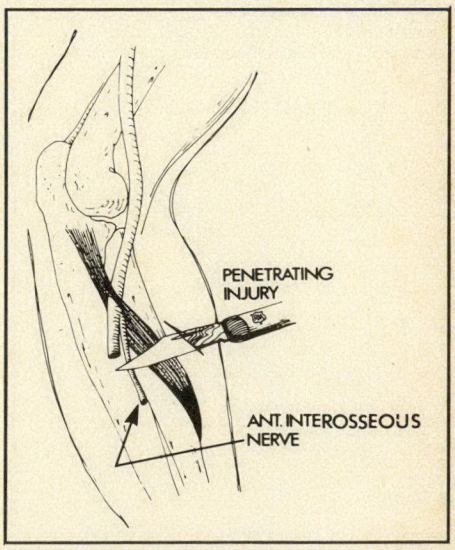

FIG. 6—Penetrating injury of anterior interosseous nerve.

Penetrating Injury

Direct trauma to the anterior interosseous nerve at the time of a penetrating injury (Fig. 6)[4] and during open reduction of a forearm fracture[4] have both caused the AIN syndrome.

Isolated Neuritis

As well as resulting from trauma or pressure at various locations along the course of the nerve, the AIN syndrome has been attributed to an "isolated neuritis",[10,11] or associated with the "shoulder-girdle syndrome".[12] Parsonage and Turner[12] suggested that a case of paralysis of the flexor pollicis longus and flexor digitorum profundus muscles of the index finger with no other involvement may have been due to poliomyelitis. They stated: "This localized paralysis cannot anatomically be of peripheral nerve or nerve root distribution and is only explicable by an anterior horn cell lesion." In the light of more recent reports,[3-13] the above diagnosis should be discarded in favour of distinct anatomical lesions of the anterior interosseous nerve.

Clinical Diagnosis

The diagnosis of the AIN syndrome is suspected if there is demonstrable weakness or paralysis of one or more of the flexor pollicis longus, radial portion of the flexor digitorum profundus, or the pronator quadratus muscles.

The weakness of the long flexors of the thumb and the index finger can be elicited by the pinch-grip test. As pointed out by Spinner,[1] the pinch-grip sign is characteristic of the AIN syndrome (Fig. 7). There is hyperextension of the distal interphalangeal joint and increased flexion of the proximal interphalangeal joint of the index finger. The metacarpal joint of the thumb is hyperflexed while the interphalangeal joint is hyperextended.

FIG. 7—Characteristic pinch-grip with anterior interosseous nerve paralysis.

The function of the pronator quadratus muscle should be assessed with the elbow flexed at a right angle to minimize the action of the pronator teres muscle.[4,7] This maneuver will permit demonstration of weak resistance to forced supination of the hand without interference from the pronator teres.

Pain is frequently mentioned as a presenting complaint. When present, pain is always poorly localized. It is most often referred to the forearm but may be felt in front of the elbow or rarely in the upper arm.

Electromyography

Electromyographic studies will confirm the diagnosis of the AIN syndrome by showing a marked denervation of the muscles supplied by the nerve. Voluntary motor unit potentials will be decreased or absent. The flexor digitorum profundus muscle will be variably involved depending on the extent of its innervation from the anterior interosseous nerve.

Table I—Data of Cases of Anterior Interosseous Nerve Syndrome

Authors	No. of cases	Treatment: Conservative	Treatment: Surgical	Proposed etiology	Final result
Parsonage and Turner, 1948[12]	6	6	—	5 associated with shoulder-girdle syndrome 1 anterior horn lesion	Not recorded
Kiloh and Nevin, 1952[10]	2	2	—	Isolated neuritis	Delayed partial recovery
Thomas, 1962[11]	2	2	—	Compared to neuritis or neuralgic amyotrophy	Full recovery
Warren, 1963[9]	2	2	—	Associated with forearm fracture	Full recovery
Fearn and Goodfellow, 1965[15]	1	—	1	Fibrous band	Full recovery
Stern, Rosner and Blinderman, 1967[6]	1	—	1	Fibrous band	Full recovery
Sharrard, 1968[16]	1	—	1	Fibrous band	Full recovery
Vichare, 1968[7]	4	—	4	2 intramuscular band 1 fibrous band 1 no cause found	Full recovery
Farber and Bryan, 1968[17]	2	2	—	No etiology proposed	Partial recovery
Mills, Mukherjee and Bassett, 1969[13]	1	—	1	Musculofibrous band	Full recovery
Spinner and Schreiber, 1969[4]	6	6	—	Associated with supracondylar fractures Proposed traction of anterior interosseous nerve	Full recovery
Spinner, 1970[2]	10	—	3	1 tendinous band 1 neuroma 1 thrombosed vessels with scar tissue	Full recovery Tendon transfer Full recovery
		5	—	Etiology not clear	3 full recovery 1 partial recovery 1 tendon transfer
		2	—	Associated with open reduction of forearm fracture	Both had tendon transfer
Schmidt and Eiken, 1971[8]	2	—	2	Fibrous bands	1 full recovery 1 nearly full recovery
O'Brien and Upton, 1972[18]	1	1	—	Segmental demyelination	Partial recovery
Gutmann, Hobbs and Wiley, 1973[3]	1	—	1	Fibrous band	Good recovery
Smith and Herbst, 1974[19]	1	1	—	Unknown	Full recovery
Lake, 1974[20]	3	2	1	1 fascial bands 2 unknown	Satisfactory recovery
Gardner-Thorpe, 1974[21]	2	2	—	Unknown	Full recovery
Krag, 1974[22]	4	—	4	1 fibrous band 3 neurogenic atrophy	Satisfactory recovery
Wiens	2	—	2	Fibrous bands	1 satisfactory recovery 1 lost to follow-up
Total	54	33	21		

Anatomical Variations

The clinical picture of the AIN syndrome can be quite variable because of differences in innervation of the muscles concerned. In fact, the flexor pollicis longus is the only muscle that is always innervated by the anterior interosseous nerve. Sunderland[14] has reported a case in which the entire flexor digitorum profundus muscle was innervated by the ulnar nerve. In the "all median hand" the anterior interosseous nerve supplies all of the flexor digitorum profundus. When a communication exists between ulnar and anterior interosseous nerves, the communication carries motor fibres to the first, second and third dorsal interossei and the adductor pollicis muscles.

We have recently treated two patients with the AIN syndrome and our experience is summarized below.

Case Reports

Case 1.—A 26-year-old man complained of aching pain, poorly localized in the right forearm and antecubital fossa. He was treated conservatively and the pain was relieved. The pain returned several months later and was accompanied by weakness of flexion at the interphalangeal joint of the right thumb. Examination revealed the characteristic pinch-grip sign associated with the AIN syndrome. He also had demonstrable weakness of pronation of the right hand. Sensory appreciation was intact over the entire right arm. On electromyography, denervation potentials were demonstrated in the right flexor pollicis longus and pronator quadratus muscles which also indicated reduced voluntary motor activity.

The median nerve was explored in front of the elbow. The anterior interosseous nerve was identified posteriorly at its site of origin and was followed distally. It was found to be stretched over a tendinous insertion of the deep head of the pronator teres muscle The nerve was attenuated but there was no true neuroma. The tendinous insertion of the pronator teres muscle was transected allowing the nerve to fall into its normal position without tension.

Two weeks later muscle power in the flexor pollicis muscle was much improved and 8 weeks later recovery was complete.

Case 2.—A 54-year-old carpenter had experienced weakness of the left thumb and index finger for 2 months. He complained of difficulty in holding nails while hammering and also in buttoning his shirts. There were also areas of numbness over the flexor aspect of the left forearm. Examination showed weakness of flexion of the distal phalanx of the left thumb and index finger. There was deep tenderness in the left forearm between the brachioradialis and the pronator teres muscles. Electromyography demonstrated denervation potentials in the left pronator quadratus and the flexor pollicis longus muscles; there was no voluntary activity in these muscles. Sensory potentials and motor conduction along the left median, ulnar and radial nerves were normal.

The left antecubital fossa and forearm were explored through an S-incision. The median and anterior interosseous nerves were identified proximal to the pronator teres muscle and were followed into the lower third of the forearm. Where the anterior interosseous nerve passed under the arch of the flexor superficialis it was compressed by a tight tendinous band. The nerve was attenuated and edematous but there was no neuroma. The tendinous band was excised and the compression of the anterior interosseous nerve was relieved.

Unfortunately, repeated attempts to contact the patient for follow-up examination have failed.

Discussion

Fifty two cases of the AIN syndrome have been reported in the English literature. These cases and our two are summarized in Table I.[2-4,6-13,15-22] The AIN syndrome and its diagnostic criteria have hitherto been only vaguely described. We believe that this condition needs to be defined. The AIN syndrome is characterized by weakness of flexion at the distal interphalangeal joint of the index finger and at the interphalangeal joint of the thumb; in addition there is weakness in pronation of the hand. The syndrome is caused by entrapment of or injury to the anterior interosseous nerve, with subsequent denervation of the flexor pollicis longus, radial portion of the flexor digitorum profundus and the pronator quadratus muscles. Clinically, the motor weakness can be demonstrated by the characteristic pinch-grip sign, and by impaired resistance to forced supination of the hand with the elbow flexed at a right angle. The criteria for diagnosis include: (a) demonstrable weakness of one or more of the three muscles innervated by the anterior interosseous nerve; (b) electromyographic findings of marked denervation potentials and decreased or absent voluntary motor unit potentials of the corresponding muscles; (c) operative evidence of isolated entrapment of or injury to the anterior interosseous nerve; and (d) increased power in the affected muscles and reversal of electromyographic changes when the nerve is released.

