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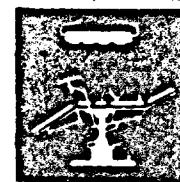
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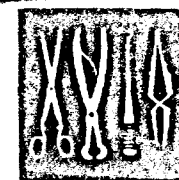
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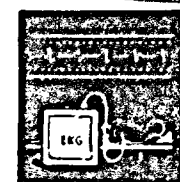
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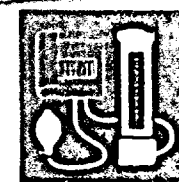
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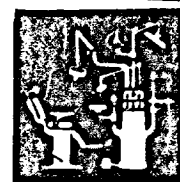
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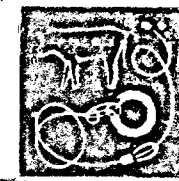
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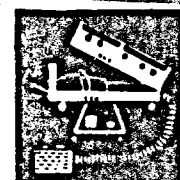
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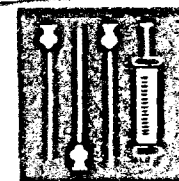
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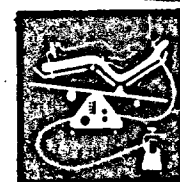
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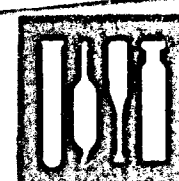
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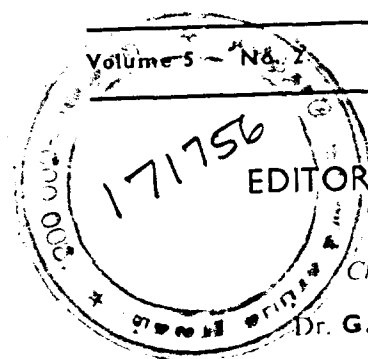
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CONTENTS

	PAGE
Infants—Why do they die?	3
The Gastro-Intestinal Tract and related structures in Obstetrics and Gynaecology— Dr. Vishnu Sarma, M.A. (Cantab.), M.D. (Cantab.), B.Chir., M.R.C.S. (Eng.), L.R.C.P. (Lond.), D.G.O. (Madras), Madras.	5
The Pathogenesis and Clinic of Immune Leucopenias— Dr. I. Szigeti, Budapest	17
Hypertension and Coronary Heart Disease	29
Protein Deficiency— Dr. Grace A. Goldsmith and Dr. Walter G. Unglaub, New Orleans	30
Carcinoma of the Gall Bladder— Y. V. Subba Rao, M.B., B.S., F.I.C.S., Guntur P. Venkateswara Rao, M.S., Vijayawada Dr. C. Sambasiva Rao, M.D., Guntur N. V. Reddy, M.S., Kurnool R. Anjaneyulu, L.C.P.S., Guntur	36
Burying Live Atoms is as expensive as Burying Dead Pharaohs— Ritchie Calder	41
Tuberculous Coxitis— Prof. P. Kornev	45
Legg-Perthes Disease in Siblings— Dr. Henry Burlington, M.D., Pennsylvania	48
Skin Manifestations in Parasitic Diseases— T. V. Venkatesan, M.B., B.S., F.A.I.M., F.A.C.A., F.C.C.P., F.D.S. (Lond.), Madurai	52
Dupuytren's Contracture— Dr. E. Doskach, Moscow, U.S.S.R.	58
The Application of Isotope Iodine-131 in Neurosurgical Practice— Dr. A. N. Ilitskaya	59
Dr. Grashchenkov joins WHO	60
Squibb's New Hormone is latest Steroid to show promise as an Anticancer Chemical	61
Untoward Reactions to Penicillin	64
Book Reviews	72

SURGICAL & MEDICAL NEWS

JANUARY 1959

INFANTS—WHY DO THEY DIE?

"I wonder what we should certify the cause of death as" said the House Surgeon examining a new born baby in the ward. "Why not put the cause down as asphyxia?" suggested his friend. This casual attitude towards certification of death of infants is to be deplored. But in our present circumstances it is very difficult to make much headway unless we can undertake an autopsy before we certify death. The neonatal mortality in our country is high. Because we cannot obtain autopsies or because we do not have either the time or energy to take that extra bit of trouble to persuade relatives to allow an autopsy to be conducted, we are inclined to take a light hearted attitude when we put down the cause for a child's death. Yet surely every child which dies must have died owing to some cause and in a great number of cases this may be demonstrable by an accurate and thorough post-mortem examination.

In Western countries certification of infant deaths are taken more seriously. Not so long ago our country had the privilege of a visit from that great American authority on the pathology of the fetus and the new born, Edith L. Potter, Associate Professor of Pathology, Department of Obstetrics and Gynaecology, The University of Chicago. In the preamble to her magnificent book "Pathology of the Fetus and the New Born" she writes "The aim of the pathologist is to promote the well-being of the living by any means at his disposal; and one of the avenues of approach is a study of the dead. The death of a fetus or infant is even yet often taken as "an act of God," regrettable but unexplainable, and dismissed as unavoidable. Every time a sperm cell and ovum unite a new being is created which is alive and which will continue to live unless its death is brought about by some specific condition. What the lethal factors are is to some extent still unknown, especially in the very young fetus, but our knowledge is being increased constantly and this is being reflected in the decreasing still-birth and infant mortality rates."

"In addition to the ultimate aim of the pathologist, of immediate practical importance is the demonstration to the attending physician of the pathologic changes found in any fetus or infant who fails to survive and the correlation of these findings with the symptoms observed during life. When symptoms can be recognized as associated with specific pathologic processes a great stride has been made toward their prevention and cure."

What she has to say is of such importance and of such great concern to us in our own country that it is worthwhile quoting still further from her preface.

"The pathology of the fetus and young infant has until recently been greatly neglected. The pathologic changes that occur during the infant's brief life are often meager and overlooked by the in-experienced investigator. He becomes discouraged and loses interest because he sees little and does not know how to interpret even the little that he may discover."

"This first year is unique in the life of any individual. During three fourths of it, existence is parasitic and the environment is very limited. The last one fourth is a period of transition and a time of adaptation to extrauterine conditions and an independent existence. Pathologic disturbances are much less varied than later and are largely a result of abnormal development, of trauma incurred in passage through the birth canal and of interference with oxygenation as a result either of disturbance in circulation through the cord or placenta before birth or of inadequate functioning of the lungs after birth. Infections are responsible for a fairly large number of deaths; in fact, for many more deaths in the new born period than in later infancy even though during the latter part of the first year after birth they are the cause of a much greater proportion of the total deaths."

The elaborate work of Dr. Edith. Potter illustrated by the most magnificent photographs collected over many years of patient work serves to demonstrate that our understanding of the cause of neonatal deaths can be advanced to a significant extent. This has great bearing on the practice of Obstetrics. It is the object of this brief editorial to urge all practitioners particularly in teaching institutions to see that as far as possible no cause for an infant's death is certified without adequate scientific evidence. Such evidence can be obtained only by a pathologist.

It is a matter for deep regret that we should have to certify the cause for an infant's death without a true understanding of the cause. We should endeavour to procure autopsy studies in each case. If only we were to submit infants to a post-mortem study we shall find the precise cause in many cases. Congenital abnormalities, disorders of the circulatory system, atelectasis of the lungs, inhalational pneumonias and last but not least trauma due to spontaneous birth or to instrumental deliveries may all to be found. We should not satisfy our conscience easily by merely putting down the cause as 'asphyxia' or 'intracranial hæmorrhage' or whatever may occur to us at the spur of the moment for each instance of a death, without evidence. Unless we can develop a scientific attitude in this matter we cannot hope to better our standard of Obstetrics as well as our knowledge of and the care of the new born child.

VASOREACTIONS IN POTENTIATED ANÆSTHESIA AND IN HYPOTHERMIA

The hypertensive action of adrenalin and the hypotensive action of acetylcholine are averted by "lytic cocktail" used for the purpose of potentiated anæsthesia. It was tempting to inquire into the question how far the adrenalin-blocking properties of chlorpromazine affect the splanchnic vascular area so essential in the regulation of blood pressure. Whether during potentiated anæsthesia the blood vessels suffer any change in their responsiveness, whether the direct effect of pitressin and bariumchloride on the smooth musculature of the veins is modified, presented further problems for investigation. Applying their method based on that of Chambers and Zweifach, authors studied the meso-appendix veins in 139 rats. They found that in potentiated anæsthesia (Largactil-Phenergan-Narconumal) no vasoconstriction was brought about by adrenalin and noradrenalin, while the efficiency of Glandutrin and bariumchloride remained unaffected. In hypothermia vaso-activity showed no decrease, even at rectal temperatures of 25°C. Judged by blood pressure responses, other vascular areas of the rat behave in the same manner. Complementary studies of the retinal vessels of cats corroborated the observations made on rats, but here the inhibitive effect of chlorpromazine on noradrenalin was less marked. This behaviour of vasoreaction would seem to confirm the slowness of the amount of energy consumed by vasoconstriction and vasodilation.

The Gastro-Intestinal Tract and related structures in Obstetrics and Gynaecology

By DR. VISHNU SARMA

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(This is the First Part of a series. The next will follow—EDITOR)

THE gastro-intestinal tract deals with the nutrition of the body. Food is ingested and it is acted upon by various enzyme containing secretions so that it is broken down into substances which can be absorbed. Material which cannot be absorbed is then cast out. By gastro-enterology is meant a study of diseases both of function and of structure affecting the gastro-intestinal tract. The territory covered by this speciality is a most extensive one and starts from the lips and includes the whole length of the alimentary tract and ends finally in the anus.

Because of the proximity of the genital tract to the intestinal tract in the pelvis there is a great deal of overlap in the frontier between the specialities of obstetrics and gynaecology on the one hand and gastro-enterology on the other. It has come to be widely accepted that a good obstetrician and gynaecologist should possess a sound knowledge both of the principles and practice of physic as well as of surgery. Without a wide knowledge of both these fields, his practice of the art will be imperfect. Indeed, a great master of midwifery, William Smellie (1697—1763) wrote "Those who intend to practise midwifery, ought, first of all, to make themselves masters of anatomy and acquire a competent knowledge in surgery and physic, because of their connections with the obstetric art, if not always, at least in many cases".

This article is a modest endeavour on the part of the author to map out those regions of overlap between the specialities of obstetrics and gynaecology and gastro-enterology. This account is not comprehensive and for all I know several important diseases may have been inadvertently omitted. The material for what has been said here has been gleaned from a great variety of obstetric books and journals many of them recovered from dusty shelves in the more remote

corners of libraries. Against this background I have superimposed observations visual, photographic and otherwise made on clinical material at the Govt. Women and Children's Hospital, Egmore, Madras, to amplify the text of this article. I have also made use of suitable specimens from the Giffard School Museum and X-rays from the radiology department of the hospital.

A tremendous volume of clinical material, much of it unharnessed cascades continuously like some turbulent mountain stream. I have tapped only a minute fraction of this. Were all this to be accurately recorded, substantiated with illustrations, drawings, X-ray reproductions, clinical photographs and photomicrographs and integrated at each stage surely it will be a veritable treasure house of knowledge to which all obstetricians and gynaecologists throughout the world will undoubtedly turn.

The term, "gastro-enterological tract and related structures" includes arbitrarily, the following:—

- | | |
|------------------------------|--|
| 1. Mouth | 12. Colon |
| 2. Lips | 13. Appendix |
| 3. Tongue | 14. Rectum |
| 4. Teeth and gums | 15. Anus |
| 5. Palate and uvula | 16. Liver |
| 6. Salivary glands and ducts | 17. Gall-bladder and bile passages |
| 7. Pharynx | 18. Pancreas |
| 8. Adenoids and tonsils | 19. Abdomen |
| 9. Oesophagus | 20. Peritoneum |
| 10. Stomach | 21. Portal, hepatic and mesenteric vessels |
| 11. Intestine | |

Almost all these structures bear a relationship to the female genital organs. This relationship is at times intimate but at other times remote. The relationship may be direct or indirect. Even when the connection

is removed its possibility should be borne in mind in the differential diagnosis of gynaecological diseases. It is only by increasing our knowledge in this respect that we can improve our practice. If one may step aside and view things from the general perspective of a biologist we can appreciate that the genital tract cannot exist unless the gastro-enterological tract performs its functions by nourishing the body. Diseases of the gastro-enterological tract may affect genital function. Sometime it gives rise to structural disturbances. In its turn the gastro-intestinal tract is influenced by the normal function of the genital tract as well as by the hormonal changes which pregnancy produces. Both these structures are ultimately influenced by higher centres and by the psyche. Functional disturbances of the mind sometimes produce gastric disturbances as well as those in the genital tract.

Gastro-enterological symptoms are not uncommon in gynaecological lesions as well as in obstetric conditions.

In the past writers have attempted to consider gastro-intestinal disturbances which result from uterine disease. So this account does not lay claim to great originality. The object has been to review the whole field because, sometimes, it does enhance our sense of perspective to see things as a whole. The only originality I may claim is for having assembled the material, taken several photographs and micro-photographs, X-ray photo-reductions, selected suitable pictures and for having drawn the illustrations myself to amplify the text.

1. MOUTH

There appears to be some extraordinary relationship between the mouth and the vulva. Both are erogenous zones; both are subject to cyclical ulcerations in relation to menstruation. Both are common sites for thrush infection; both show changes in conditions of nutritional deficiency, such as anaemia and ariboflavinosis. (Fig. 1). Dietary deficiencies are so common in India that angular stomatitis is by no means an uncommon condition in a significant proportion of patients who come to a hospital for women's diseases. It is a part of the general care of a patient to improve her nutritional status before subjecting her to major gynaecological procedures. Although buccal cancer is a common type of malignant disease in this part of the world it is not generally encountered as a



Fig. 1
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)
Angular stomatitis and glossitis are characteristic of deficiency disease. The correction of the nutritional status of a patient is an important part of general treatment. This patient was a 17 year old primigravida.

co-existing lesion in a patient who consults an obstetrician or gynaecologist.

2. LIPS



Fig. 2
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)
This 17 year old patient, pregnant for the first time showed both cheilitis and angular stomatitis. No cause was discovered. She was delivered normally and had an uneventful puerperium. There was some response to treatment.

From time to time cheilitis is encountered (Fig. 2). Acute cheilitis is usually associated with stomatitis. Herpes stomatitis sometimes affects both the lips and the external genitalia. A female patient sometimes develops an exfoliative cheilitis due to the use of cosmetics. The lesions of spirochætal infections may

be obvious only on the lips. It should be remembered that the portal of entry is usually by way of the external genital organs, at sexual congress.

3. TONGUE



Fig. 3
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)
This twenty year old primigravida was admitted to the hospital having had several eclamptic fits outside. This photograph illustrates how the tongue may be severely injured during a convulsion unless preventive measures are taken.