Of 52 cases meeting the criteria for the AIN syndrome compiled from the English literature, the majority were due to pressure applied by a fibrous or tendinous band, or were associated with trauma. It seems clear from the literature that palsy associated with closed fractures should be treated in the expectation of good results. In cases not associated with fracture, exploration should be performed; the results are gratifying. Prolonged conservative management appears unwarranted.

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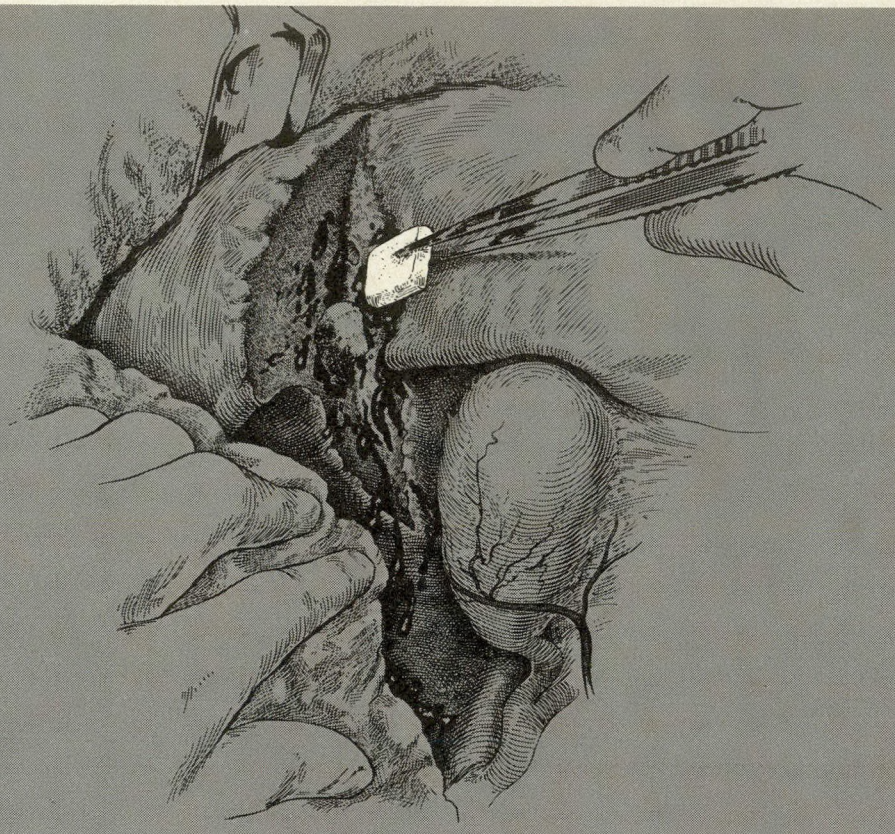

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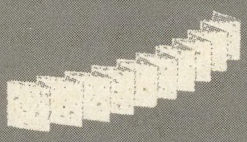

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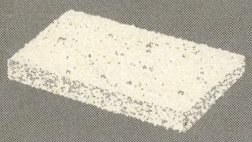

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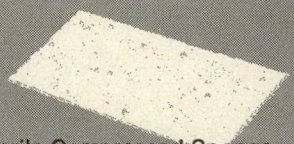

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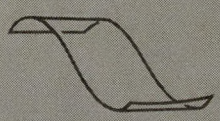

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Congenital Syndactyly: A Reappraisal

MARTIN A. ENTIN, MD, CM, M SC, FRCS[C]*

Digital syndactyly is a common congenital anomaly and is associated with other anomalies affecting the digits, the hand, the arm or even the entire body.

In the past it has been considered a single entity. However, recent information provided by experimental embryology, studies of morphogenesis and other sources, suggests that there are at least two distinct entities: primary syndactyly due to interference with the sequence of events that normally culminate in the division of digits into discrete parts and secondary syndactyly due to readhesion of adjacent digits as a result of close contact between raw surfaces.

Primary syndactyly may arise de novo, or it may occur as a manifestation of a mutation phenomenon or as a genetically controlled syndrome. Secondary syndactyly is the result of mechanical adhesion of adjacent parts involved in a general reparative or healing process. The initial insult leading to amputation of a portion of the digits may or may not be genetically controlled; adhesion is fortuitous.

Management of syndactyly is determined by the complexity of the malformation. For simple cutaneous syndactyly the surgeon should make a zigzag incision and provide a rectangular, proximally based flap for the floor of the web, usually before the child is 2 years of age. A full- or split-thickness skin graft should be applied to the defects. For complex deformities involving several digits and associated with postural or osseous malformation, several operative procedures may be required. The surgeon must be vigilant to note and correct the sequelae resulting from recurrent contractures and imbalances associated with growth.

La syndactylie est une malformation congénitale fréquente qui est associée à d'autres anomalies des doigts, de la main, du bras ou même du corps tout entier.

On l'a considérée dans le passé comme une entité simple. Toutefois, l'information récente issue de l'embryologie expérimentale, des études de morphogénèse et d'autres sources indiquent qu'il y a au moins deux entités distinctes: une syndactylie primaire due à une interférence dans la séquence des évènements qui culmine normalement par la division des doigts en parties séparées, et une syndactylie secondaire due à un recollement des doigts adjacents, résultant d'un contact étroit entre deux surfaces vives.

La syndactylie primaire peut survenir de novo, ou elle peut être la manifestation d'un phénomène de mutation ou représenter un syndrome contrôlé génétiquement. La syndactylie secondaire résulte de l'adhésion mécanique de parties adjacentes impliquées dans un processus de réparation générale ou de cicatrisation. L'agression initiale conduisant à l'amputation d'une partie des doigts peut être ou ne pas être sous dépendance génétique; l'adhésion est fortuite.

Le traitement de la syndactylie est déterminé par la complexité de la malformation. Dans le cas d'une syndactylie cutanée simple, le chirurgien devrait faire un incision en zigzag et préparer un lambeau rectangulaire rattaché à la partie proximale et destiné à servir de membrane interdigitale; l'opération devrait habituellement être pratiquée avant l'âge de 2 ans. Une greffe cutanée pleine épaisseur ou demi-épaisseur devrait être appliquée sur les défauts. Pour les difformités complexes impliquant plusieurs doigts et associées à des malformations de la posture ou des os, plusieurs interventions chirurgicales peuvent être nécessaires. Le chirurgien devrait être prêt à noter et corriger les séquelles résultant des contractures récurrentes et des déséquilibres associés à la croissance.

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Digital webbing is a common congenital anomaly. It accounted for about 20% of 350 cases of congenital digital malformation recently reviewed at the Royal Victoria Hospital and Shriners Hospital for Crippled Children in Montreal.[1] Webbing of the digits may be an isolated entity or may be associated with other anomalies of the hand, the arm, or the entire body. In the past, syndactyly was considered to be a single entity. Recent studies of morphogenesis[2-6] suggest that there are at least two distinct forms of syndactyly: *primary syndactyly*, which results from interference in the normal sequential development of the parts, and *secondary syndactyly* which is caused by readhesion of adversely affected or partially amputated adjacent parts. Both forms of syndactyly can either arise de novo or be secondary to genetic causes; the latter form may recur in succeeding generations.[7] While the subject is still controversial, we can best begin to understand the pathogenesis of these conditions by considering the evolvement of the upper limb.

Morphogenesis of Anomalies

The upper limb begins its evolvement as a limb bud; within the bud a sequential reciprocal process takes place between the outer epiblast and the inner mesenchyme. Epiblast thickens to form an ectodermal cap which induces the mesenchyme to differentiate. The differentiation begins proximally and continues in a distal direction. In this manner the various areas of the upper arm, forearm and the hand are established.[8]

This regionalization begins about the fifth week of gestation. Each area is destined to produce the appropriate component parts: the proximal portion will form the humerus and surrounding soft tissue; the ulnar portion will form the ulna and the ulnar digits; the radial area will form the radius, the thumb and the appropriate carpal bones; and the central region will form the index and middle fingers with their carpal bones.[6,9] Malformations occur when any one of these regions is adversely affected by a deforming force, but the force must act before differentiation takes place. After the seventh

week of gestation all elements of the hand have been laid down and normally only maturation and growth will subsequently take place.

The deforming forces affecting the developing limb may be environmental or genetic. The genetic manifestations may occur sporadically as a mutation when one or several genes may be affected. In addition, these genetic alterations may be inherited in a dominant or recessive mode. The local defect may occur by itself or may be part of a systemic condition associated with other malformations. If such associations occur repetitively a syndrome complex may be described.[7,10]

The malformation can occur as a result of the adverse effect of a teratogenic agent or of the environment on the developing embryo. Interesting information became available from careful analysis of pregnant mothers who took thalidomide and subsequently gave birth to children with malformed limbs. It was established that the effect was produced between the 39th and 50th day after the last menstrual period.[11] Other agents may affect the developing limb in similar sequences, but the type of deformity and the timing of its production depend upon the susceptiblity of the differentiating cells and the specificity of the teratogenic agent.[11]

Primary Syndactyly

There is a progressive division of cartilaginous masses destined to form the bones of individual digits from the fifth to eighth week of embryonic development. If this evolvement is interfered with, either by a gene or by a teratogenic agent, and the process of division is delayed or arrested, syndactyly occurs; it may be a simple cutaneous syndactyly or a combined bony and cutaneous form (Figs. 1 and 2). This nondivision produces a "primary" syndactyly whose complexity depends on the timing and the severity of action of the teratogen or on the penetrance of the genetic factor.

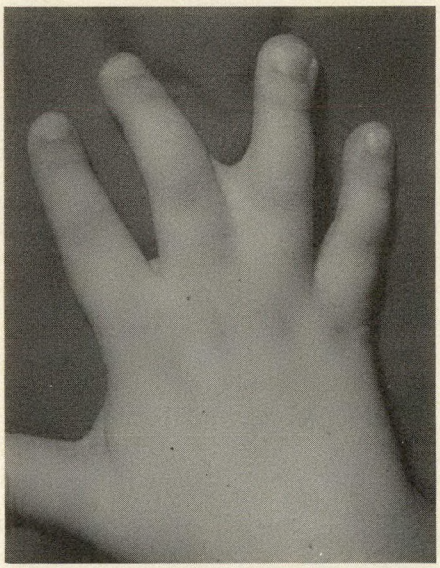

Fig. 1a

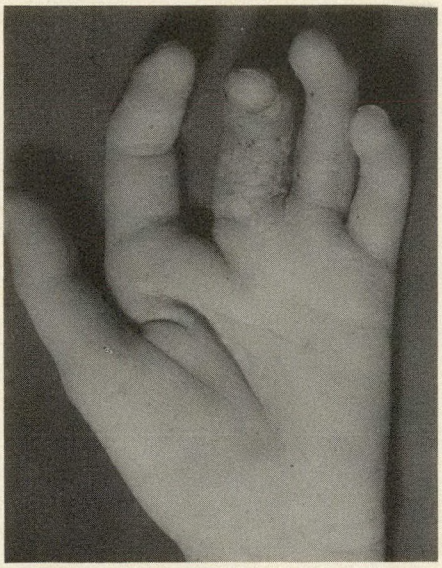

Fig. 1c

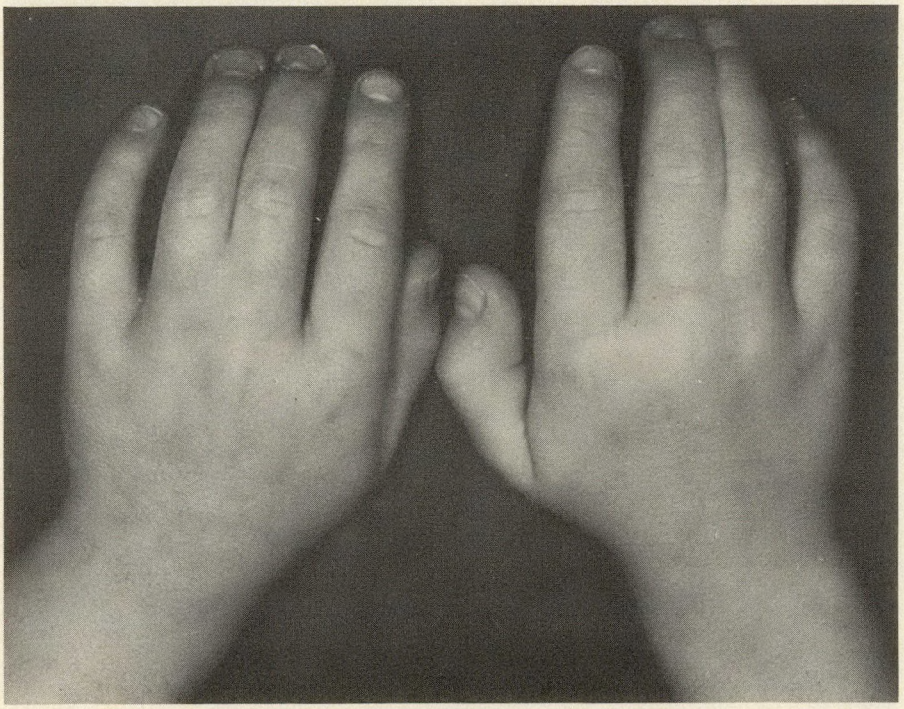

Fig. 1b

FIG. 1—Primary syndactyly. (a) Partial syndactyly between middle and ring fingers in child. (b) Bilateral cutaneous syndactyly which is usually familial. (c) Cutaneous syndactyly between middle and ring fingers showing secondary contracture.

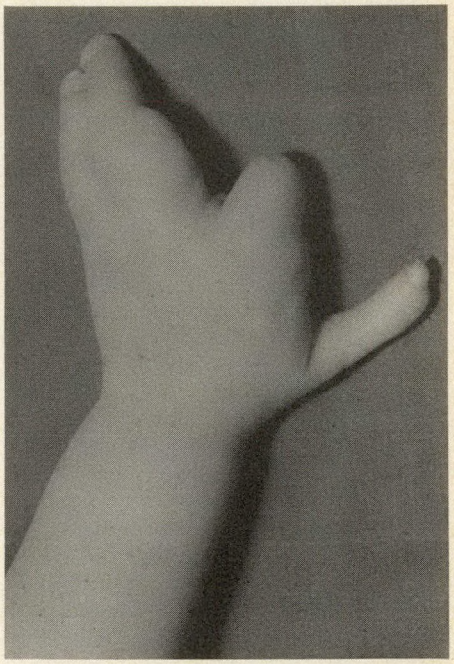

Fig. 2a

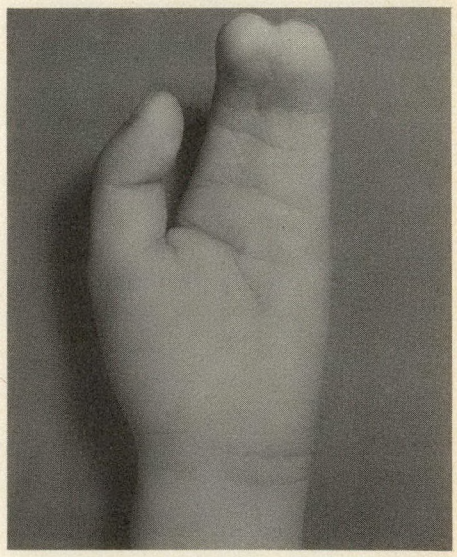

Fig. 2b

FIG. 2—Complex syndactyly. (a) Complex syndactyly with amputation of index finger and hypoplasia of thumb. (b) Complex syndactyly affecting index and long fingers associated with absent ring and little fingers.

Several anomalies may be produced simultaneously in different areas of the body by the same gene or teratogenic factor. New syndromes are described when several anomalies consistently occur together in the same individual. Several syndromes occur in association with syndactyly: for example, craniosynostoses may be associated with syndactyly of the fingers (Fig. 3).[2,5,12-14] These patients suffer from a premature closure of the cranial and facial sutures. As a result brain growth is restricted and brain damage may result. Characteristic facial deformities also occur. In Poland's syndrome[15-18] as well as syndactyly there is absence of a portion of the ipsilateral pectoralis muscle. Digital webbing is prominent in a number of other syndromes[1,7,10,19] such as oculodentodigital dysplasia and the orofaciodigital syndrome.

Secondary Syndactyly

Lösch[5,20] was the first to point out the difference between primary and secondary syndactyly; he based the distinction on his careful anatomical studies of a number of hands with webbed digits. Differentiation of the mesenchymal structures into individual phalanges takes place about the fifth to sixth week of gestation; consequently, the end of the fifth week is the critical time for formation of osseous syndactyly.[5] In his anatomical dissections Lösch was able to clarify the detailed structural alterations of the osseous, ligamentous, tendinous and cutaneous elements in cutaneous and osseous syndactyly.[20]

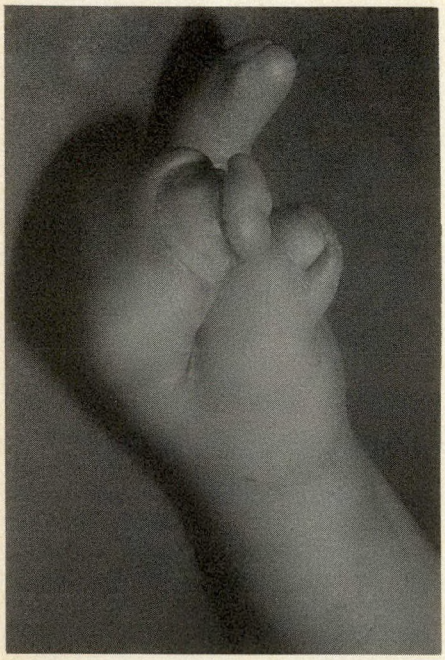

FIG. 3—Complex syndactyly with craniosynostosis of Apert's type showing fused nails of three fingers.

Even after the various parts of the limb have been formed, environmental or teratogenic factors may adversely affect their development and bring about secondary changes through vascular complications or through some other mechanism.[21] These changes may alter or destroy developing parts and produce necrosis. The ulcerated segments then become fused during the process of healing. Because these malformations result from antecedent defects, it may be appropriate to term them "secondary" syndactyly. The findings among several patients in our series who were seen at birth and followed through childhood substantiate the concept of secondary syndactyly (Figs. 4 and 5).