A dry furred tongue is common in pelvic infections. Apathous ulcerations sometimes occur both on the tongue as well as on the vulva. Anaemia may produce glossitis. The syndrome of anaemia, constipation and vaginal discharge is a well-known one. The correction of nutritional deficiency and attention to the bowels quite often clears up an intractable and persistent vaginal discharge. The tongue is liable to injury during an eclamptic convulsion (Fig. 3). Occasionally the lesions of syphilis may be seen on the tongue, but this is not generally of help in the diagnosis of genital infection by the spirochæte.

4. TEETH AND GUMS

There is a saying that "a woman loses a tooth for every child she bears". The relation between diseases of the teeth and the reproductive system has been known since the days of Hippocrates (460 B. C.). Septic teeth may act as a nidus of infection. Like other keratinised mucous membranes of the body, the gums soften during pregnancy, lose their surface keratin and are readily traumatized. Gingivitis during pregnancy may take different forms (Fig. 4). The margin of the gums becomes inflamed and œdematous



Fig. 4
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)
This young woman photographed in the antenatal clinic shows gingivitis which is common. Attention to the teeth and gums is advised in the prenatal period.

and take on a dull red colour. The gums become hyperplastic and bleed profusely when probed the "Raspberry red gum of Miller". Sometimes gingivitis takes the form of a generalized hypertrophy and the gums which are swollen are often of a bright red colour. The gum papillæ become hypertrophied. This is termed 'hypertrophic gingivitis of pregnancy'. In some rare instances large proliferations form in localized areas. These masses of hyper-plastic tissue protrude as a tumour which may be either sessile or pedunculated. This form is termed a "pregnancy tumour" (Blum 1931) (Fig. 5). The gingival tumour of pregnancy usually occurs as a single lesion with a



Fig. 5
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)
This 25 year old 2nd para 3rd gravida has a sessile red pedunculated mass which caused mechanical discomfort and irritation. It bled when the patient cleansed her teeth. She had a normal delivery.

predilection for the upper incisor region. It is purplish in colour with a red border and may ulcerate. It seldom exceeds 2 c. m. in size and occurs usually between the 3rd and 5th month of pregnancy and persists in the puerperium and enlarges in the next pregnancy. Histologically it is made up of a mass covered with squamous epithelium with a stroma similar to fibro-angioma. Surgical excision is the treatment of choice for these tumours. That gingivitis may have a hormonal factor in its aetiology is suggested by the occurrence of hyper-trophic gingivitis in association with hormonal dystrophy occurring at the time of puberty.

5. THE PALATE AND UVULA

These structures may become involved in lesions which affect the oral cavity.

6. SALIVARY GLANDS AND DUCTS



Fig. 6

(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

This patient had an abortion which became septic. She had a severe pelvic inflammation with peritonitis which responded to treatment. During her lengthy stay in hospital she developed bilateral parotitis.

Excessive salivation sometimes complicates pregnancy. This is called ptyalism. Although this is usually mild, excessive saliva (as much as 1000 to 1600 ml. daily) may be produced in severe cases. The aetiology of this condition is unknown. It is believed to be a type of pregnancy toxæmia.

Parotitis may complicate mumps. In mumps the gonads may be affected. Although orchitis is well-known in the male it is believed that a corresponding oophoritis may occur in the female and cause sterility. Parotitis may occur as a complication following gynaecological conditions such as septic abortion with peritonitis (Fig. 6).

That parotitis may occur after operations on the female genital organs has been known since ancient times though W. Goodell (1884) believed it was due to a relationship between the sexual organs and the cervical and salivary glands.

In the post-operative care of patients oral attention helps to reduce if not prevent the incidence of parotitis as a complication.

7. PHARYNX

Disorders of the pharynx give rise to difficulty in swallowing. Dysphagia is a feature of Plummer Vinson syndrome (iron deficiency anæmia) which occurs almost exclusively in women.

8. ADENOIDS AND TONSILS

Infected tonsils and adenoids sometimes act as distant portals of entry for organisms which give rise to pelvic sepsis. It is a wise precaution that such infections be cleared up before embarking on elective operations in gynaecology. The hazards of administering inhalational anaesthesia to such patients are too obvious to require mention.

9. ŒSOPHAGUS

This structure may be considered along with the stomach. It is affected by the general loss of tone of involuntary muscles during pregnancy. The gastro-œsophageal mechanism may be disturbed in pregnancy. The laxity of the sphincter may be a cause of reflex regurgitation of gastric fluid which may manifest itself as heart burn. Heart burn has nothing to do

with the composition of the gastric juice. It is essentially a neuro-muscular disturbance consequent upon diminished gastric motility. The latter is a common feature of pregnancy. A reverse of the peristaltic waves allow stomach contents to regurgitate into the œsophagus. The irritation of the œsophageal mucosa causes heart burn. Perhaps this might be an explanation for the more frequent incidence of œsophageal stricture in the female.

The œsophagus is compressed in mitral heart disease by left atrial enlargement which may be precipitated by pregnancy. The indentation into the œsophagus may be demonstrated by a Barium swallow (Fig. 7)



Fig. 7

(Courtesy: The Govt. R.S.R.M. Hospital, Madras) This barium meal swallow of a patient, whose pregnancy was complicated by heart disease demonstrates admirably indentation of the œsophagus due to right atrial enlargement of the heart.

10. STOMACH

That there is a close relationship between disorders of the stomach and the genital tract has been recognized since antiquity. Soranus of Ephesus (2nd Century A. D.) is believed to have stated "When the uterus is diseased it causes the stomach and membranes to suffer in sympathy." The progressively growing pregnant uterus takes up more and more space in the abdominal cavity and displaces the stomach and

intestines. The extent of mechanical displacement has been radiologically studied (Williams 1941). The stomach which is normally vertical in position is slowly pushed upwards and to the left beneath the diaphragm and it comes to occupy a horizontal position. In addition to mechanical displacement, functional alterations take place in the gastro-intestinal tract. The tone of the stomach tends to decrease in pregnancy. The stomach takes long to empty and this fact should be borne in mind particularly when the patient is given an anaesthetic. The hazard of inhalational pneumonia due to aspiration of the gastric contents into the respiratory tract is one that should constantly be borne in mind. The decrease in motility may account for various symptoms such as nausea, heart burn, flatulence and vomiting.

It would appear that increased intra-abdominal pressure during pregnancy may encourage the formation of a hiatus hernia in a patient who has weakness in the hiatal region. Such hernias occur late in pregnancy but sometime slight uterine enlargement coupled with nausea, vomiting and straining due to constipation cause herniation as early as the fourth month. They often disappear after delivery.

There is a diminution in acidity and a definite fall in free as well as total hydrochloric acid during pregnancy. Hypochlorhydria which is most obvious between the third and sixth months interferes with the absorption of iron thus leading to anæmia.

"The majority of pregnant women have a significant reduction in the free hydrochloric acid and total acidity of their gastric juice, accompanied by a parallel reduction in ferment content and hydrogen-ion activity. While wide individual variations occurred, there was, on the average, a 50% decline in maximum free acidity from the third to the sixth month of gestation with a rise in the last month to a level observed in the third month. According to these observers the gastric juice, after delivery, contains three times as much free acid as during the sixth month and double the quantity secreted during the major portion of pregnancy (Strauss & Castle 1932)". These findings are confirmed by recent observations (Way 1945).

Different types of psychological dyspepsias and the development of tastes and other whimsical fancies for various types of food (pica) is so common a feature of pregnancy that it is taken to be almost a normal event. So, too, is early morning vomiting of pregnancy.

When vomiting is severe and jeopardises the welfare of the patient giving rise to severe metabolic disturbances it is termed hyperemesis gravidarum. Severe and protracted vomiting is a notable feature of this ailment which is considered to be a form of pregnancy toxæmia. Sometimes vomiting in early pregnancy is associated with the presence of vesicular mole. It is a well known fact that patients often tend to vomit during active labour when the cervix is dilating.

Because there is a tendency for hypo-acidity peptic ulceration does not commonly complicate pregnancy. Indeed pregnancy is believed to exercise a favourable effect on the course of peptic ulcer (Clark 1953). Peptic ulcer symptoms are relieved in 90% of pregnancies and in most of these remissions occur early in pregnancy and persist to term. After parturition, particularly, during the first six months ulcer symptoms are likely to recur. This is probably due to the decrease in the tone of involuntary muscles which leads to relaxation of the stomach and pylorus as well as reduction in acid secretion. Occasionally, however, the symptoms of peptic ulcer may be aggravated and the patient may complain of dyspepsia, nausea, vomiting and epigastric pain.

In patients with toxæmia the ulcer symptoms do not appear to be materially relieved during pregnancy (Langmade, 1946).

Complications such as perforation or massive hæmorrhage have been a cause of death in many patients who have otherwise recovered from pre-eclamptic toxæmia or eclampsia. Any patient with toxæmia who complains of epigastric pain should be observed for perforation and hæmorrhage from an acute peptic ulcer.

It should be borne in mind that the diagnosis of peptic ulceration should not be overlooked merely because the symptoms of nausea, heart-burn and indigestion are common in pregnancy. A peptic ulcer may occasionally perforate or give rise to other complications. Perforation of a peptic ulcer in pregnancy has to be differentiated from other acute abdominal conditions.

In the non-pregnant patient achlorhydria is sometimes associated with pruritus vulvæ (Jeffcoate 1949). The lesions improve considerably when a mixture containing dilute hydrochloric acid is prescribed.

Dyspeptic symptoms may sometimes arise from direct pressure on the stomach from lesions of the genital tract, such as large fibromyomas or ovarian cysts. (Fig. 8)



Fig. 8
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

This x-ray is that of a 50 year old woman with multiple fibroids. A large tumour is rising out of the pelvis. See how the colon is displaced. The soft tissue tumour mass represented by the white opacity in the picture is ringed by gas shadows of the colon. A fibromyoma with hyaline change was seen at operation. The tumour rose 3" above the umbilicus. Venous engorgement of the broad ligament veins was present.

In 1896 Krukenberg described a peculiar type of ovarian tumour which was secondary to a carcinoma arising from the stomach or other parts of the gastrointestinal tract or rarely even from the breast. He called it 'fibrosarcoma muco-cellulare carcinomatodes'.

The tumour in the abdomen is often inconspicuous and therefore overlooked by the clinician. The primary growth in the pelvis is generally the presenting feature of the disease and overshadows the gastric lesion. Krukenberg tumours (Fig. 9) are always bilateral, moderate in size, solid, lobulated and smooth and preserve the external appearance of enlarged ovaries. In one third of the cases ascites is

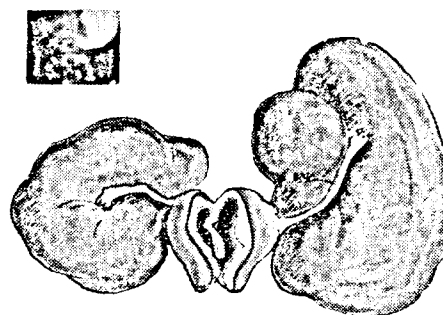


Fig. 9
(Courtesy: The Govt. Stanley Hospital, Madras)
This drawing shows some of the characteristics of bilateral Krukenberg tumours. Careful investigation often demonstrates a pyloric cancer, shown in the x-ray (inset) as a filling defect.

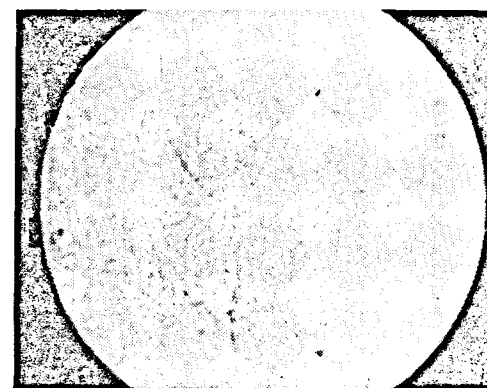


Fig. 10
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)
This histo-photograph taken by the author demonstrates the characteristic histological appearances of a Krukenberg tumour of the ovary.

also present. The histological features of Krukenberg tumours are quite unmistakable (Fig. 10). In the fibromatous ovarian stroma, there lie scattered typical signet cells with a large ovoid or spherical shape and distended by mucin which pushes the nucleus to one pole of the cell flattening it out against the cell membrane at that spot (Shaw 1926). It is thought that the carcinomatous cells from the primary growth in the stomach reach the ovaries by means of retrograde peritoneal lymphatic permeation rather than across the peritoneum or through the blood stream. A good gynaecologist whenever he is confronted with solid bilateral ovarian tumours at a laparotomy will invariably palpate the stomach and pylorus and the

accessible portions of the intestinal tract to exclude the presence of a neoplasm.

From time to time there are reports in the literature, of curiosities. Fibromyomas sometimes arise from the stomach. In a discussion relating to certain gastrointestinal diseases which might be mistaken for gynaecological lesions, held at the Royal Society of Medicine, London, the author has heard of a myxosarcoma of the stomach which was mistaken for an ovarian tumour (Proc. Roy. Soc. Med. 1953).



Fig. 11
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)
This 40 year old patient presented with amenorrhoea and an abdominal swelling, both of 8 months duration. She complained in addition of anorexia. Radiological barium meal studies of the stomach showed the presence of an advanced gastric carcinoma and the pelvic masses represented bilateral solid ovarian tumours, the result of metastases from the gastric cancer.

Other than Krukenberg tumours gastric carcinoma may give rise to deposits in the ovaries (Fig. 11). In cases where the abdomen has been opened up, the gynaecologist may find it necessary to perform a palliative gastro-enterostomy. (Fig. 12).

Acute dilatation of the stomach may complicate the pre-operative period. The gynaecological surgeon therefore needs to know how to manage this serious condition.

11. INTESTINE

The growing uterus may displace the small intestines but no harm results unless adhesions are present in the abdomen. (Fig. 13). Obstruction to the small intestines or strangulation by bands is uncommon in early pregnancy but if it occurs at all, it will be encountered in the last few weeks.

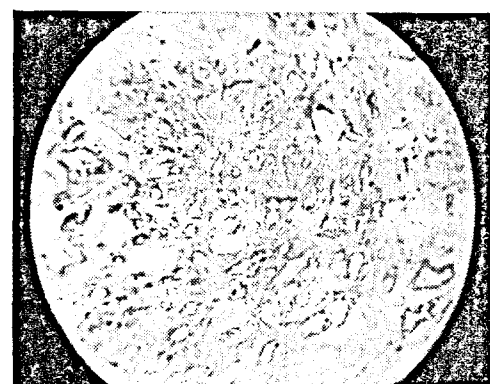


Fig. 12

(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

A 40 year old patient was admitted with the complaint of abdominal pain and vomiting of 9 months duration. The pain was aggravated by taking food and was relieved by vomiting. The vomit was not bloody or blood stained. She was often troubled with constipation. The periods were normal. She was extremely emaciated and dehydrated and could hardly retain even bits of bread. The liver was enlarged and tender and had a sharp margin. Vaginal examination showed the presence of a hard mass in the pelvis which could be readily felt through the right fornix of the vagina. A barium meal showed a hyper-peristaltic dilated stomach with a filling defect at the pylorus. In view of the gastric lesion and pelvic masses the possibility of Kruckenburg tumour was entertained. After the general condition of the patient was improved, a laparotomy confirmed that a pyloric growth was present. The pelvis was filled by a hard tumour mass. A biopsy obtained from the tumour showed the structure of an adeno-carcinoma but there was no evidence of the typical Kruckenburg pattern. A palliative gastro-enterostomy was carried out.