The specific cause of secondary syndactyly is still controversial. Several different mechanisms have been suggested, each having its supporters. Ring constrictions have been considered important by several authors.[2,5,22,23] Annular constrictions are frequently found in individual fingers adjacent to obviously "amputated" digital remnants. Constrictions are also found on digits associated with webbing of neighbouring digits. Under such circumstances, the webbed digits invariably lack their distal portions. Consequently, this is considered to be one of the mechanisms whereby coalescence of raw or ulcerating neighbouring structures can produce "secondary" syndactyly of previously separated digits.[1,20]

It has been suggested that the formation of amniotic bands associated with some defect in the amnion is the specific morphogenetic factor that leads to intrauterine amputation. The amnion becomes separated from the chorion leaving a mesh of mesodermal threads or bands in which the fetal parts become entangled. Such constricting bands around trapped fingers can produce edema, ischemia, atrophy or, if

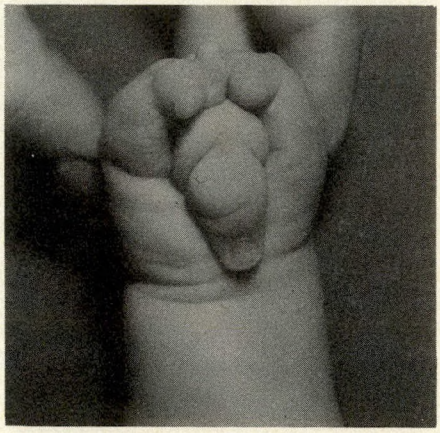

Fig. 4a

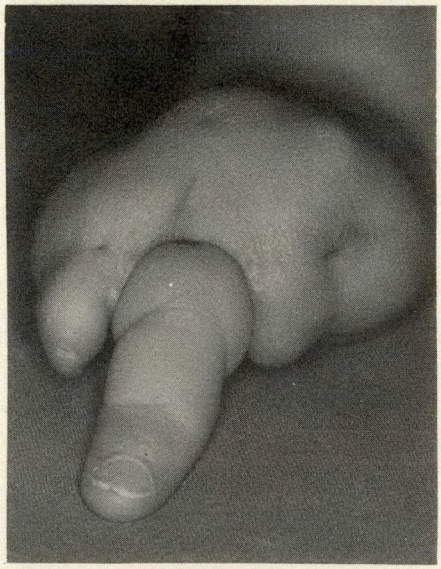

Fig. 4b

FIG. 4—Secondary syndactyly. (a) Right hand of 1-week-old male infant showing constriction of middle finger by adhesion of stump of thumb to adjacent ring and little fingers. (b) Immediate surgical release was carried out to improve circulation to middle finger. Dimple between stumps of ring and little fingers is remnant of web space.

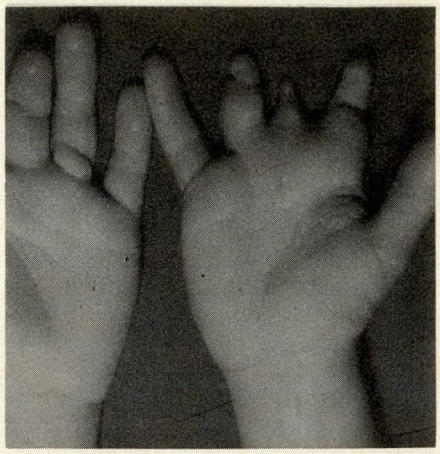

Fig. 5a

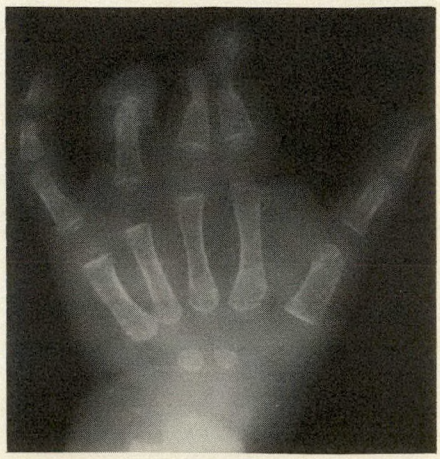

Fig. 5b

FIG. 5—Secondary syndactyly. (a) Right and left hands of 7-year-old child. Ring constriction on missing distal phalanges on right hand suggests intrauterine amputation (acrosyndactyly). (b) Roentgenogram of right hand shown in (a).

they persist, complete amputation.[19,24]

The association of the amniotic band syndrome in pregnant mothers exposed to lysergic acid (LSD) with the birth of infants having "distal" syndactyly has been reported.[22,24] However, others[10,21,25] support different theories of etiology. They state, on the evidence of vascular anomalies, that it is not the amniotic bands but rather the paucity of mesodermal proliferation or the necrosis of tissue that is responsible for this type of digital webbing. In any case, these entities do not appear to be genetically controlled,[7,10] although the problem of morphogenesis still awaits elucidation.

Classification of Syndactyly

It is essential to have a classification even if it is not universally accepted; otherwise the reports become a mere listing of seemingly isolated items, and comparative studies of, for example, the incidence and the results of treatment are not possible.[26-29]

We have chosen the basic classification of congenital anomalies of the upper extremity that was originally recommended by the American Society for Surgery of the Hand and that was subsequently adopted by the International Federation of Hand Societies[30,31] and later modified by the International Society of Prosthetics and Orthotics.[31] It comprises seven main divisions.

Syndactyly belongs primarily to the second division of the classification, namely, the failure of differentiation of parts. The malformation of syndactyly is confined to the digits of the hand, but frequently associated are conditions affecting other areas and remote organs. These too must be included in the classification. As mentioned earlier, the anomalies that are due to failure of differentiation or separation are considered as "primary", whereas those that appear to result from antecedent defects and are produced by "refusion" are termed "secondary" syndactyly. Based on these considerations, the syndactylies are classified as described in Table I. It is particularly difficult to provide an all-inclusive classification of congenital malformations associated with syndactyly because almost any type of congenital deformity involving the digits may have some element of syndactyly. While there may not be universal agreement on this classification, it should be adopted provisionally by centres involved in treatment of these conditions so that the evaluation of the collated results will be meaningful.

Management of Syndactyly

While it is not our purpose in this presentation to consider the treatment of various forms of syndactyly, we would be remiss if some basic principles of management were not outlined. The ideal is to restore normal function and appearance to the malformed limb. There is no universal agreement regarding the timing of the individual surgical procedures. In complex deformities early intervention is mandatory, especially if in the developing infant there is interference with prehensile function of the hand.[26,27,32]

For simple cutaneous syndactyly a zigzag incision and fashioning of a generous dorsal, proximally based, rectangular flap for the floor of the web are usually carried out before the child reaches 2 years of age. Full-thickness skin grafts from the groin or moderately thick split-thickness grafts taken from the lateral aspect of the buttocks provide coverage for the lateral skin defects.

Earlier separation of digits may be desirable for complex syndactylies associated with postural deformities and flexion contractures. If several digits are affected, the marginal fingers are separated first.

In secondary syndactyly, a constricting effect may threaten the survival of a digit soon after birth; under these circumstances surgical release becomes an immediate necessity (Fig. 4).

Table I—Classification of Syndactyly

- Primary (nondivision)
  - Cutaneous or simple
    - Soft tissue only
      - Two digits only
      - Multiple digits without postural deformities
  - Complex
    - Soft tissue
      - Synonychia
      - Multiple digits with postural deformities
    - Skeletal
      - Fusion
        - Phalangeal
        - Metacarpal
      - Brachysyndactyly
      - Disarray
      - Others*
    - Syndromes
      - Poland's, Apert's, orofaciodigital, oculodentodigital and others
- Secondary (refusion)
  - Cutaneous
    - Terminal fusion
    - Associated with digital amputation
  - Skeletal
    - Acrosyndactyly
    - "Mitten hand"
    - Others*

*Syndactyly may be associated with a variety of malformations such as reduction in number of digits (ectrosyndactyly) or increased number of digits.

Recurrence of webbing and contracture may take place, and newer imbalance may occur with unequal growth of affected parts. Constant vigilance is required to correct these deformities.

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Renal Artery Embolism: Diagnosis and Treatment

M.B. BUCKSPAN, DDS, MD, FRCS[C] AND M.R. GOLDBERG, MD, M SC, FRCS[C]

A 59-year-old woman presented with flank pain, atrial fibrillation and a nonfunctioning left kidney. A diagnosis of renal artery embolism was made and she was treated successfully by embolectomy. A review of the literature reaffirms the role of embolectomy, even in cases with delayed diagnosis.

Une femme de 59 ans s'est présentée souffrant de douleur au flanc, de fibrillation auriculaire et de blocage du rein gauche. Un diagnostic d'embolie de l'artère rénale a été posé et la patiente a été traité avec succès par embolectomie. Une revue de la littérature confirme le rôle de l'embolectomie, même dans les cas où le diagnostic est retardé.

Renal artery embolism as a clinical entity is uncommon. However, Hoxie and Coggin[1] reported finding renal infarction in 1.4% of 14 411 consecutive autopsies. Trabue[2] first described this condition in 1856, but it was not until 1962 that a successful renal artery embolectomy was described by Duncan and Dexter.[3]

In patients who present with the syndrome of flank pain, atrial fibrillation and a nonfunctioning kidney, the possibility of a renal artery embolus must be considered. If the diagnosis is confirmed, even after some delay, prompt treatment may preserve normal renal function.

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Case Report

A 59-year-old woman was admitted for elective cholecystectomy. She had rheumatic heart disease with chronic atrial fibrillation but no other cardiac symptoms. Her blood pressure was 140/90 mm Hg and her pulse rate 90 beats/min and irregular. There was a grade 2 mitral diastolic murmur and no clinical evidence of heart failure. The electrocardiogram showed atrial fibrillation and right ventricular hypertrophy.

Digitalization was commenced and 24 hours later she suddenly experienced severe left flank pain associated with tenderness in the left loin, and nausea and vomiting. A provisional diagnosis of left ureteral colic was made, but urinalysis at that time disclosed no abnormal findings. Intravenous pyelography did not visualize the left collecting system. Cystoscopy revealed no efflux of urine from the left ureteric orifice, and on retrograde pyelography the left collecting system appeared unobstructed (Fig. 1). An isotope flow study and renal scan showed no perfusion of the left kidney (Figs. 2 and 3). An emergency aortogram showed a single left renal artery, which was obstructed just distal to its origin (Fig. 4). Selective arteriography demonstrated the occlusive embolus and propagated thrombi in several of the secondary intrarenal vessels (Fig. 5).

Operation was performed approximately 12 hours after the onset of symptoms. The abdomen was opened through a long midline incision and the left colon mobilized, exposing the aorta and the origin of the left renal artery. The kidney was soft and cyanotic and no pulsation was noted in the left renal artery distal to its origin. The embolus was removed through a transverse arteriotomy and a Fogarty catheter was passed proximally and distally. The vessel bled immediately and retrograde bleeding was also noted. The arterial incision was closed with 6-0 Polydek vascular sutures. Good pulsations were evident and there was some bleeding from capsular vessels at the lower pole of the kidney.

FIG. 1—Preoperative retrograde pyelogram showing unobstructed left collecting system.

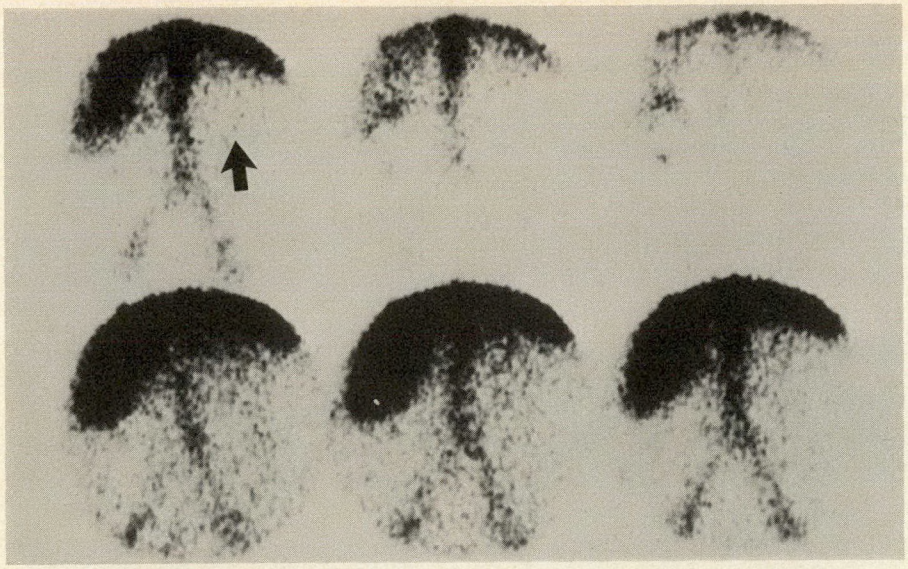

FIG. 2—Preoperative renal isotope flow study showing no perfusion of left kidney.

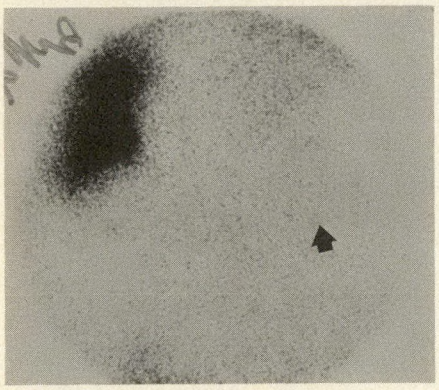

FIG. 3—Preoperative renal isotope scan showing nonfunctioning left kidney.

The patient received heparin intravenously 12 hours after the operation and warfarin after 24 hours. Her postoperative course was uneventful and her renal function and blood pressure were unchanged from their preoperative values. A renal scan obtained on the fourth postoperative day showed improved renal perfusion (Fig. 6) and an intravenous pyelogram on the 10th postoperative day showed a functioning left kidney (Fig. 7).

She was discharged from hospital on the 12th postoperative day and treatment with digoxin and oral anticoagulants was continued. Three months later her blood pressure and renal function were normal. Mitral commissurotomy is to be considered.

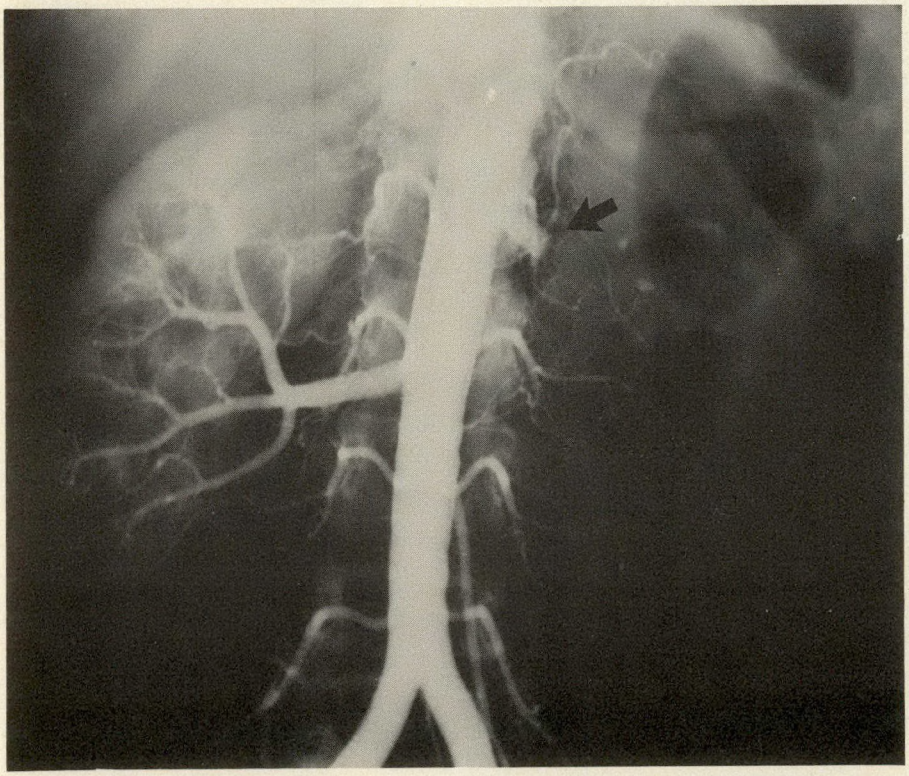

FIG. 4—Preoperative aortogram showing single left renal artery obstructed distal to its origin.

Discussion

The principal condition antecedent to acute renal artery embolism is mitral valvular disease with fibrillation, secondary to rheumatic or atherosclerotic heart disease. Other less common causes are congenital valvular disease, mural thrombi developing after myocardial infarction, subacute bacterial endocarditis and emboli from prosthetic heart valves and primary cardiac tumours. Paradoxical emboli originating in the deep venous system can pass across intracardiac septal defects into the systemic circulation.[4]

In recent years, atheroembolic renal disease has been reported with increasing frequency, either as a primary condition presenting as rapidly progressive irreversible renal failure, or as an acute complication of aortic surgery or aortography.[5] There have been reports of bilateral renal artery embolism,[6] and emboli to a solitary kidney.[7] In both these circumstances the patients were anuric and this would constitute a surgical emergency.

Renal artery embolism usually affects the elderly. The youngest reported patient was aged 25 years. The reported duration of ischemia has ranged from 5 hours[8] to 35 days[9] before surgical intervention. In all reported cases there was sudden onset of flank pain, failure of the kidney to be visualized on intravenous pyelography and no evidence of ureteral obstruction.

The length of time before irreversible, total loss of function occurs in the human ischemic kidney is not known, but has been estimated at 20 minutes

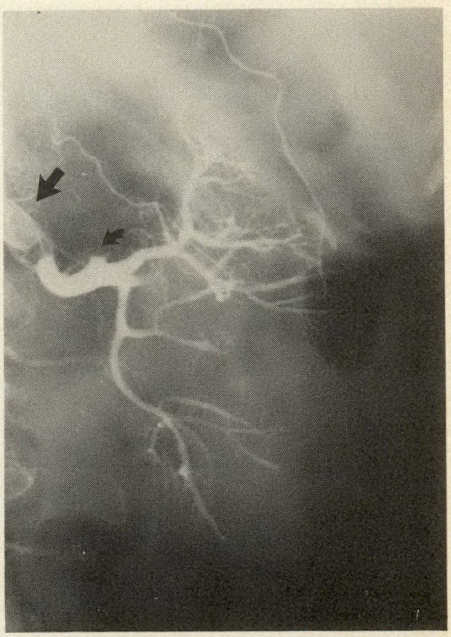

FIG. 5—Preoperative selective left renal arteriogram showing embolus just distal to artery's origin, with propagated thrombi in several secondary branches and poor parenchymal perfusion.

to 2 hours. Recent investigations have shown collateral intrarenal arterial anastomoses and an extrarenal supply from capsular vessels.[10] Therefore, acute renal artery obstruction, while rendering the kidney ischemic, may not actually produce necrosis. Urine formation may be suppressed temporarily but may improve after revascularization. While prompt recognition and treatment are important, a delay should not contraindicate embolectomy in patients medically fit for surgery. Nor should the gross appearance of the kidney at operation lead to nephrectomy or abandonment of planned embolectomy.