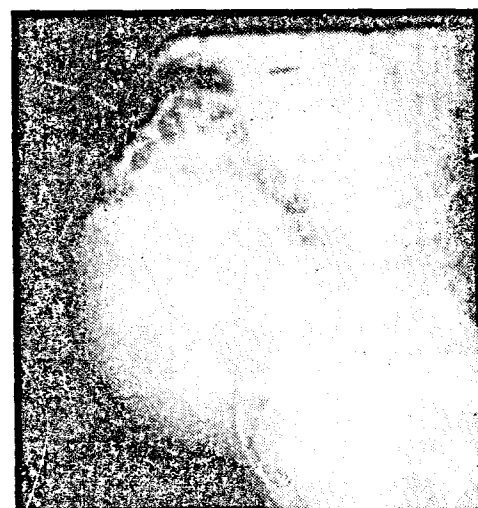


Fig. 13

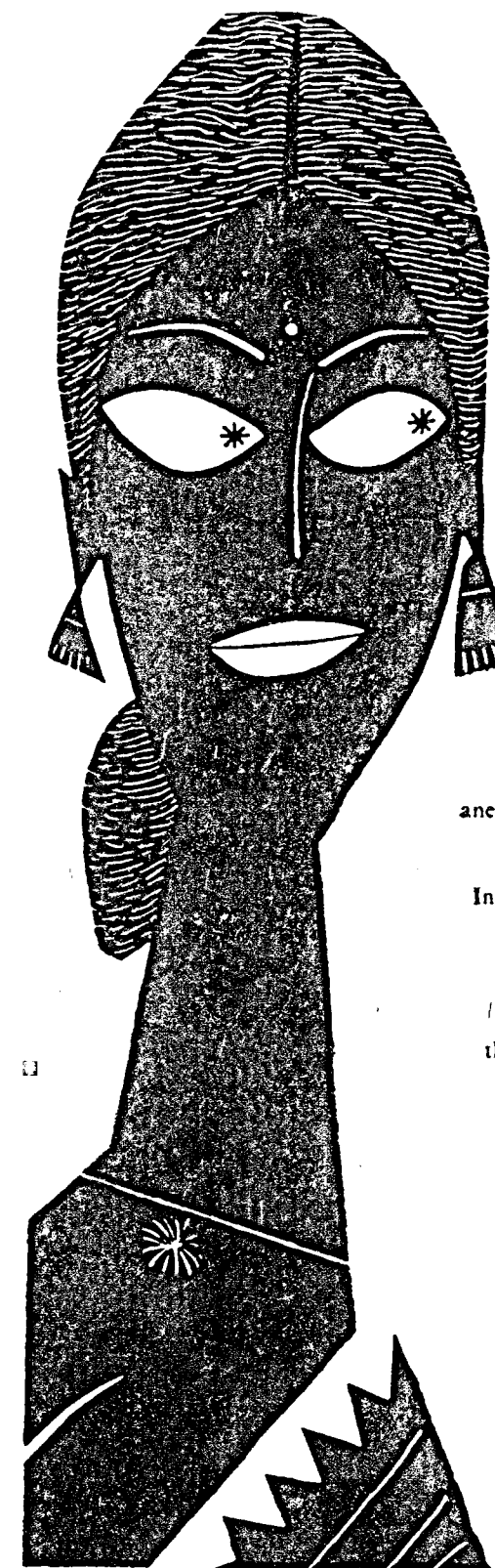
(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

This soft tissue x-ray of a pregnant abdomen shows clearly how the intestines are displaced by the growing uterus. Incidentally the placenta is situated on the anterior uterine wall.

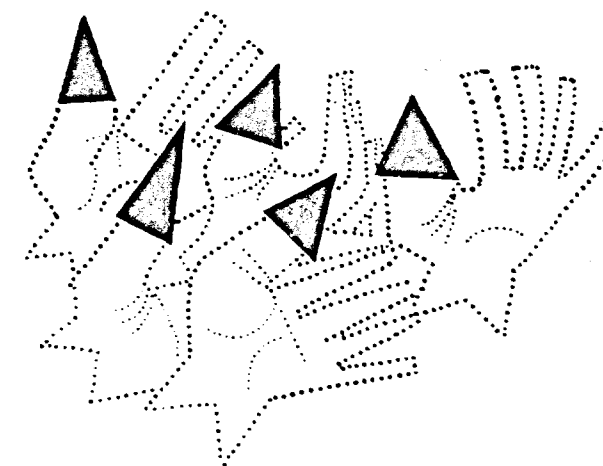
Intestinal obstruction in pregnancy is a rare but serious complication. The difficulty of early diagnosis in part accounts for the high maternal mortality rate of 40 — 60% reported by Wangenstein (1945) but probably much less today. When abdominal pain of obscure origin occurs in a pregnant woman intestinal obstruction should be considered. If other evidence is present laparotomy may be justifiably performed. (Fig. 14).

Parasitic worms may block the intestines. In tropical countries this cause of intestinal colic should be kept in mind.

True ileus of the intestine may occur in severe infections of the genital tract in which there is peritonitis. Ileus may also occur as a post-operative complication following operations such as myomectomy, removal of a twisted ovarian cyst, the removal of a tube for a ruptured ectopic gestation, or a laparotomy for endometriosis. (Fig. 15). Occasionally conditions such as gangrene, trauma, volvulus, obstruction due to adhesions and various diseases of the intestine may create problems which the gynaecologist has to diagnose and resolve. A large pelvic mass which may simulate a lobulated ovarian cyst may turn out at a laparotomy to be loops of adherent indurated gangrenous intestines caught in a volvulus or by an occluding adhesion. (Wharton 1947).



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Fig. 14

(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

A 30 year old patient pregnant for the fifth time was admitted to the hospital complaining of abdominal pain, distension and vomiting. She was 9 months advanced in her pregnancy. The abdomen was distended and a ladder pattern was observed. The uterus was pushed towards the right side. Excessive intestinal sounds were audible. The diagnosis of intestinal obstruction was made and a laparotomy was performed. There was an obstruction to the small intestine at the jejuno-ileal junction, as a result of an adhesion band. The photographs show distension of the abdomen externally as well as distended loops of bowel outside. A Caesarian section was performed and a deeply asphyxiated child was delivered. The adhesion band was divided and the stenosed portion of the bowel was repaired and a side to side anastomosis was done. The patient survived only for three days after the operation.

The "unskilled criminal abortionist may perforate the uterus and draw out a loop of bowel. Regional ileitis (Crohn's disease) (Fig. 16) and other lesions of the abdomen (Fig. 17) sometimes gives rise to a tumour in the right iliac fossa which may be mistaken for pelvic gynaecological disease. (Fig. 18).

Genital endometriosis may sometimes affect the



Fig. 15

(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

Paralytic ileus in peritonitis complicating an operation for a twisted ovarian cyst in a 33 year old woman. Note how the diaphragm is raised on the left. Gas is present in the coils of ileum and large intestines.

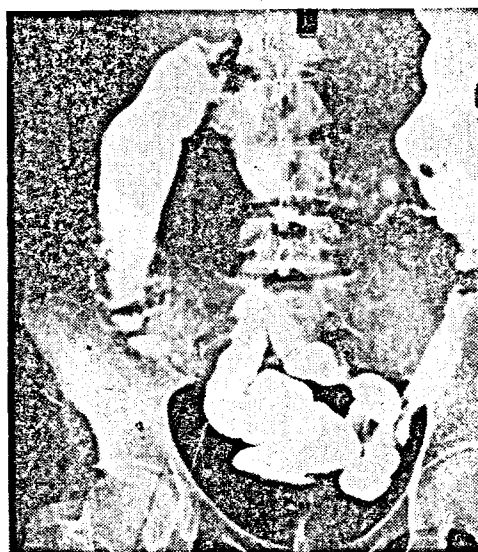


Fig. 16

(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

This is a barium enema of a 32-year-old patient who complained of abdominal pain. The appearance is in favour of chronic ulcerative colitis. The descending and sigmoid colon shows the ribbon like pattern with loss of haustration. The colon is narrowed in places.



Fig. 17

(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

The intestine in pelvic tuberculosis.

A 30 year old woman who complained of abdominal pain was found on examination to have pelvic masses. A nodular mass was felt in the right iliac fossa and a diagnosis of Ileocaecal tuberculosis was made and this was confirmed by finding the characteristic intestinal filling defects in the barium meal study. A chest x-ray was taken. It showed active pulmonary tuberculosis. In the differential diagnosis of abdominal tumours one has to consider tuberculous lesions. In this case the right sided Ileocaecal tuberculoma may have been easily mistaken by a casual examiner for a mass arising from the ovary.

intestines and give rise to obstructive lesions. The small bowel may occasionally be involved when there is extensive spread of a carcinoma arising from the body of the uterus. Rare conditions have been reported such as a neurofibroma or a sarcoma of the small intestine which was mistaken either for a fibroid or for an ovarian cyst.

The small bowel has been used in various plastic procedures in the past for the creation of an artificial vagina. In Schubert's method the lower loop of ileum is resected and the continuity of the intestinal tract restored by end to end anastomosis. The isolated loop drawing its blood supply from the mesentery which has been left undamaged is then brought to a tunnel previously prepared in the perineum. These intestinal transplant operations have been modified,



Fig. 18

(Courtesy: The Govt. Women & Children's Hospital, Egmore, Madras)

A 40 year old patient was thought to be harbouring a malignant growth in the abdomen. A barium meal was done. After five and half hours, barium was found in the terminal ileum and caecum. The radiological appearance was in favour of a hard pelvic mass displacing the small intestines.

but so great has been the mortality and so unsatisfactory the results, of these difficult operations, that they all have been abandoned in favour of more modern plastic procedures such as the one practised by Sir Archibald Mackintosh of St. Bartholomew's Hospital, London.

A loop of ileum is sometimes used as a receptacle into which ureters are transplanted in certain cases of vesico-vaginal fistulae for which surgery has failed to effect a cure. Although a formidable surgical undertaking, the dangers of metabolic upsets associated with implantation of ureters into the sigmoid are considerably diminished.

The intestine may be injured during gynaecological operations particularly when adhesions have to be divided.

(To be continued)

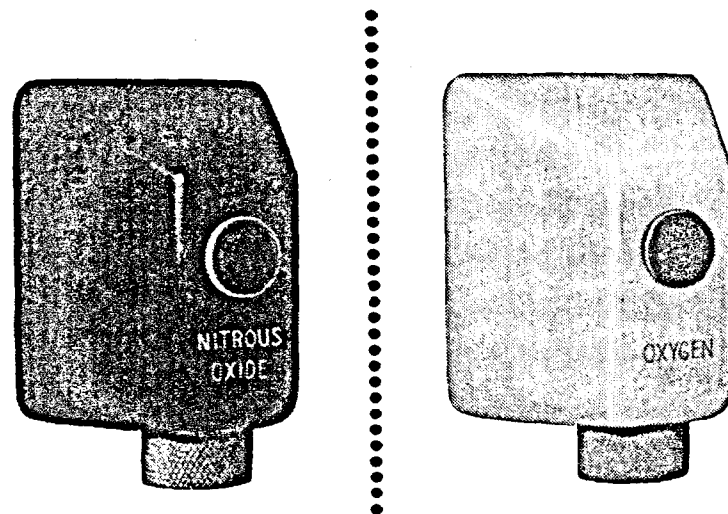
The Pathogenesis and Clinic of Immune Leucopenias

By DR. I. SZIGETI

(Third Dept. of Medicine, Medical University of Budapest)

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DURING the past 50 years the recognition of diseases originating from an immuno-biological mechanism has brought great advance also in the field of diseases of the blood, first of all in that of acquired hæmolytic anæmias and thrombopenias; research into the immuno-mechanism has gained great significance, particularly in the elucidation of pathogenesis. More recently, knowledge concerning the pathogenesis and clinical aspects of leucopenia and agranulocytosis (in the following i. l. and i. agran.) has been considerably widened by allergy research, by the advance in immunology and serology. Studies on the autosensitisation mechanism of acquired hæmolytic anemias, thrombopenias, and leucopenias have brought many new results in the diagnosis and therapy of the diseases of the blood.

The role of allergic processes in the pathogenesis of leucopenias has been known since Pirquet and Schick published their report in 1905 (2). Leucopenia developing in connection with the antigen-antibody reaction was described in 1934 by Vaughan (3) as the characteristic of allergic diseases. Allergic agranulocytosis was first described by Schultz in 1922, then Bock, Heilmeyer and Rohr (4) described it. In 1952 Moeschlin and Wagner elucidated the mechanism of agranulocytosis and leucopenia due to drug allergy (5a). Shortly after the ingestion of the drug antileucocytic agglutinins were demonstrated in the serum of sensitized subjects.

An antibody-mechanism has been for long suspected of being involved in the pathomechanism of leucopenias of other origin, in which the role of exogenic allergens could be excluded. Leucopenia could be induced in normal subjects by transfusion and the leucocytic agglutinins were demonstrated in vitro, too.

The recognition and the elucidation of the pathogenesis of acquired immuno-hæmolytic anemias preceded by more than half a century etiological research into the pathological conditions occurring in the leucocytic system, and into immunoleucopenias. This is not so astonishing if we realize that the clinical incidence of anemia is much higher and that anemias are much easier to recognize than leucopenia and thrombopenia.