In patients whose condition contraindicates emergency surgery, systemic anticoagulation or selective administration of thrombolytic agents through the angiography catheter may be given a trial.[11]

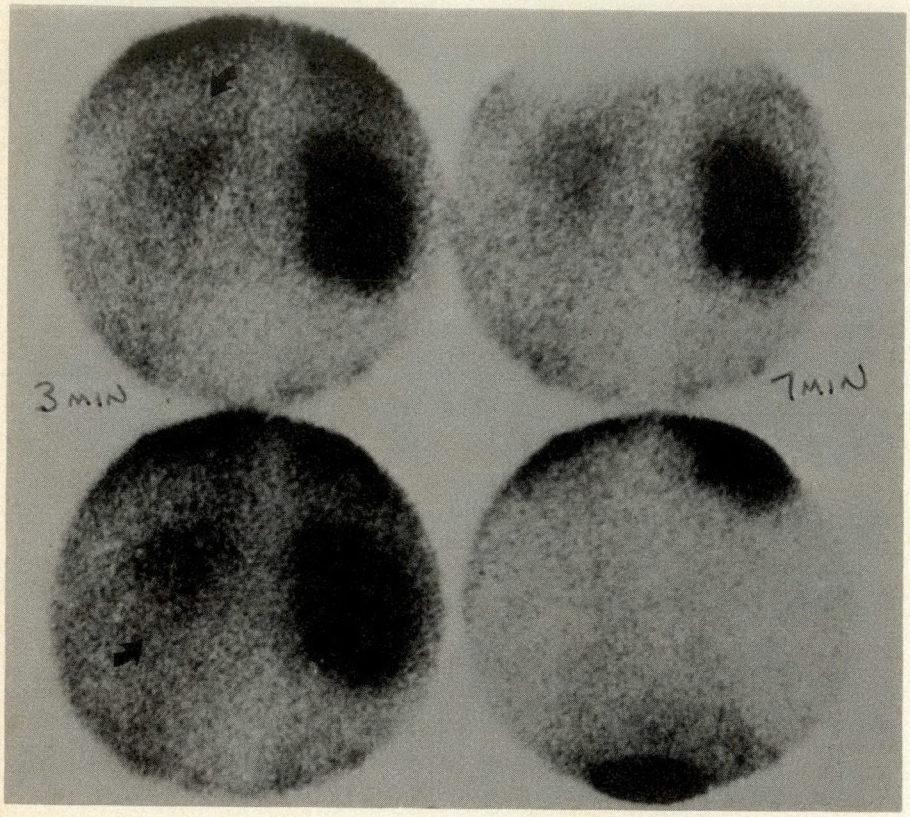

FIG. 6—Postoperative isotope renal scan showing improved left renal function, especially at upper pole.

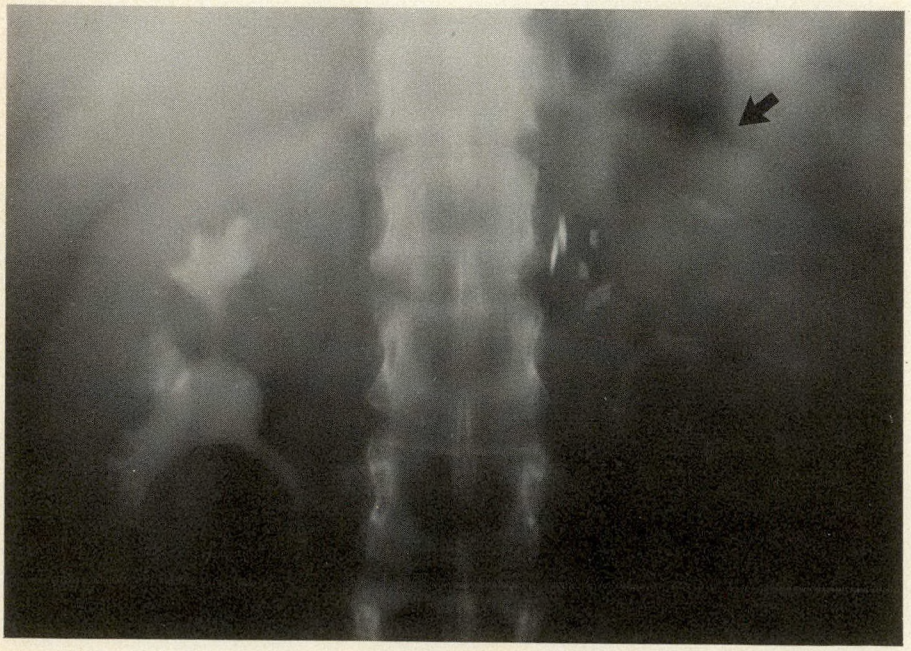

FIG. 7—Postoperative nephrotomogram showing functioning left kidney.

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treated patients with lymphedema, but they have had insufficient concrete information on which to base their planning for long-term management. Investigators interested in experimental and clinical research of the lymphatic system have been confronted with a diverse literature. Papers often were written in a foreign language and appeared in foreign journals. The editor of this text has solved many of these problems by bringing together an international panel of authorities to deal with the subject; they have done their work in a refreshingly critical scientific manner.

In two excellent chapters, Clodius correlates detailed experimental investigations with carefully documented clinical cases providing the requisite long-term follow-up. The review of secondary lymphedema of the arm will be of particular interest to the general surgeon and to the radiotherapist. Olszewski offers a rational scheme explaining the pathophysiology of lymphedema, which is supported by detailed experimental studies. Casley-Smith, Foldi and other contributors offer a stimulating and scholarly review of new concepts in lymphatic anatomy and physiology. The book is profusely illustrated with accurate photographs plus the necessary tables and is extensively referenced.

The only criticism of the text is directed at its publisher. There are numerous spelling errors and an inconsistency in refer-

Cake Kidney with Abdominal Aneurysm

MARTIN G. MCLOUGHLIN, MD, FRCS[C], TIMOTHY J. GARDNER, MD AND G. MELVILLE WILLIAM, MD

The authors describe a case of cake kidney occurring in association with a ruptured abdominal aneurysm with special reference to preoperative evaluation by angiography. They discuss the need to prepare these patients for possible in-vivo or ex-vivo renal manipulation during the removal of the aneurysm and the placement of the Dacron graft.

Les auteurs décrivent un patient ayant un rein en galette et une rupture d'anévrisme abdominal. Une attention particulière est accordée à l'évaluation préopératoire par angiographie. Ils discutent également du besoin de préparer ces patients en vue d'une manipulation rénale éventuelle in vivo ou ex vivo, durant la résection de l'anévrisme et la pose d'un greffon de Dacron.

Complete fusion of the nephroblastic masses early in fetal development results in the formation of a solitary renal mass commonly termed a cake kidney. This rare renal anomaly has been described in association with renal vascular malformations[1] but not with an abdominal aortic aneurysm. We describe one such case, associated with a ruptured abdominal aneurysm, with special reference to the use of angiography in defining the renal blood supply. By this means the surgeon can prepare the patient for possible in-vivo or ex-vivo renal manipulation to ensure adequate exposure for removal of the leaking aneurysm.

Case Report

A 64-year-old man experienced sudden onset of abdominal pain on the left side radiating to his left hip. He was admitted to his local hospital where a diagnosis of a leaking abdominal aneurysm led to an emergency laparotomy. Exploration revealed a large retroperitoneal hematoma and a cake kidney overlying an aortic aneurysm. The incision was closed, the patient's condition was stabilized and he was transferred to the Johns Hopkins Hospital, Baltimore, for further assessment.

His blood pressure on admission was 210/120 mm Hg, his pulse rate was 100 beats/min and his temperature was normal. Blood urea nitrogen concentration was 13.6 mmol/L (38 mg/dL) and serum creatinine concentration 221 μmol/L (2.5 mg/dL). After the blood pressure was controlled, a retrograde femoral arteriogram was obtained which confirmed the presence of an abdominal aortic aneurysm with an overlying cake kidney. The vascular supply to this kidney appeared as a single anteriorly placed vessel originating proximal to the aneurysm. Severe back pain indicated further leakage from the aneurysm. An exploratory operation disclosed a large retroperitoneal hematoma that had extended up into the lesser sac. Compression of the aorta below the origin of the single renal artery provided enough vascular control to allow the cake kidney to be separated from the aneurysm, aneurysmectomy performed and a bifurcation Dacron graft inserted. Postoperatively the patient required supportive therapy for respiratory, hepatic and renal insufficiency but was discharged after 4 weeks with a serum creatinine value of 309 μmol/L (3.5 mg/dL) and a blood urea nitrogen value of 23.2 mmol/L (65 mg/dL) (he had some renal ischemia but was recovering). He is now enjoying an active life and requires no medication.

Discussion

The early fusion of the metanephric elements in utero prevents the ascent and rotation of the renal mass to its normal position.[2,3] In its lower abdominal ectopic position the single fused cake kidney is usually described as a flat retroperitoneal mass with a lobulated anterior surface and an anteriorly placed pelvis.[4] The blood supply is variable but usually arises from the adjacent vessels. These abnormally situated kidneys are prone to ureteral obstruction, blunt trauma and infective episodes.

The association of cake kidney with ruptured aortic aneurysm has not been previously reported. Angiography in our patient defined the anomalous blood supply to the kidney and enabled us to plan the definitive surgical procedure. If the blood supply had arisen from the section of the aorta involved in the aneurysm, we were prepared to remove the kidney, perfuse it in an ex-vivo setting, then perform the aneurysmectomy and place the Dacron graft and finally replace the cake kidney in the abdomen and anastomose its vascular supply to the vena cava and Dacron graft. This patient was fortunate to have the renal blood supply arising above the aneurysm, thus permitting proximal control of the aorta below its origin after mobilization of the cake kidney anteriorly.

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ence styles. In the second edition one would like to see an expanded format dealing with each aspect of the lymphatic system from embryology through pathology to diagnostic modalities and treatment. Both primary and secondary lymphedema should be covered.

In summary, this text will be of value to surgeons of all specialties and to researchers dealing with the various vascular systems. We are all indebted to Leo Clodius for its obvious academic excellence and careful editing. He has, in the final analysis, produced the modern equivalent to Gasparo Aselli's classical treatise on the structure and function of the lymphatic system, but with emphasis on clinically important conditions and surgical treatments.

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PHYSIOLOGY OF THE HEART AND CIRCULATION. Robert C. Little. 334 pp. Illust. Year Book Medical Publishers, Inc., Chicago, 1977. Price not stated, paperbound. ISBN 0-8151-5475-5.

This text contains material presented to medical and beginning graduate students. The author, who is chairman of the de-

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Interstitial Pregnancy Following Ipsilateral Salpingo-oophorectomy

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A case of interstitial pregnancy, which occurred 12 years after ipsilateral salpingo-oophorectomy, was managed by cornual wedge resection. Internal (transuterine) migration of the fertilized ovum is the most probable explanation for this ectopic gestation. During the past 10 years three other cases of interstitial gestation have been managed at St. Michael's Hospital, Toronto, an incidence of 3% of all ectopic pregnancies seen at the hospital during that period.

Une grossesse interstitielle, survenant 12 ans après une salpingo-oophorectomie ipsilatérale, a été traitée par résection en pointe de la corne utérine. Une migration interne (transutérine) de l'ovule fertilisé est l'explication la plus plausible de cette gestation ectopique. Durant les 10 dernières années, trois autres cas de gestation interstitielle ont été soignés au St. Michael's Hospital, Toronto, pour une incidence de 3% de toutes les grossesses ectopiques vues à l'hôpital durant la même période.

Interstitial (uterine cornual) pregnancy is an uncommon type of ectopic gestation and its occurrence following total ipsilateral salpingectomy, with or without associated oophorectomy, is rare. Kalchman and Meltzer[1] found 73 reports of interstitial pregnancy in the literature up to 1966 and added two cases which occurred after ipsilateral salpingectomy. Our search of the world literature located three reports[2-4] not included in the Kalchman and Meltzer total and a further 12 cases[5-12] reported after 1966. We describe what is presumably the 91st such case and review our experience with interstitial ectopic pregnancy during the past 10 years.

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Case Report

A 31-year-old white woman complained of crampy abdominal pain located in the midline and left lower quadrant that was associated with nausea and the passage of several loose stools during the previous 2 days. These symptoms, although annoying, had not prevented her from performing housework and supervising young children at a day-care centre. Her last menstrual period had begun 6 weeks previously; she was not using contraception and a urine test for pregnancy done by her family doctor 3 days earlier had given a negative result.

At the age of 19 years the patient had had a serous cystadenoma of the right ovary which had necessitated salpingo-oophorectomy. The operative report described cross-clamping of the right cornual area which was then oversewn. In 1974 she was delivered vaginally at term of a normal female infant. In October 1976, following a Shirodkar procedure for cervical incompetence at 24 weeks' gestation, premature labour began and she was delivered of a stillborn infant.

On admission the patient weighed more than 145 kg and was not greatly distressed. Mild lower abdominal tenderness, especially to the left of the midline, was present but there was no guarding or rebound tenderness. There was no vaginal bleeding. Bimanual examination was unsatisfactory because of the extreme obesity but movement of the cervix to the right produced pain.

During 24 hours of observation and bed rest the patient's symptoms remained unchanged. Because of persisting cervical excitational pain, laparoscopy was undertaken. Clotted blood was seen on the fundus of the uterus. At laparotomy, performed through a Pfannenstiel incision, approximately 300 mL of old clotted blood was seen in the peritoneal cavity. The left ovary contained a corpus luteum and the normal left fallopian tube was freely mobile. The uterus, which was slightly enlarged and soft, had a bluish swelling 3 cm in diameter at the right cornu, to which organized blood clot and omentum were adherent. No active bleeding was evident. Trophoblast had invaded and penetrated the cornual area and had become implanted on the peritoneum overlying the bladder. No tubal remnant could be identified and the right ovary was absent.

A deep wedge resection of the cornual lesion was performed and the uterine defect was closed in layers. The right round ligament was used to cover the cornual scar. The implant of trophoblast on the bladder peritoneum was incompletely removed by blunt dissection and hemostasis effected by electrocauterization. The abdominal wall was closed in layers and drains were placed in the subfascial and subcutaneous spaces.

Despite the patient's obesity, there were no respiratory or wound complications. She was discharged home on the seventh postoperative day. Menstruation resumed 5 weeks after the operation. When the patient was seen 2 months postoperatively she was completely well, was following a program for weight reduction and had agreed to use contraception for at least 1 year.

Discussion

The rare cases of interstitial pregnancy following total ipsilateral adnexectomy emphasize that salpingectomy, with or without cornual resection, does not invariably protect against a subsequent ectopic gestation at the ipsilateral cornual area. There are several theories to explain this occurrence. Implantation of the fertilized ovum on the serosal surface of the uterus and subsequent invasion of the myometrium has been suggested.[13] Or the cornual remnant of the tube may recanalize to open onto the serosal surface and thus permit entry of the fertilized ovum at the site of previous surgery. However, the observation that the fallopian tube is attracted to the developing follicle and that the fimbria are almost a necessity for egg entrapment makes the random transfer of an ovum from the ovary to a nonmobile uterine aperture seem improbable.[14] When the ipsilateral ovary is also absent, as in the case we report, transperitoneal migration of the ovum, a second improbable occurrence, must also be postulated. We believe that internal migration across the uterine cavity of an ovum that was captured by, fertilized in and transported through the contralateral normal fallopian tube is a distinct possibility. The internal route of migration favoured in the recent literature reflects a better appreciation of the requirements for ovum capture than was available a decade ago.[6,15,16] In support of the internal migration

theory is the explanation of McElin and Iffy[17] that reflux menstrual flow, which occurs early when the conception cycle has a shortened luteal phase, carries the embryo to the uterine cornual area.

Interstitial pregnancies, and indeed ectopic gestations whatever their location, usually rupture through the implantation site and the conceptus dies. It has been postulated that abdominal pregnancy occurs in most cases as a result of the gradual delivery of the intact "embryo-trophoblastic unit" through the uterine wall.[18] In our case the trophoblast had penetrated the uterine cornu and become implanted on the peritoneum overlying the bladder. Although intraperitoneal bleeding had occurred, the cornu had not ruptured and the omentum was sealing off the area of trophoblastic invasion. These findings are consistent with the above genesis of abdominal pregnancy, but whether this interstitial pregnancy would have suffered the same fate can only be conjectured.

In most reports the ipsilateral interstitial pregnancy has developed shortly after the total salpingectomy. Since the healing operative site may predispose to ectopic implantation, contraception for at least a year following cornual resection has been advised.[19] The interval of 12 years between the initial operation and the interstitial gestation in this case is longer than in all earlier reports but one[20] and the interposition of two intrauterine pregnancies is unusual.

Between January 1966 and March 1977 three other patients with an interstitial ectopic pregnancy were managed at St. Michael's Hospital, Toronto, out of a total of 135 women in whom a diagnosis of ectopic pregnancy was proven by the pathological findings. The incidence of interstitial pregnancy has therefore been 3%; in the literature the figure varies from 1% to 6% of all extrauterine gestations.[7] The thickness of the uterine wall surrounding the interstitial portion of the tube in comparison with the peritoneum covering the remainder of its length permits longer growth of a pregnancy in the cornual area. Consequently, interstitial,[21] angular,[5] and cornual[22] ectopic pregnancies usually cause symptoms late in the first or in the second trimester. This greater gestational size combined with the vascularity of the uterine cornu can lead to severe hemorrhage. Most patients with an interstitial pregnancy are first seen when in hemorrhagic shock and represent an acute surgical emergency. The benign presentation in this case was unusual. A pregnancy at the cornual area, although it may in theory be suspected from the asymmetrical uterine growth, is usually not recognized prior to rupture.

The surgical management of ectopic gestation in all locations is individualized according to anatomic factors (extent of the rupture, associated pelvic disease), the patient's desire for more children, and her clinical state at the time of operation. When salpingectomy is indicated, we believe that a cornual resection (which should not be so deep as to enter the uterine cavity) will prevent a "stump recurrence" and will lessen, although not eliminate, the possibility of a future interstitial pregnancy.

According to reports in the literature of women with an interstitial gestation as many have had a hysterectomy as have had a wedge resection of the cornual area.[1,6,7,21] The more conservative form of operative management can be accomplished without hazard to most patients. Prompt recognition of intraperitoneal bleeding, accessibility of surgical units, early operation, availability of blood and fluid replacement, improved techniques of anesthesia and accurate physiologic monitoring of acutely ill patients have reduced the surgical risk to women with ectopic gestation. In performing an extensive cornual resection we recognize that a myometrial scar is left similar to that produced at a classical cesarean section or a uterine reunification procedure, and infrequently the scar may rupture during a subsequent pregnancy.[23] Simpson, Alford and Miller[16] found in the literature at least nine recorded instances of rupture of the gravid uterus at the site of a defective cornual scar. We have discovered one further case[19] reported since 1961. Therefore, we believe that there is insufficient evidence to justify the conclusion that conservative surgery may jeopardize future reproduction. Furthermore, there is no evidence to support or refute the suggested desirability of performing elective cesarean section in women who have had a previous cornual resection for an interstitial pregnancy.[7,16]

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Total Replacement of the Hip Joint Affected by Paget's Disease

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In seven patients with Paget's disease involving the bones about the hip joint, associated degenerative changes of the joint caused such severe pain and disability that total hip replacement was necessary. The results were uniformly satisfactory and no serious complications were encountered.

Chez sept patients souffrant de maladie de Paget avec atteinte des os de la hanche, les modifications dégénératives de cette articulation qui s'ensuivirent ont été la cause de tellement de douleur et d'incapacité qu'un remplacement complet de la hanche a été nécessaire. Les résultats ont été uniformément satisfaisants et aucune complication sérieuse n'est survenue.