The basis for elucidation of the pathogenesis of i. l. has been furnished by the *clinical* experiments concerned with damage to and destruction of the leucocytic system. In 1925 Franck reported (6) that aleukia may be due to the destructive action of some toxic material on the mature leucocytes in the circulation and in the bone marrow. Normal leucocytes introduced by transfusion into the patient disappeared quickly from the circulation; incubation at 37°C of the patient's plasma with normal leucocytes, or with leucocytes from individuals with leukosis or infectious leucocytosis resulted within hours in a destruction of from 35 to 50 per cent. of the leucocytes. Surviving leucocytes of the bone marrow were destroyed at a similar rate, whereas the stem-cells and the immature myelocytes showed very little damage (6). In 1927 Lindstrom used leucotoxic or leucolytic serum in the treatment of myeloid leucemia and found that the number of leucocytes decreased in some cases (7). Later, leucolysins were found to be present in certain granulocytopenias (8). More recently, Bracco, Curti, and Masera (9) produced leucopenia in the blood and bone marrow by the use of anti-bone marrow serum, with a destruction of mature elements, a hyperplasia of the immature elements in the bone marrow, and an extreme shift to the left. Their picture is in many respects similar to the immuno-leucopenia in man, which Moeschlin et al. (10) have reproduced in *guinea pigs* by the use of leucocyte antiserum. Before that Chew and Cajano (11) had found a retention of the leucocytes in the lungs after their disappearance from the circulation as a result of an injection of anti-leucocytic serum. By the transfusion of leucocytes labelled P³² and by cross transfusion other authors (12) have demonstrated that the agglutinated leucocytes are destroyed in the lung capillaries and do not re-enter the circulation. The same phenomenon is observable in human i. l. and i. agran. (13) The intracardiac injection of serum caused anaphylactic shock symptoms, whereas the subcutaneous injection employed by the proper techniques, caused lasting leucopenia. Moeschlin et al. (14) have succeeded in isolating the active principle of the anti-leucocytic serum by absorption on guinea pig leucocytes. Subsequently, the presence of anti-leucocytic agglutinins was proved by serological tests.

The i. leucopenias are divided into two main groups: (1) allergic leucopenia and agran., the principal representative of which is the pyrimidin-agranulocytosis of Moeschlin-Wagner; (2) leucopenia and agran. elicited by the *true antileucocytic antibodies*.

In the first case the allergic antibodies can be detected even in the untreated and in the inactivated serum, whereas the autoantibodies are demonstrable first of all, but of course not always, in the inactivated serum. The allergic antibodies agglutinate homologous and heterologous leucocytes, whereas the autoantibodies agglutinate the homologous leucocytes under certain conditions only, because in the overwhelming majority of cases blocking or inhibitory antibodies are present (15). The antibodies formed in the course of induction of sensitivity to drugs absorb into the surface of leucocytes. On re-introduction the drug, which has become a complete antigen, reacts with the antibody on the surface of the leucocytes and thus causes agglutination (16). The drug may act also as a complete antigen. In such case the antibody acts against the chemical substance and the antigen-antibody complex resulting from the immunological process will then

combine with the corpuscular elements of the blood, damaging them. It has been reported (17, 18) that the transfusion of blood from patients with idiopathic leucopenia and thrombopenia into normal subjects caused within hours the development of a transient thrombopenia and leucopenia in the latter. The leucopenic factor was present in the globulin fraction of plasma and first of all caused an agglutination and destruction of leucocytes circulating in the peripheral blood. Also in the case of drug-induced immune agranulocytosis an antigen-antibody complex appears in the blood shortly after the introduction of the responsible drug (chemical) and correspondingly it was possible to cause in vitro an agglutination of normal leucocytes with sera drawn at those points of time. The transfusion of blood shortly after the introduction of the allergen produces leucopenia in the control subjects. Subsequently, the serum loses the ability to agglutinate leucocytes, but regains it when the drug is admixed to serum in vitro.

In drug-agran., the substance responsible for the agglutination of leucocytes may be demonstrable within two to fifteen hours after appearance of the symptoms.

Later than that all attempts to demonstrate primary leucocytic agglutinins failed, even in the presence of the severest symptoms. In general, the bone marrow shows a shift to the left in granulopoiesis, and myelocytic or promyelocytic hyperplasia. Prolonged stress (as an effect of repeated or protracted antigen-antibody reaction) results in an exhaustion of the bone marrow, i. e. a failure to compensate the peripheral leucocyte loss. This condition is marked by hyperplasia, a shift to the left, the bone marrow may even become extremely poor in cells, empty, with an increase of reticulum, and secondary leucopenia may develop. In such cases anti-leucocytic agglutinins could not be demonstrated in the majority of instances on loading, despite the increased intensity of leucopenia.

To the other group of immuno-leucopenias belong the diseases associated with the formation of anti-leucocytic *auto-antibodies*. The auto-antibodies are specific antibodies directed against the corresponding antigen of the leucocytes.

Metschnikov (19) was the first to prove the antigenic character of leucocytes and it was later confirmed by several authors (20) that the plasma proteins, erythrocytes, leucocytes and blood platelets were of different antigenic properties, this difference being greater between the erythrocyte and platelet than between the leucocyte and platelet. Anti-leucocytic sera of high titre agglutinate erythrocytes, but after the exhaustion of haemolysins the anti-leucocytic effect remains unaffected. Wichels and Lange were the first to describe the group-specificity of leucocytes in the ABO group (21). This finding was confirmed later by other authors (22) by the use of cross agglutination and absorption techniques and more recently by Schmid and Moeschlin (23) by agglutination tests performed with compatible and incompatible plasma. Ballowitz (24) succeeded in demonstrating O antigen in leucocytes by the use of anti-O serum from a child with Fanconi anemia.

The species-specific and group-specific antigenic structures of leucocytes are equivalent with the A and B antigens of the blood group system. The question emerges whether there is also a specific leucocytic *group-antigen*. The answer is not yet clear. The more frequent occurrence of anti-leucocytic antibodies after repeated transfusions of blood of the same group seems to confirm the existence of such antigen. The difference between the leucocytic and lymphocytic antigen has also been demonstrated (25). So far, on

specific *isoantibodies* corresponding to the leucocytic antigen could be demonstrated in serum. On the other hand, incompatible immune-isoantibodies may appear in the blood after sensitisation due to transfusion or pregnancy. On transfusion of blood from such individuals into recipients with heterologous leucocytic antigen the latter develop transient granulocytopenia.

The mechanism, by which autosensitisation develops in the body is the following: in response to some external influence (physical, chemical noxa, bacterial, viral or protozoic infection, appearance of pathological globulins) or as a result of tissue destruction due to inflammation or tumour, the *protein structure* of the cells or tissues *suffers an alteration*. Even some plasma protein fractions may be altered in response to endogenous or exogenous toxins and may be converted into auto-antigens. By the auto-antigen the RES is stimulated into antibody production. The antibodies thus formed react with the autoantigen, either in vivo or in vitro. The autoantibodies, combining with the hapten (leucocyte), initiate the process in vivo and in vitro. This process has been denoted by the term auto-aggression (26), and is understood to mean damage to the body, breakdown or destruction of single cell systems.

Autosensitisation may be brought about by several mechanisms:

(1) Absorption of the virus to the respiratory epithelium and vascular endothelium has been proved by Ivanovics et al. (27). (2) According to Wiener (28) the other mechanism consists in the complex antibody to the antigen of the virus cell reacting with the blood cell elements. After incubating human and chicken erythrocytes with the viruses of influenza and Newcastle disease, antisera that could be produced in the rabbit or in the chicken agglutinated and lysed the normal and virus-treated blood cell elements. (3) Auto-antibody production may be induced by proliferation of e. g. tumour or reticulum, without changes in the structure of leucocytes. An example for this is Levine's (29) female patient with gastric cancer, who developed anti-T blood group antibodies, without incorporating the corresponding factor in her own blood cells. (4) The bacterium possessing Forssman antigen (for example the pneumococcus type III) or the human A-antigen may often be the initiator of auto-antibody production. It is known that in response to immunising stimuli (transfusion, bacterial, viral, protozoal,

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metazoal invasion, introduction of blood cell antigen as when an anti-A subject is immunized with A-antigen) the increase in the level of natural isoantibodies is accompanied by an increase in the incomplete auto-antibodies with wide heat-amplitude and avidity which sensitize the blood cell elements against the Coombs serum.

The significance of anti-A immunisation is very great; according to the investigations of British immunologists, in group-incompatible pregnancy or after treatment with heterologous serum, heterologous group-specific hæmolysins (18 per cent.) and agglutinins (48 per cent.) can be demonstrated by the indirect Coombs test (30). Thus incomplete antibodies appear in the serum, and, after the complete exhaustion of the natural isoantibodies, will sensitize the A-blood cells to the Coombs serum. From this it follows that in case universal donors within 3 months' time had received some serum injection or some vaccine, e. g. treatment with diphtheria toxoid, although their blood will be suitable for transfusion into a recipient of group O, it may cause some hæmatological damage in an A-group recipient because of the presence of incomplete antibodies. (5) The heteroagglutinins occurring in human and animal sera may also cause damage to blood cells. The sheep anti-erythrocyte agglutinins reacting at 37°C can be absorbed to staphylococcus, Bang and Proteus X_{19} bacilli, as well as to live trichinella larvæ, mature schistosomes and ascaris extract. This indicates that the hæmagglutinin formation of sheep serum is correlated with infection. The infecting organisms produce a blood group antigen similar to A_2 which immunizes the host. The Anti- A_2 antibody appears as an agglutinin of sheep red cells in infected man or animal. (6) Hetero-agglutinins may be formed also as a result of immunisation in infectious diseases, or after the ingestion of animal protein. After injection of normal or immune horse serum also such heteroagglutinins may be formed as absorb to homologous blood cells, too, in case the blood cells in question have the appropriate antigenic property. (7) In infectious granulomas, malignant neoplastic diseases pathological globulins, paraproteins may combine with the blood cell elements and, acting as antibody, may give rise to hæmagglutination, leucopenia, thrombocytopenia, pancytopenia (cirrhosis of the liver, chronic nephritis, amyloidosis, myeloma, rheumatoid arthritis, L. E. (disseminated), Felty's syndrome, polyarteritis nodosa). (8) Products and metabolites of bacteria, viruses, and protozoa may combine also with the lipoids and polysaccharides of

the body to form a complete antigen and the auto-antibodies produced, uniting with the antigen, may cause severe damage, for example to blood cell elements.

All these blood cell lesions, which are based on the antigen-antibody reaction, differ from the classic immune or allergic reactions in that both in vitro and in vivo certain conditions, *accessory factors* are required to cause damage to the cells, agglutination and lysis. Not infrequently auto-antibodies can be demonstrated in serum without the presence of development of clinical disease, such as hæmolytic anemia, agran. or thrombocytopenia. According to Dacie and Mollison (31) the autoantibodies must reach a certain concentration to be able to cause any serious damage to the cellular system or to make it susceptible to other kinds of noxæ. A lower antibody concentration in milder, or moderately severe cases causes only a sensitisation of blood cells, and some appropriate accessory factor, like stasis, trauma, increased complement concentration, elevated conglutinin level, or increased splenic activity is required to cause destruction of cells.

THE CLINICAL FORMS OF IMMUNOLEUCOPENIAS

(1) Acute agran., (2) chronic persistent, (3) chronic cyclic, (4) immunoleucopenias or i. agran. based on the L. E. phenomenon.

The clinical picture of the *agran. of Schulz* occupies a separate place. It resembles an infectious disease developing when the subject is apparently in the best of health. Drugs, chemicals, or most frequently infection only trigger off the process of auto-immunisation. The septic febrile condition with necrotic inflammation of the mouth develops only later, in the absence of systemic defense (32).

To this group belongs the leucopenia or agran. developing during or in the convalescence phase of viral pneumonia or of any bacterial pneumonia. In severe viral pneumonia (Moeschlin et al., 33) leucocyte agglutination develops with a very high titre (1:8000) and wide heat amplitude, clinically marked by severe hæmolytic anemia, leucopenia, and sometimes pancytopenia. The Coombs test, by both the direct and indirect method, is very strongly positive. The transfused compatible (group-identical) erythrocytes and leucocytes agglutinate immediately and disappear from the circulation. In a certain percentage of cases the antibodies, even without any treatment,

disappear from the blood within days. Therapeutic measures should be instituted only when the anemia and leucopenia are extreme or of long duration. On ACTH treatment hæmagglutination and hæmolysis cease, the erythrocyte and granulocyte counts return to normal. Parallel with this the cold agglutinin titre steeply decreases in the serum, then the cold agglutinins disappear altogether. After prolonged discontinuance of ACTH and cortisone treatment the cold agglutinin titre may rise again and the severe anemia and agran. may recur. Because of the tendency to relapse, ACTH and cortisone administration should be continued for weeks or months.

Hansen and Dameshek (34) studied the changes in blood proteins and in the hæmatological picture in chronic paraproteinæmic diseases during treatment with ACTH and cortisone. The first noticeable effect, marked decrease of the previously increased gamma globulin fraction, then normalisation of the neutrophilic leucocyte count and the gamma globulin level was seen on the 10th to 12th day of treatment. Discontinuance of ACTH treatment resulted in a relapse.

In the case of *chronic persistent i. leucopenia* described by Martenson (35) the cause of the increase in the leucocytic agglutinins remained obscure. The agglutinins were found to be bound to the gamma globulin fraction. According to data in the literature, the incidence of such chronic persistent forms in adults is very low. In Moolten's opinion (36) the precipitating factor may be some viral infection, drug or protein allergen is never demonstrable.

Chronic essential leucopenia of childhood (Fanconi-Gassner's disease) is most uncommon. If it lasts longer than three months and the number of neutrophils sinks below the critical level (1000/ml.) furthermore when all known ætiology can be excluded, we may speak about primary essential chronic leucopenia. The condition is characterized by familiar allergoses and a tendency to infection. Enlargement of the spleen is seen only in the phase of infection. Benign forms leading to recovery occur, but there are also malign forms ending in death.

In *cyclic agran.* (37) drug-sensitisation and infection can be excluded. So far about 20 cases have been

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described in the literature. The chronic recurrent cyclic form can be differentiated from acute malign cyclic agran. and from the chronic stationary form. According to Heilmeyer, Ferrioli, and Pieri splenic reticulosis, as well as the reticulosis of other RES organs is apparently responsible. Reticulosis is associated with the formation of pathological globulin, which may cause damage to the leucopoietic system.

Chaiken (38) has failed to prevent the development or influence the course of neutropenia by treatment with ACTH and cortisone in cyclic benign neutropenia. The spontaneous course of neutrophilic hyperplasia and inhibition of maturation in the bone marrow remained unchanged. Infection is a secondary sequel. In some cases the spleen is moderately enlarged. Splenectomy fails to bring improvement (Doan, Owren, 39).

Kromme and Spek (40) have called attention to the significance of the Rh-, ABO- and MN-blood group factors in the development of maternal isoimmunisation resulting from foetal viral infections, such as rubella, in the first place. In such cases the maternal isoantibodies may cause foetal erythroblastosis or, less frequently, chronic essential persistent and chronic cyclic benign leucopenia, or hæmorrhagic diathesis. In such cases Cavelti, Wiener, Dameshek and Swartz (41) have succeeded in demonstrating the presence of auto-leucoagglutinins and auto-hæmolysins in the organs of the foetus or in the maternal serum.

Leale, Rutledge, Doan, Teal and Owren were the first to describe malign cyclic leucopenia and agran. (42). This is a well-defined clinical and hæmatological syndrome, with an average course of five years. It resembles an acute drug-induced agran. relapsing about every two to three weeks; it is an acute septic disease with necrotic stomatitis. The precipitating factor is yet unclear, the bacterial infection is but secondary. Antibiotics have a favourable influence on the clinical picture of infection, but fail to cause any change in the hæmatological picture.