Total hip replacement has provided relief of pain and improvement in function for patients suffering from various pathologic conditions of the hip joint. One of these conditions is Paget's disease, where involvement of one or both hip joints may cause disability sufficient to justify total hip replacement. Yet the orthopedic surgeon is often reluctant to perform replacement in such patients because of the possibility of excessive bleeding and later loosening of the prosthesis, and because of technical problems related to bowing of the femur. This paper describes our experience with total hip replacement in seven patients with Paget's disease involving the hip, in none of whom these complications developed.

Patient Data

Seven patients underwent total hip replacement for Paget's disease (by Müller's technique[1]) at the Wellesley Hospital, Toronto between 1970 and 1975. All had severe pain and stiffness of the hip. Six patients could walk only with the help of a cane and one was unable to walk at all. All were women. Their average age was 75.5 years. At the time of writing all patients were alive. The shortest follow-up was 2 years and the longest 7 years (average, 44 months).

Only one patient was receiving calcitonin preoperatively (60 MRC units three times a week, subcutaneously). She had the most severely deteriorated hip joint, associated with advanced Paget's disease involving the pelvis and femora. A similar dosage of calcitonin was prescribed for another patient following surgery. Two of our patients had Paget's disease of the pelvis and femur (Fig. 1), and the other five of the pelvis only (Fig. 2). The serum alkaline phosphatase value was elevated in all of our patients (average, 343 IU; normal range 25 to 90 IU). All our patients except one had an elevated erythrocyte sedimentation rate (average, 34.4 mm/h; normal value: men, < 10 and women, < 20 mm/h). There was no serious technical difficulty owing to hardness of bone. Blood loss ranged from 500 mL to 1500 mL (average, 915 mL), without the use of hypotensive anesthesia. (The blood loss in total hip replacement in 10 randomly selected uncomplicated osteoarthritic patients ranged from 400 mL to 1500 mL [average, 850 mL].) The radiologic appearance of degenerative arthritis of the hip associated with Paget's disease has been described previously.[2,3]

The results of total hip replacement were assessed clinically and radiologically with respect to fixed flexion deformity (FFD), flexion, abduction, adduction, and external and internal rotation, using the Harris hip rating.[4]

Results and Discussion

The overall subjective and objective results were satisfactory. Pain was relieved in all seven patients, except in one woman with a Pagetoid pelvis, who complained of only minor hip pain 6 years after the hip replacement.

This patient had no clinical or laboratory evidence of infection. Radiographic examination revealed progression of the Paget's disease so that it involved the whole pelvis. There was

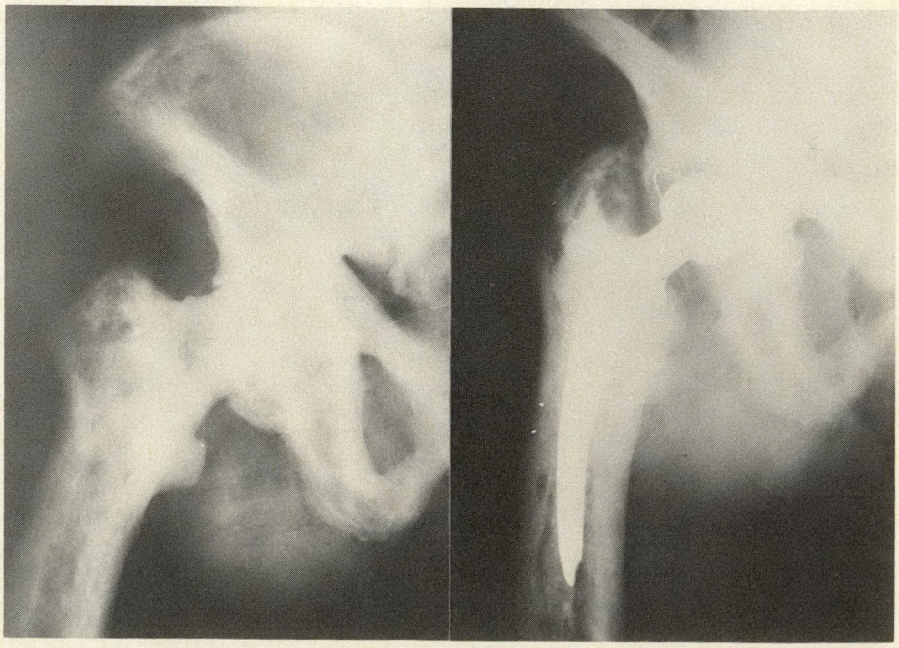

FIG. 1—Paget's disease of pelvis and femur with associated degenerative arthritis of hip joint.

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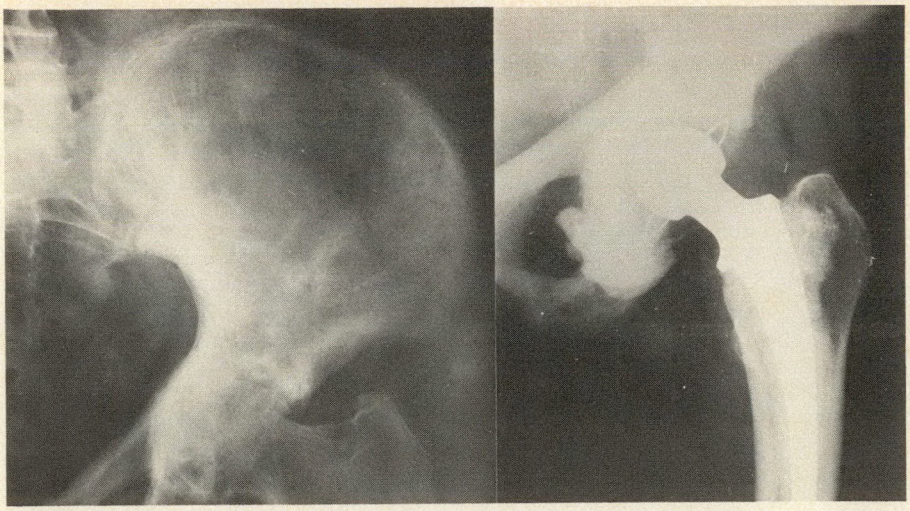

FIG. 2—Paget's disease of pelvis with associated degenerative arthritis of hip joint.

Table I—Comparison of Range of Movement (in Degrees) (Pre- and Postoperatively) in Seven Patients Who Had Total Hip Replacement

Patient no.	Fixed flexion deformity		Flexion		Abduction		Adduction		External rotation		Internal rotation	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	15	0	60	90	5	25	5	15	5	20	5	15
2	15	0	95	90	20	45	25	30	10	40	0	15
3	5	0	75	90	10	30	5	20	10	25	5	25
4	0	0	70	90	20	45	20	30	20	40	0	30
5	20	5	70	80	10	20	20	20	5	15	0	10
6	5	0	115	95	5	20	5	20	15	25	0	10
7	10	0	70	90	10	30	15	25	10	20	5	15

no indication of loosening of the prosthetic components. We believe therefore that the pain was due to active Pagetoid involvement of the pelvis.

Postoperatively, five patients were able to walk independently and two required a cane. Hip flexion contractures were corrected, and all had a greater range of joint movement (Table I). The results were uniformly satisfactory; according to the Harris hip rating,[4] the average increase was from 39 preoperatively to 91 postoperatively.

Although this is a small series, our experience parallels that of others[5] and indicates that total hip replacement is an effective method of treatment for patients with pain and deformity associated with Paget's disease and hip involvement. We believe that operative bleeding is not excessive when compared with that of total hip arthroplasty for other arthritic conditions.

The increased osteoclastic resorption of existing bone which occurs in Paget's disease could theoretically produce an increased incidence of prosthetic loosening. However, our early results in the small number of cases reported here do not support this supposition.

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partment of physiology and professor of medicine at the Medical College of Georgia School of Medicine in Augusta, has designed the book with these readers in mind, although it would also constitute an excellent concise review of the field for those further advanced in their careers.

There are three sections, on physiologic principles, the heart and the circulation. The first section considers fluid movement in the body, composition of blood, cardiac anatomy and biophysics of the cardiac cell. The second concerns the electrical and mechanical aspects of myocardial contraction, electrocardiography, cardiac output and its control, and cardiac metabolism. In the final section the author describes the anatomy, hemodynamics and regulation of the circulation; particular emphasis is placed on the control of blood pressure and regional circulation.

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The book does not pretend to be encyclopedic, and for the sake of brevity conflicting interpretations have been avoided in favour of generally accepted opinion. The book is of special value because it is the work of a single author who has a broad perspective and experience. The text includes much worthwhile information and it is illustrated with clear line drawings, graphs and charts.

The author has succeeded in providing a concise readable text that summarizes basic cardiovascular physiology.

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TECHNIQUES OF PATIENT CARE. A MANUAL OF BEDSIDE PROCEDURES. 2nd ed. Clarence E. Zimmerman, 272 pp. Illust. Little, Brown and Company, Inc., Boston, 1976. Price not stated, paperbound. ISBN 0-316-98868-5.

This small book attempts to discuss the bedside procedures that most of us learned by unsupervised trial and error or by word of mouth from our peers. Four of the chapters concern the use of needles in vascular techniques, aspiration techniques, lumbar puncture and biopsy. Three chapters about tubes include respiratory techniques, nasogastric intubation and urethral catheterization. The remaining chapters deal with skin preparation and infiltration, endoscopy, nasal packing, dialysis techniques, dressing care and techniques of resuscitation.

In general, each section is treated by listing the material and equipment necessary followed by a detailed description of "how I do it". Reference is made to indications, complications and subsequent management. Adequate line drawings and diagrams supplement the text in most instances.

The book will be a source of reassurance to medical students, interns and in some areas to junior residents. It will provide easily readable information about the techniques of patient care that are so often relegated to that group. Senior residents and consultants having mastered the techniques described will find little of interest.

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