Symptomatic cyclic leucopenia has been described to occur in such forms of Hodgkin's disease in which the changes of the liver and spleen, i. e. of the RES organs, preponderate. Hyperactivity of the spleen is no explanation for the leucopenia and anemia, splenectomy being ineffective. In the case described by Wuhrmann (43) the basic disease had been cured in six years as a result of x-ray and nitrogen mustard treatment, the

patient reaching the state of clinical and hæmatological freedom from symptoms. During a relapse hypergammaglobulinemia developed and the Coombs test demonstrated high titres of sessile and circulating incomplete antibodies. Treatment with x-ray and nitrogen mustard effected clinical improvement and a disappearance of symptoms and signs.

Finally, we wish to discuss one of the peculiar forms of damage to the leucocytic system, notably the so called *L. E. phenomenon*.

Those describing it for the first time (44) thought it to be characteristic for systemic lupus erythematosus. The essential feature in the phenomenon is the presence of the L. E. cell, a mature phagocytic neutrophilic leucocyte with inclusion bodies susceptible to nuclear staining. The nucleus of the L. E. cell is forced to the periphery making the cell resemble a signet ring. At the pole opposite to the nucleus a narrow granulated cytoplasmic margin can be seen around the homogenized, phagocytosed inclusion body showing nuclear staining. This homogenous amorphous nuclear material varies in colour from purple to light pink and is composed of depolymerized desoxy-ribonucleic acid. The difference in the shade of colour between the phagocytosing leucocytic nucleus and the phagocytosed mass is characteristic. Rosettes are a typical feature of the L. E. phenomenon. The rosettes are *free-lying* homogenized nuclear fragments, so-called oval bodies, surrounded by a ring of phagocytosing leucocytes. Rosette formation is not characteristic and is hence of no diagnostic value by itself. L. E. cell formation is caused by the Haserick factor whose presence was demonstrated by Wuhrmann with electrophoresis in the gamma globulin fraction. When added to the bone marrow or to the blood, this factor produces leucocyte agglutination, then the typical L. E. phenomenon.

The L. E. cell and phenomenon commonly occur in drug-allergy (penicillin, sulphonamide, hexamethonium, apresoline, etc.), in other collagen diseases, in diseases of the hæmopoietic system associated with leucopenia, as well as in septic bacteriemic and viremic conditions (45). In drug-allergy, withdrawal of the discriminated drug and ACTH and cortisone treatment result in remission marked by disappearance of the L. E. cells.

Marmont (46) has mentioned the occurrence of the L. E. phenomenon in epilepsy and lues. In the latter

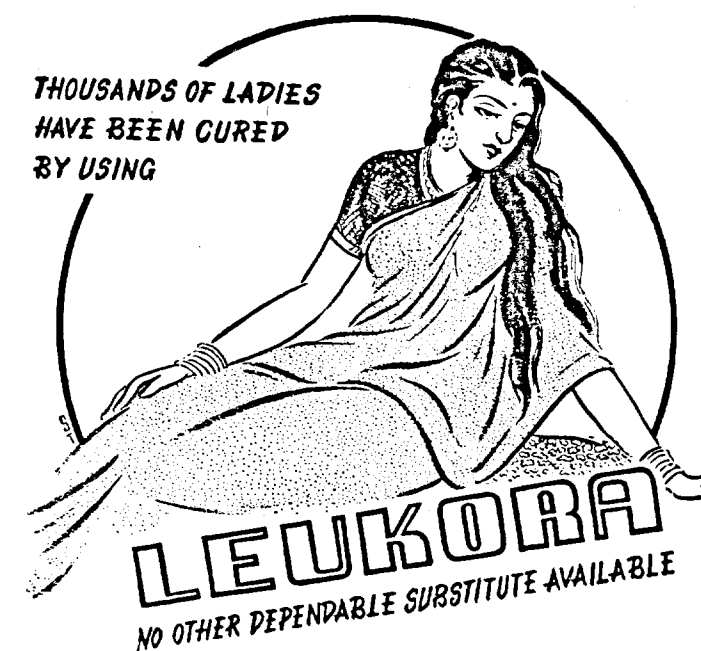
disease auto-sensitisation is commonly known to occur. Owing to the immunohæmatological relations, it should be mentioned that nocturnal paroxysmal hæmoglobinuria is often associated not only with hæmolysis, but also with leucopenia; the condition is thought to be related to syphilitic infection.

Inderbitzin's experiments (47) are worth mentioning. In these experiments the L. E. phenomenon was induced in human leucocytes by treatment with heparin, or polyvinylalcohol and polysulfonate esters, *without* the addition of pathological serum or blood, on the one hand, and the L. E. cell could be produced by treatment with heparin or some physico chemically related compound linked to the gammaglobulin fraction of normal serum, on the other. This fact seems to justify the view that in mesenchymal diseases the noxious agent damages the ground substance, causing a breakdown to mucopolysaccharides, hyaluronic acid, and chondroitine sulphate, and after completing with these so-called heparinoides it assumes auto-antigenic properties, thus initiating the production of anti-leucocytic antibody or the Haserick's factor.

As to the ætiology and pathogenesis of the conditions associated with the L. E. phenomenon it can be stated on the basis of evidence in the literature (48, 49, 50) that the auto-immunisation process responsible for damage to the mesenchyma, for allergic inflammation is precipitated by a prolonged exposure to bacterial, viral infections and to certain drugs. The therapeutic significance of ACTH and cortisone must be stressed (51). In spite of the rapid improvement in the clinical and hæmatological changes treatment should be continued for many months (8 to 10 months) to effect a lasting remission. The use of Atebrin has greatly enhanced the success of therapy. For historical data the reader should consult (52, 48). Dubois inactivated the L. E. factor in vitro by treatment with Atebrin. On high doses of Atebrin the L. E. cells disappear more quickly than on treatment with ACTH and cortisone.

DIAGNOSTICS OF IMMUNOLEUCOPENIAS

It is known from the reports published in recent years that in cases of clinical and experimental i. l. and agran. anti-leucocytic antibodies could be detected



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in serum, partly by the *direct* agglutination test, partly by the transfusion transmission experiment (53, 54, 55). The most extensively used agent is the so-called antihumanglobulin rabbit serum, or Coombs serum (56), which gives positive agglutination by the direct or indirect method after sensitisation of the leucocytic system.

As to the serological methods of the demonstration of antibody, reference is made to the works by R. Backhausz, S. Benko, and E. Kovacs (57, 58, 59).

The methods commonly used in immunoserology, for example the Coombs test, can be employed for the detection of auto-antibodies exclusively in the case of cellular antigens. In the case of immune leucopenias, however, one requires methods which are suitable for the demonstration of the complex antigen formed in response to the entry into the body of the exogenous allergen. The more recently published method of Coombs (60, 61, 62) makes this possible. The essentials of the method are: The protein antigen in question is linked to the anti-blood cell antibody by a tetrazotated benzidine linkage. The corresponding incomplete antibody combines with the antigen and the incomplete antibody thus linked is readily demonstrated by the Coombs serum.

By virtue of its diagnostic importance the *nephelometric method* of Hoigne and Storck (63, 64) merits mentioning. This method detects the responsible allergen in anaphylactic and allergic conditions, irrespective of the complete or incomplete nature of the pathogen. The method makes the precipitation of the subvisible antigen-antibody complex sensitive, recognizable, and measurable by the application of photoelectric principles.

Infrequently, the anti-leucocytic antibodies may have an *opsonic* effect. Bessis (65) has described the phenomenon of autophagocytosis, phagocytosis of pathological leucocytes by normal leucocytes. Baumgarten (66) has studied this problem more closely and by guinea pig experiments he succeeded in demonstrating excessive tissue, blood, and bone marrow leucophagocytosis with antiglobulin serum. According to Baumgarten the common differential blood staining methods are superior to the histological methods of examination.

NEW VIEWPOINTS IN THE TREATMENT OF IMMUNOLEUCOPENIAS

The significance of ACTH and cortisone therapy has already been stressed. These hormones act by suppressing antibody formation. But treatment of the fundamental disease should not be omitted; in infection the proper antibiotics and chemotherapeutics should be employed. It should be borne in mind that as a result of their frequent use drugs often cause sensitisation. In mild or moderately severe cases due to drugs or other chemical agents the suppression of the harmful influence may by itself lead to recovery. Improvement may be evident within days and complete recovery may result within one or two weeks. In the presence of extreme neutropenia antibiotics should be given even before the symptoms of secondary infection (oral or enteric sepsis) appear, because otherwise in the absence of systemic defense, there is little hope of averting infection. In the presence of more severe allergic or anaphylactic symptoms anti-histaminics and sedatives may be helpful. (Alongside foreign preparations the Hungarian drugs Dehistin, Pernovin [anti-histaminics], Sevenal [barbiturate], Plegomazine [chlorpromazine] and Rausedyl [ataraxic] have proved their value.) In infectious granuloma and in cases of malignancy it is absolutely essential to employ irradiation with x-ray and administration of nitrogen mustard (the Hungarian mannitol mustard preparation "Degranol") and other cytostatics as causal therapy. After preparation surgery may, in combination with the above therapy, bring complete recovery in operable cases of malignancy.

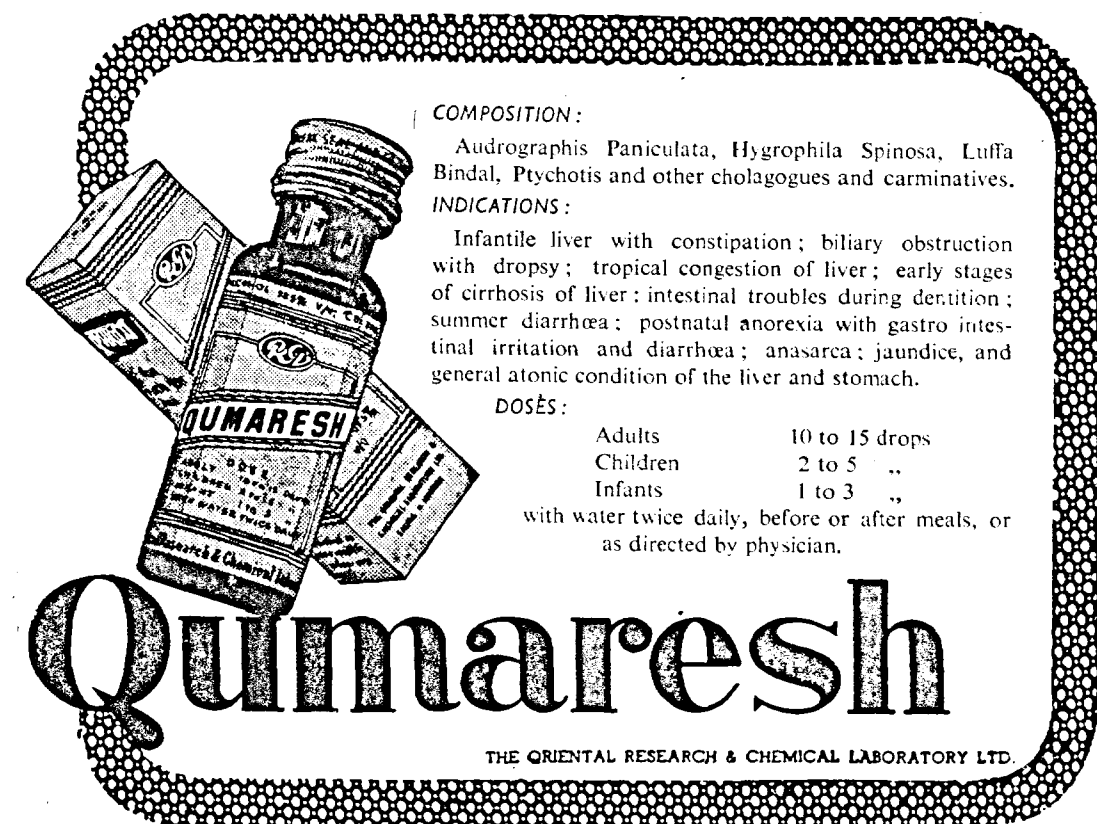
The problem of *splenectomy* is of great importance. Whereas according to estimates in the literature excellent results may be expected in about 50 per cent. of hæmolytic anemias, in the various forms of immunoleucopenia usually no benefit is obtained. Results are good in the presence of hypertrophy and hyperfunction of the spleen (hypersplenism). Over production of the anti-splenic hormone suppresses hæmopoiesis in the bone marrow and may cause pancytopenia. In general, splenectomy should be performed in case repeated intensive ACTH and cortisone treatment, effecting an involution of the spleen and other lymphatic tissues and inhibiting antibody formation by the RES, fails to prevent recurrent clinical relapses. When the antibody titre does not change after splenectomy, or when a transient decrease is followed by another rise, in spite of disappearance of clinical symptoms a relapse may in most cases be expected

to occur after years, especially on exposure to conditioning factors. However, full recovery has been described to take place in such cases, too. Although splenectomy eliminates the biggest organ of the RES, the others may show compensatory hyperfunction, especially when auto-sensitizing stimulation persists or if it arises repeatedly. In circumscribed lymphoma packets of granulomatous glands or in the much cited ovarian dermoid cyst of Dameshek the surgical removal or the irradiation and treatment with cytostatic drugs of the tissue initiating, maintaining antibody formation, or forming the antibody, may result in transient or final recovery (in symptomatic cyclic leucopenia, especially in Hodgkin's disease).

More recently, Italian authors (67) have described the *blocking action of heparin on antibody activity* in immunohæmagglutinating and hæmolytic conditions. There exist such incomplete cold agglutinins which are not fixed to blood cell elements in the absence of complement. The prompt inhibition *in vivo* is ascribed to an anti-complement action of heparin. It is also conceivable that heparin act in the phase of tissular RES activity of hæmagglutina-

tion, which follows the intravascular phase, and in which the blood cell elements, loaded with the antibody or agglutinated, are supposed to be phagocytosed or destroyed by the lysocithinase. Heparin is highly valuable especially in the acute stage of damage to the blood cells, because it is capable of promptly blocking antibody activity and of suspending hæmolytic and leucocyte destruction. The effect of ACTH and cortisone therapy cannot be expected earlier than one or two weeks after the start of therapy. In general, on grounds of theoretical considerations and of clinical experience the method of choice is to employ intermittent ACTH and cortisone administration in acute and chronic immuno-leucopenias or pancytopenias. Should clinical and hæmatological remission fail, or should new and new relapses occur, splenectomy is performed.

Transfusion, as an acute life-saving procedure, should be employed *very cautiously*. Especially when the antibody titre of the patient's serum is very high the introduction of great amounts of conglutinin or X-factor with the donor's plasma into the circulation of the patient may cause severe damage to the blood



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cells and elicit a crisis or anaphylactic shock. We prefer the transfusion of blood cell suspension to whole blood transfusion. Even then it may often occur that, despite the greatest care in determining the group antigen, the serum of the patient will agglutinate the donor's blood cells, owing to the high antibody and conglutinin content of the patient's serum. In such cases the transfused blood cells are destroyed in a few minutes without being able to restore the deficient blood cells. In these cases transfusions cannot be carried out because of the danger to life they involve. And if we realise that repeated transfusions may induce isoimmunisation antibody formation, we feel bound to say that in i. i. and in pancytopenias transfusion is but an emergency procedure, which should be carried out with utmost care and caution.

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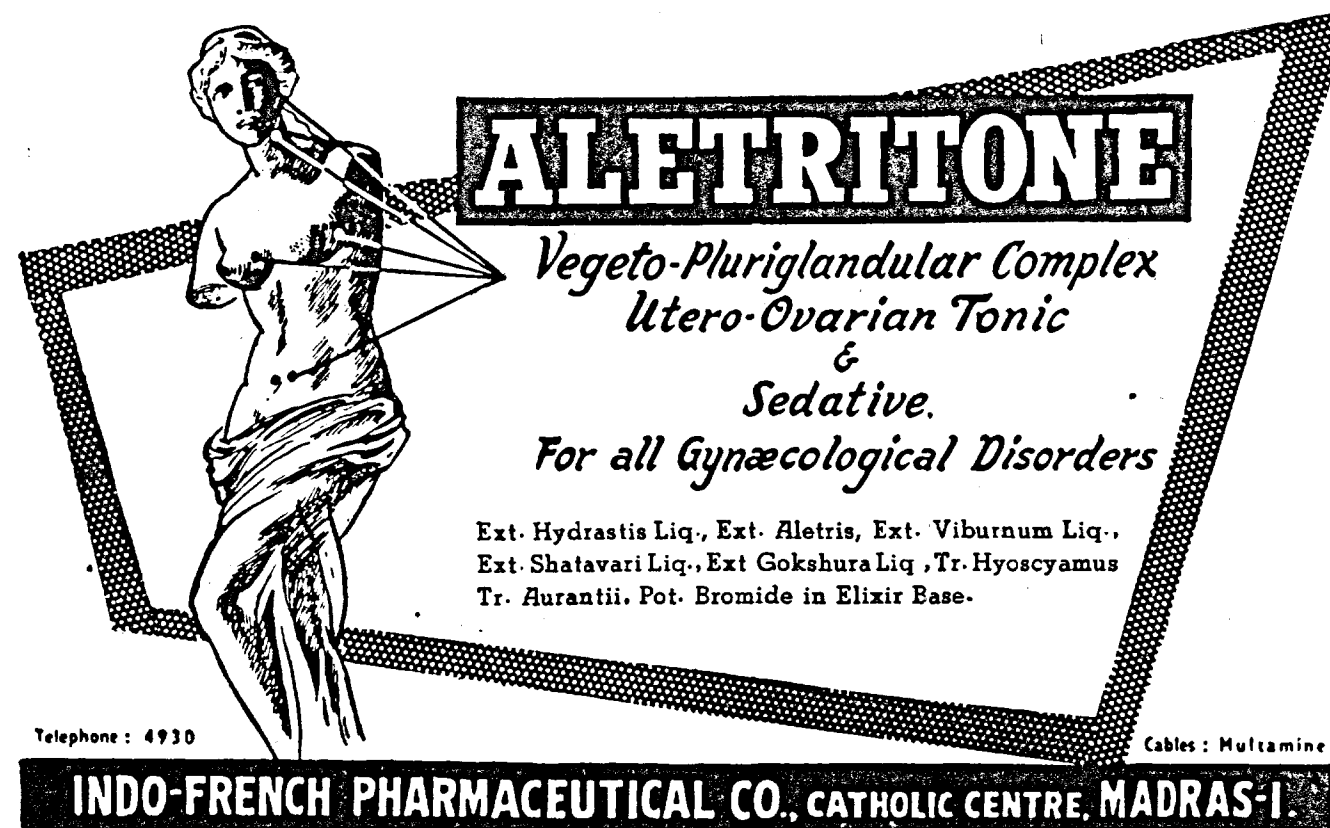
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Data Concerning the Regulation of the Albumin and Globulin Plasma Level

Experimental findings concerning the regulation of plasma proteins are scarce. The sites of protein production, the function of protein stores, various endocrine factors, the nervous system, capillary permeability, renal function, etc., may play a part in the process. The authors undertook to furnish evidence on the role of the liver as a regulator. It is known from the literature that loss of proteins is followed by an increase in the albumin content of the blood leaving the liver. Loss of protein results in a fall of the colloid-osmotic pressure in the plasma and in a decrease of the volume of circulating proteins; these two factors appear to play a part in regulation. The authors studied the albumin and globulin content of the blood in the portal vein and in the hepatic vein of dogs after infusions of plasma, isooncotic dextrane solution, and hyperon-

cotic dextrane solution. Under the effect of plasma or hyperoncotic infusions the albumin content of the blood in the hepatic vein diminished; the globulin content increased as compared to the albumin and globulin levels of the blood in the portal vein. Isooncotic solutions did not affect the relative albumin and globulin values in the portal vein and the hepatic vein. Intravenous procaine was found to bring about a transient blockade of the effect observed during infusions with plasma and hyperoncotic solutions. From their experiments the authors conclude that the liver is an important factor in the regulation of albumin and globulin plasma levels. The process of regulation is of a reflexogenic nature. The volume of circulating proteins and colloid-osmotic pressure play a decisive part in its initiation.



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Hypertension and Coronary Heart Disease

HYPERTENSION and coronary heart disease are now the most important of all cardiovascular diseases from a public health point of view, according to the Expert Committee on Cardiovascular Diseases and Hypertension of the World Health Organization, which met recently in Geneva under the chairmanship of Dr. J. Groen of Hadassah Medical School, Jerusalem.

The Committee also briefly reviewed the public health importance of congenital, syphilitic, pulmonary, and rheumatic heart diseases, as well as bacterial endocarditis.

Hypertension and coronary heart disease are frequently found together and constitute a major portion of the cardiovascular disease of adult life. While their importance is well established, available statistics cannot be relied upon because these diseases tend to be either under or over reported in different countries or even in different regions of the same country. Substantial differences for example are regularly reported in national death rates from coronary heart disease: thus the rate reported in the USA is substantially greater than that of Finland, which in turn, is substantially greater than the Norwegian. The rate in Norway is, in turn, considerably higher than in Japan.

For many reasons these statistics must be treated with caution and regarded only as clues to the prevalence of this affection. The figures concerning hypertension are even more questionable, and the experts called for accurate studies to discover the true incidence of these two diseases.

The Committee established criteria for the diagnosis of hypertension and coronary heart disease to be used in epidemiological studies. It stressed the importance of carrying out such studies in different countries in order to obtain clues to the causation of these diseases, thus leading to possible preventive measures. The recommended criteria, if generally accepted and used would render the results of these studies comparable.

Studies on the incidence of these diseases among different groups, e. g., smokers and non-smokers, sedentary versus physically-active workers, people eating different diets, etc. are also recommended.

(Continued on page 30)

The Committee reviewed the factors believed to be involved in the development of coronary heart disease.

NUTRITION

The role of saturated and unsaturated fatty acids in diets in raising and lowering blood cholesterol levels has been clarified in recent studies and may have an important bearing in the development and prevention of coronary heart disease. The evidence, however, is so far inadequate to warrant any general recommendation for changes in diets or food habits with respect to fats.

EXERCISE

Physical activity seems to affect the occurrence of coronary heart disease, but there are conflicting reports from studies carried out in different countries on this factor.

SMOKING

Here again, the evidence is contradictory. Several studies show a strong relationship, particularly in early middle-age, others have found no connection.

PSYCHO-SOCIAL FACTORS

Very little work has been done on the possible relationship between psychological, environmental and sociological factors and the occurrence of coronary heart disease.

HORMONES

Because women are far less susceptible than men to coronary heart disease much work is being done on the relation of hormones in men and women at various ages and coronary heart disease. No definite conclusions have yet been reached on their role in the development of this affection or their usefulness in treatment of patients.

The Committee made several recommendations concerning further studies on these factors and outlined the various tasks which the World Health Organization might undertake to encourage and co-ordinate international work on cardio-vascular diseases.

PROTEIN DEFICIENCY

By

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PROTEIN deficiency is one of the most serious and widespread nutritional problems in the world today. Many inhabitants of Africa, Asia and Central and South America exist on diets that are too low in protein to permit normal growth in childhood or to maintain health in adult life. Although the diet of most people in the United States is usually adequate in protein, protein deficiency is encountered frequently as a complication of disease conditions.

Protein plays a major role in regulating the vital processes of the body and an inadequate intake limits growth, decreases fertility, diminishes vigour and leads to serious impairment of health.

COMPOSITION AND DAILY REQUIREMENTS

Proteins are complex organic compounds that are composed of long chains of amino acids in various combinations. When protein is ingested, it is broken down in the gastro-intestinal tract by digestive enzymes to amino acids, which are absorbed and transported to the liver by the blood. From these compounds, the body builds or synthesizes its own protein. The body can manufacture some of the amino acids from simpler chemical substances. Other amino acids must be obtained from protein in the diet and so they are called essential amino acids. Through his recent studies, Rose has shown that eight amino acids are essential for man — lysine, tryptophan, phenylalanine, leucine, isoleucine, threonine, methionine

and valine. The minimum requirements in young adult men for these amino acids have been determined, and a few studies of requirements in infants have been done. Recent studies have shown that part of the methionine requirement may be filled by the non-essential amino acid cystine and part of the phenylalanine requirement may be filled by tyrosine.

The diet must furnish not only the essential amino acids, but also enough nitrogen for the body to manufacture non-essential amino acids and sufficient calories to satisfy energy requirements. In addition, all of the amino acids that are needed for the formation of protein must be available at the same time, and they must be present in the proper proportions, if the body is to build or repair tissue. This means that all the indispensable amino acids should be present in the food that is eaten during a meal.

The minimum daily protein requirement for an adult is about .5 gm. per kg. of body weight. The Food and Nutrition Board of the National Research Council recommends one gram of protein per kilogram of body weight daily. The additional quantity above the minimum need represents a factor of safety to allow for differences in individual requirements and for variations in the quality of protein in the diet. More protein is needed during the period of growth than in adult life. The requirement is related to the rate of growth or to the amount of new tissue which is being formed each day. In infancy, 3.5 gm. of protein per kg. of body weight is the recommended daily intake.

(Continued from page 29)

The Committee's report will be submitted to the WHO Executive Board in January and published upon approval.

The members of the Committee were: Chairman: Prof. J. GROEN, Jerusalem; Vice-Chairmen: Dr.

H. E. HILLELOE, New York State; Prof. J. J. SPERANSKY, Moscow; Rapporteur: Dr. J. N. MORRIS, London; Prof. P. W. DUCHOSAL, Geneva; Prof. F. ROJAS, Santiago de Chile; Dr. D. D. RUTSTEIN, Harvard Medical School; and Prof. O. TORGERSON, Oslo.

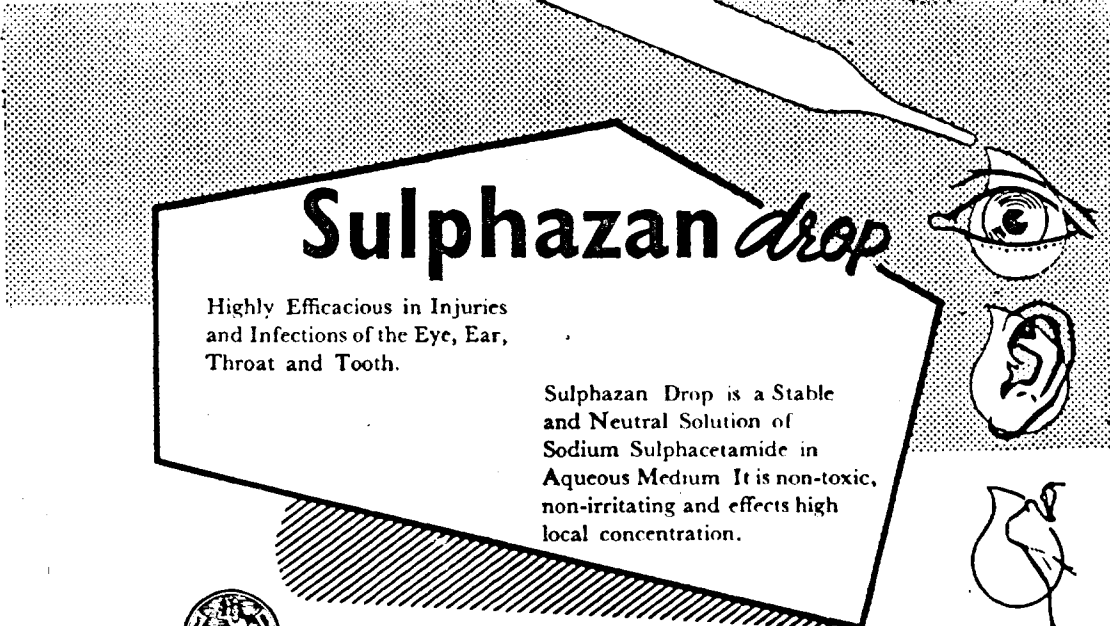
In later childhood, the need gradually decreases to about 2.5 gm. per kg. at the age of 5, and 1.5 gm. per kg. at the age of 16.

Protein requirement is increased during pregnancy and during lactation. The recommended allowances of protein are approximately 1.5 gm. per kg. of body weight daily during pregnancy and 2.0 gm. during lactation. Many pathologic conditions increase the protein requirement. Whenever tissue has been damaged, protein is required for the reparative process.

Proteins which contain all the essential amino acids have high biologic value. Protein from such animal sources as meat, fish, eggs, milk and milk products are in this category. Vegetable proteins often have low biologic value because they are deficient in one or more of the essential amino acids. For example, zein, the corn protein is low in lysine and tryptophan. It is possible, however to obtain all the essential amino acids with a vegetarian diet if a proper combination of vegetable proteins is included.

FUNCTIONS OF PROTEIN

Protein is an essential part of all cells of the body and of all body fluids, except bile and urine. It is obvious, then, that normal growth, which implies an increase in size of all tissues and organs of the body, will require an abundant protein intake. A continuous supply of protein is needed to maintain cellular structure after growth has ceased. The body's proteins are constantly being broken down and reconstituted, and there is dynamic equilibrium between breakdown and synthesis. Schoenheimer and others have made studies of these important metabolic processes, using "labelled" amino acids. The components of protein are labelled with "heavy" hydrogen or nitrogen, with elements such as sulfur or carbon which have been made radioactive in the atomic pile. The labelling permits them to be traced in the body; the chemical changes that they undergo can be followed in the functions they perform can be determined. With such techniques, it has been shown that the average half life of protein in man is about 80 days. The rate of amino acid exchange, or turnover, varies in



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different tissues of the body. It is rapid in the liver and blood plasma; every week, one half of the protein in the liver and blood plasma; every week, one half of the protein in the liver is regenerated. This constant turnover of protein explains the necessity for a continuing adequate supply in the diet.

Proteins have an important role in regulating the fluid balance of the body. They help in maintaining balance between the fluid of the blood the fluid which is present in the tissues that surround the cells (extracellular fluid) and the fluid within the cells (intracellular fluid). When protein deficiency occurs, the extracellular fluid increases and edema results.

Proteins are important in other ways—they form a part of body enzymes and hormones which are the important regulators of chemical processes and which keep the various organs of the body functioning normally. Proteins are needed, too, in the reactions which produce immunity to disease and in the repair of tissue after injury, and certain specialized proteins are required for normal clotting of blood.

The functions of individual amino acids are only beginning to be appreciated. Some amino acids are particularly important in forming hormones; others help in detoxifying harmful compounds or in protecting the liver from damage. One of the amino acids, tryptophan, is a provitamin; it can be converted by the body to niacin which is one of the B group of vitamins, proteins that are not used for special purposes are used to supply energy or they are stored as fat. Each gram of protein can yield four calories of energy. Some of the amino acids of protein can be transformed into glucose and some can be transformed into fatty acids.

One of the ways of studying the adequacy of protein intake is the determination of nitrogen balance. Protein is the source of nitrogen for the body and by measuring the amount of nitrogen present in the diet and the amount excreted in the urine and stools, it is possible to determine whether the intake and output are equal or in balance. If more nitrogen is excreted than is ingested, nitrogen balance is negative and the body is losing protein. This occurs in protein deficiency. If less nitrogen is excreted than is ingested, nitrogen balance is positive and protein is being stored. This occurs during growth and in rehabilitation following injury or protein deficiency.

CLINICAL FINDINGS

Protein deficiency, due to inadequate dietary intake, can occur alone or in combination with a deficiency of calories. The manifestations differ somewhat in these two situations. The signs of protein deficiency during the period of growth also differ from those that are observed in adult life. Protein deficiency which is secondary to disease shows the findings of the primary disease as well as those of deficiency state.

One of the most important syndromes of dietary protein deficiency is kwashiorkor, a nutritional disorder of infancy and childhood which is very common in Africa, Asia and Central and South America. It is encountered very rarely in the United States. This condition has been designated by many names; in Central America, it is known as Síndrome Policarencial Infantil. The African term, kwashiorkor, refers to a disease in the child who has been displaced from nursing at this mother's breast because of the arrival of a new baby. The displaced child is fed inadequately on cereal gruels, starchy root vegetables and similar foods that are low in protein. Sometimes sufficient calories are provided but often the caloric intake is inadequate. Kwashiorkor can occur in the late breast feeding period when the mother's milk is deficient in quantity and the child does not receive supplementary food. In Central America the disease has been reported in children up to the age of 12 years.

The chief findings in kwashiorkor are retarded growth, edema, changes in the liver which include enlargement, an excessive amount of fat and fibrous tissue or death of some of the liver cells, and alterations in pigmentation of the skin and hair. In many instances the skin becomes depigmented while the hair assumes a reddish tint and falls out readily. Other skin abnormalities or dermatoses also occur, including increased skin pigmentation, redness, and keratinization. At times the skin changes resemble pellagra. When the child has kwashiorkor, loss of appetite, digestive upsets and diarrhea are common. Mentally, he is apathetic and listless, yet he is peevish when handled. Anemia is common. Unless good dietary protein is provided, the death rate is high. While much remains to be learned about this disease, it is due basically to severe protein deficiency and it occurs in the age group in which protein need is greatest. Vitamin deficiencies and lack of calories may complicate the clinical picture. Skim milk powder is an

excellent form of treatment, but milk is scarce and expensive in many areas of the world. Accordingly a search is being made for combinations of vegetable protein which will be effective in therapy. Soyabean meal, peanuts and sunflower seeds, all contain good protein and they are being tested. Fish flour is another source of good protein which may prove useful.

In the same areas of the world in which kwashiorkor is common, older children are often retarded in growth and in adults, there is a high incidence of cirrhosis of the liver. Chronic, long standing protein deficiency is one of the most important factors which contribute to these findings. In Africa, a type of heart disease has been described which appears to be due to the protein deficiency.

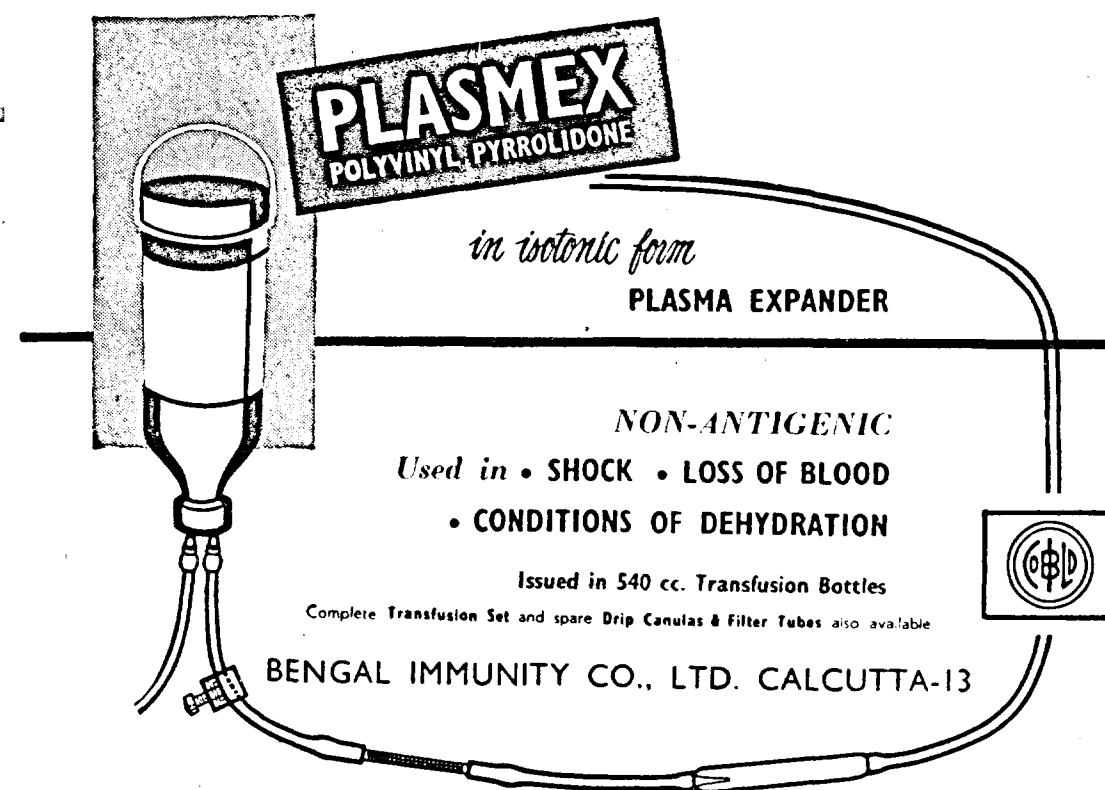
Severe protein deficiency in adults, whether it is due solely to dietary deficiency or whether it is secondary to some other disease, is characterised by loss of weight, wasting of muscles, weakness and edema. The edema may become extensive and include accumulation of fluid in all of the body cavities. The body temperature falls, the blood pressure and heart rate decrease

and the basal metabolic rate declines. Pigmentation of the skin, anemia and a decrease in gastric acidity are common.

LABORATORY TESTS

When dietary protein is insufficient to meet daily needs, body tissues are broken down. This leads to negative nitrogen balance. Determination of nitrogen balance is difficult and time-consuming, so the test is carried out only in special research studies.

The proteins that circulate in the blood serum are decreased when protein deficiency is severe. Normally the level of total serum proteins is 6 to 8 gm. per 100 cc., of which albumin furnishes 4 to 5.5 gm. and globulin furnishes 1.5 to 3 gm. In protein deficiency, serum albumin shows the greater decrease, globulin being affected less significantly. A decrease in serum proteins, which help to maintain fluid in the blood stream is one of the factors that lead to edema. When serum proteins are lowered, this indicated that a large loss of protein from other tissues of the body has occurred.



Elman estimated from studies in animals that each gram decrease in total circulating serum protein represents a loss of 30 gm. of tissue protein. If this holds true for man, reduction in protein concentration from 6 to 5 gm. per 100 cc. of serum in a patient with a plasma volume of 3000 cc. would represent a loss of about 900 gm. of tissues protein. All of this protein must be replaced if the patient is to be rehabilitated. This explains the long period that is often required for recovery in persons whose serum proteins are only moderately lower than normal.

ASSOCIATED DISEASES

Protein deficiency which is secondary to medical or surgical disorders is relatively common. Diseases which increase basal metabolism increase the need for protein and may lead to deficiency. Such diseases include prolonged febrile illnesses, hyperthyroidism, leukemia, congestive heart failure, and other less common conditions. Many diseases are associated with loss of appetite and poor food intake; some cause impaired digestion and absorption of protein, such as chronic diarrhea, certain operations on the intestinal tract in which a section is removed or by-passed, or pancreatic fibrosis with insufficient production of digestive enzymes. Improper utilization of protein may occur in diseases of the liver and excessive breakdown of body protein is observed in uncontrolled diabetes mellitus.

There is excessive loss of protein from the body in many conditions. In certain types of kidney disease, such as nephrosis, large amounts of albumin are lost in the urine. When fluid is removed from patients who have pleural effusion or ascites, protein is lost in the fluid. Large amounts of protein are lost from extensive burns and weeping wounds. In a burn of one half of the body in a man of average size, the nitrogen loss may correspond to two quarts of blood plasma.

As much as 50 gm. of protein may be lost daily in exudates. Hemorrhage, too, means loss of protein. Following all types of trauma, such as fractures, wounds, and surgical operations, nitrogen balance becomes negative. Some studies have shown that the average nitrogen loss following fractures is 220 gm. which represents 1400 gm. of protein—the equivalent of 15 pounds of muscle. It is often impossible to supply enough protein to prevent the negative nitrogen balance of trauma. Probably it is unnecessary to do

so unless the patient's stores of protein are inadequate at the time of injury. In this case, efforts to supply extra proteins are well worthwhile and may save the patient's life.

When protein deficiency exist, shock is more likely to occur. There is also interference with wound healing. Pulmonary edema occurs readily and unless it is treated promptly, it may prove fatal.

The diagnosis of protein deficiency is not easy, particularly in mild cases which are secondary to other diseases. The dietary history is most useful in evaluating the adequacy of protein intake. Continuous weight loss is an important physical finding because it may be indicative of protein deficiency. When edema is present, or when a decrease in serum proteins is observed, deficiency has usually reached an advanced stage. If early protein deficiency is to be detected new laboratory tests must be developed. Urinary excretion or blood levels of amino acids can be measured, but these determinations have not been of much assistance in evaluating protein nutrition.

MANAGEMENT OF THE DEFICIENCY

The most satisfactory method of treating protein deficiency is to provide the patient with a diet that is rich in good protein—meat, fish, milk, cheese and eggs. The patient may need two, three, or even more grams of protein per kilogram of body weight daily, particularly when loss of protein must be replaced as well as tissue stores replenished. Many persons are unable to ingest this amount of protein as ordinary food. In these instances, protein concentrates may be added to the diet. Two tablespoons of dried skin milk added to one cup of whole milk will furnish about 14 gm. of protein; the addition of an egg to this mixture supplies another 6 gm. Other protein supplements are dried yeast, soyabean or peanut flour, edible casein and commercially prepared protein concentrates such as Amigen, Protinal, Essenam and Melactin. These supplements may be incorporated in the diet in baked dishes, soups, bread, cake desserts and sandwich spreads or the concentrates may be mixed with milk or water. If the patient is unable to eat the prescribed diet, he may be fed through a tube. Numerous formulas are available which supply 200 gm. or more of protein daily.

If the patient is unable to take any food by mouth,

the situation becomes very difficult. Blood transfusions are indicated in shock or severe anemia. Concentrated plasma has been used in protein deficiency states but it is undesirable because of the high salt content and the amount of fluid which must be administered. Excessive fluid and salt intake tend to increase edema and may lead to circulatory failure. Another danger is that the virus of hepatitis may be transmitted in plasma. Salt-poor human albumin may be given to replace protein but, like plasma considerable fluid is required for its administration.

Protein hydrolysates or mixtures of amino acids may be given intravenously to help maintain protein nutrition. Approximately 3000 cc. of 5 percent protein hydrolysate in 10 percent glucose solution may be given in 24 hours. This furnishes 1800 calories and 150 gm. of protein. It is difficult to increase this amount without producing toxic reactions. The caloric intake of this regimen is relatively low and if sufficient calories are not given to take care of energy needs, protein will be used for energy instead of for more vital functions. There is a need for preparations containing fat, which can be given intravenously, to supply energy. These have been tested and found useful but they are not available for general application due to difficulties in preparation and storage.

OUTLOOK FOR THE FUTURE

Much remains to be learned about protein nutrition. In the future it is anticipated that attention will be directed to the amino acids that are supplied by protein rather than to protein per se. The functions of individual amino acids, interrelationships among them, and amino acid balance need to be made clearer. Methods for evaluating protein nutrition in man need to be improved. There are many problems involved in supplying adequate protein with the proper amino acid composition to large areas of the world where protein deficiency is common. Although more information is needed, the dissemination and practical application of knowledge we now have should help to

improve the health of large segments of world's population.

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—(The American Journal of Nursing)

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Carcinoma of the Gall Bladder

By

Y. V. SUBBA RAO, M.B., B.S., F.I.C.S.¹P. VENKATESWARA RAO, M.S.²R. ANJANEYULU, L.C.P.S.⁵DR. C. SAMBASIVA RAO, M.D.³N. V. REDDY, M.S.⁴

THE carcinoma of the gall bladder is becoming rarer in the countries where they are removed on roentgenological abnormality anatomical, physiological or pathological. They are removed on laparotomy if found abnormal to the sight or touch. But in our country where silent solitary stone do not compel their carriers with excruciating colic or intense progressive jaundice to approach a surgeon, become invariably potential victims of future carcinoma of the gall bladder.

Carcinoma of the gall bladder was first described by Maximillion-deStoll in 1771. Judd and Baumgartner (1929) found chronic inflammation or stones or both in 94 per cent of their Mayo clinic series. In more than 90 per cent of carcinomata a long history of gall bladder dyspepsia would be present. W. J. Mayo (1903) found 5 per cent carcinoma in 405 gall bladders he removed. This 5 per cent has fallen to 0.5 per cent. In Hanemann Hospital, Philadelphia 2.8 per cent of gall bladders removed showed histological changes of carcinoma. The neck and fundus seem to be the commonest sites of carcinoma. It is the cause for 9 in 1,00,000 deaths. It forms 8 to 10 per cent in general carcinoma.

Lazarus-Barlow ascribed carcinogenic action of the gall stones to the presence of radioactive salts in the stones. Some say it is the mechanical irritation of stones that brings about carcinomatous change.

PATHOLOGICAL VARIETIES

(1) Scirrhus carcinoma:—is a hard invasive tumour some times difficult to differentiate at operation between chronic cholecystitis. 70 per cent of all cases show small contracted and defective-functioning gall bladders on cholecystography. The first case of ours was a scirrhus carcinoma.

(2) Papillary Carcinoma:—It accounts for 15 per cent of all gall bladder carcinoma. It arises in the fundus. It may show filling defects on cholecystography.

(3) Proliferative-columnar-cell carcinoma:—forms 10 per cent. It forms a soft bulky mass and fills most of the lumen.

(4) Colloid Carcinoma:—forms 8 per cent.

(5) Squamous-cell-carcinoma:—forms 3 per cent. It is composed of stratified epithelium with prickle cells, cell nests, and little or no keratinisation. It is preceded by chronic cholecystitis or irritative leukoplakia of the mucosa.

Our second case is from clinical picture, and gross appearance a squamous cell carcinoma. It had an ulcer with indurated base on the posterior wall of the gall bladder. A bunch of secondary glands enlarged, adherent, and surrounding the common bile duct were found supraduodenally producing extraductal pressure, and consequent biliary obstruction, and progressive jaundice.

CLINICAL FEATURES

(1) Previous history of chronic cholecystitis or cholelithiasis is present in 94 per cent of carcinoma of the gall bladder. In 5 per cent of pathological gall bladders removed by W. J. Mayo in 1903 there was a histological picture of carcinoma. 75 per cent give a history of gall bladder dyspepsia.

(2) Rarely it is found earlier than fifty. Our first patient was sixty years old, sturdy, and strong. Second was 64 years old anæmic, and jaundiced. Rhodes and Greenblat (1937) reported about an young patient of twenty four, an American negro.

(3) Women are more often affected than men. According to Webber in 1927 among the women affected 80 per cent were multiparous. Both of our patients were men.

(4) There is right upper quadrant pain, vomiting, anorexia, and loss in weight. Loss in weight is not as much in carcinoma of the gall bladder as carcinoma at other sites. In 24 per cent the clinical picture is indistinguishable from chronic cholecystitis.

(5) There is a palpable and a painful gall bladder in about 50 per cent of the cases.

(6) Jaundice may be due to liver involvement or from pressure of enlarged glands on the common bile duct. It is present in about 25 per cent of cases.

(7) Internal fistula may be present between the gall bladder and the stomach or colon. Spontaneous biliary fistula is very often suggestive of the gall bladder carcinoma.

(8) Plain X-ray abdomen:—soft part shadow may show thick shadow of the gall bladder, calculus or gas pocket from internal fistula.

(9) Cholecystogram:—may be very often indistinguishable from chronic cholecystitis, and cholelithiasis. There may be stones, and defective function of the bladder. Papillary and proliferative columnar cell carcinomata may show filling defects.

(10) Barium meal may show as in our case extraduodenal pressure or extragastric pressure of glands or both the gall bladder, and the secondary glands.

(11) Blood Examination:—Normal values are Serum Bilirubin — 1 mgm%, Serum diastase 3 mgm% W. b. c; R. b. c; Hb%, Serum proteins 7.2 G%, Icterus index less than 5, and Vandenberg reaction. Bleeding and coagulation times are estimated.

(12) Liver function tests:—Lævulose tolerance test, and Thymol turbidity tests are also done.

(13) Urine: is examined for bile salts, bile pigments and urobilin.

(14) Motion: Color, analysis (Steatorrhoea), and estimation of faecal stercobilin are looked into.

DIFFERENTIAL DIAGNOSIS

(1) Chronic Cholecystitis: it may be difficult to differentiate unless there is filling defect or internal fistula.

(2) Cholelithiasis: In both stones may be present, and defective function of the gall bladder. Sometimes it may be difficult to diagnose pre-operatively.

(3) Pancreatic pathology: (a) It may be infection which may also result from biliary obstruction. It can sometimes be found by serum diastase rise, and widening of the duodenal curve on Barium meal. (b) Carcinoma head of the pancreas: This also produces progressive olive colored obstructive jaundice. Cholecystography and Barium meal series may help in differentiation.

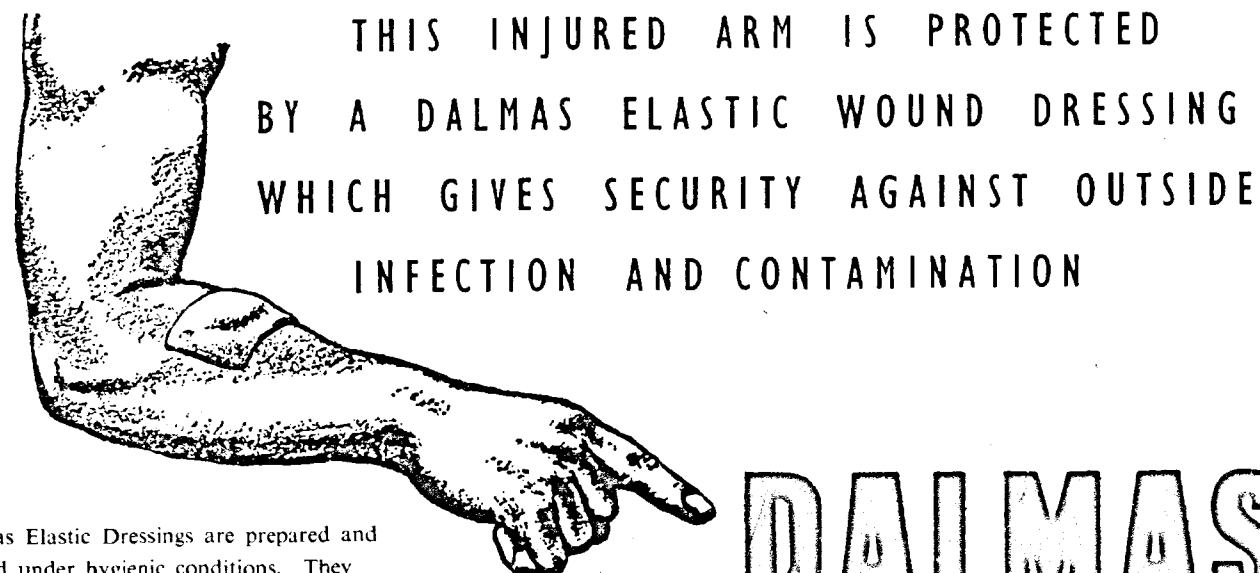
(4) Pyloric Carcinoma with extraductal pressure may bring about the same picture. Barium meal series will exclude this disease.

(5) Malignant hepatoma: Usually does not have pain, and does not bring about jaundice early.

(6) Peptic ulcer: In the early stages of gall bladder carcinoma it may be confusing as some cases may show sympathetic gastric dyspepsia.

Treatment: Whatever may be done results are very temporary and mortality very high. There are few more than two-year survivals that were reported. The only five years cures would have been in cholecystectomies where there was postoperative histological diagnosis. Only in about 50 per cent cholecystectomy is possible. Mortality according to Jones in 1950 was 88 per cent. In less than 10 per cent a cholecystectomy has given 5 year cure. Booher and Pack 1949 had reported a case of 5 year cure with cholecystectomy and gland excision round the common bile duct. Russel and Brown 1950 could do only on seven cases out of twenty-nine cases with no five year cure at the Cleveland clinic. Judd and Baumgartner in 1929 were able to do partial or complete cholecystectomy on thirty nine out of fifty five cases, out of which fifteen lived for over an year, and four only for more than five years. Finney and Johnson (1945) removed eighteen malignant gall bladders, and had only one patient alive, and free from recurrence after two years.

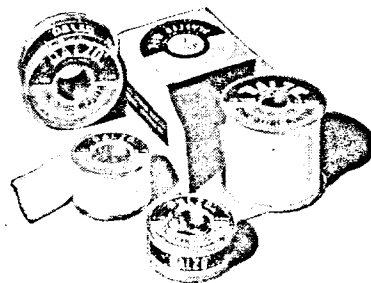
¹Sanjivi Clinic, Guntur. ²Surgeon, Pinamneni Clinic, Vijayawada. ³Physician, Govt. General Hospital, Guntur, and Clinical Professor of Medicine, Guntur Medical College. ⁴Present Surgeon, Govt. General Hospital, Kurnool, and Professor of Operative Surgery, Kurnool Medical College. ⁵Guntur.



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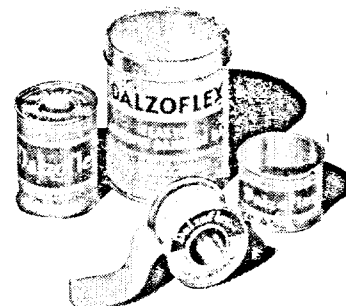
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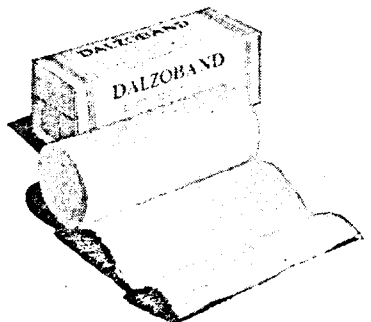
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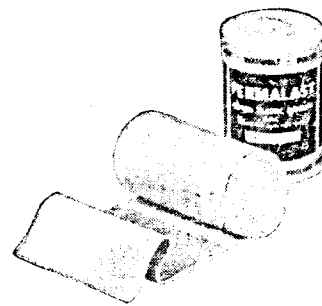
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In a few cases, gall bladder removal, and wedge resection of the infiltrated liver done was reported.

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Where gall bladder cannot be removed and secondary glands produced obstructive jaundice, if there is an inch of healthy wall as in our case cholecystojejunostomy can be done as only a palliative measure like proximal gastro-jejunostomy in inoperable carcinoma of the stomach.

CASE 1

C. K. 60 admitted in September 1953 with dyspepsia and vague pain right hypochondrium. Barium meal series did not show any gastro-intestinal pathology; while those pictures and plain X-ray abdomen showed a good size single stone in the region of the gall bladder.

Well built old man never had jaundice before, nor definite colick except vague upper abdominal dyspepsia. Clinical examination did not reveal anything more. Bp 120/80, pulse 88, temperature 98.4°, urine: no sugar, no bile salts or pigments, Bleeding and coagulation times were within normal limits.

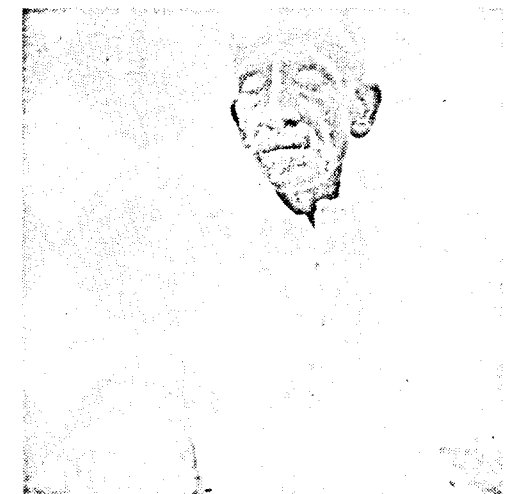
10—10—1953. Under spinal upper right paramedian rectus muscle-slitting incision abdomen was opened. Nodular, and firm appearance of the gall bladder infiltrating into the liver was seen. There was caking appearance around the cystic, and the common bile ducts, suggesting the dissection of structures was impossible. The operation was concluded by closing the abdomen. The period after laparotomy was uneventful.

6 months later he developed jaundice. Gradually went down hill in health and died in three months time after the onset of jaundice.

CASE 2

K. B. 64. Admitted in Sambasiva Rao's medical clinic for olive colored progressive jaundice, generalised pruritus, high colored urine, clay colored stools, vague pain, and painful mass upper abdomen towards the right. He had vague dyspepsia for some

years. Jaundice and aggravated symptoms began three months prior to the admission into the clinic.

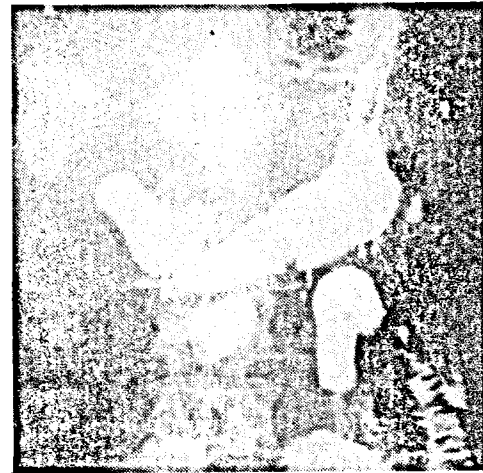


Showing the patient.

Lean, emaciated, anæmic and an oldish individual intensely jaundiced; clinical examination showed hemispherical mass moving with respiration, and painful. There was no free fluid in the abdomen. Liver and spleen were not palpable. Blood: R. b. c. 3.8 million, W. b. c. 8200, Serum proteins not done, vanderberg direct positive. Icterus 50 units, Serum bilirubin 6 mgm. per 100 c. c. Bleeding and coagulation times were within normal limits. Urine: no sugar, bile salts and pigments were present, urobilinogen estimation was not done. Urine was intensely colored. Motion: analysis and stercobilin estimation



X-ray showing extra and supraduodenal pressure.



Showing persistent extraduodenal pressure.

were not done. Barium meal: series and screening did not show gastroduodenal pathology. Duodenal curve was not widened. But there was a suggestion of vague extraduodenal pressure above and below.

One bottle of 'A' group blood was given very slowly. There was no trouble after transfusion. He was given Felamine, Synkavit oral, and parenteral, and penicillin parenterally.

17—7—58. Pethidine 50 mgm. atropine 1/200 gr. and heavy spinal. Position adjusted for upper abdomen. Upper right paramedian rectus-muscle-slitting incision extending upto the costal arch was used. There was a firm growth on the lower surface of the gall bladder, and a mass of glands around the common bile duct (supraduodenally). Individual structures above could not be felt separately. The obstruction to the common bile duct was from these glands. Pancreas and gastroduodenum were normal. So we felt it was impossible to remove the gall bladder and the glands around the duct; the anastomosis of common hepatic duct to the jejunum was non-feasible with so much of infiltration around. So as a palliative measure anastomosis between healthy anterior wall of the gall bladder and jejunum was done in two layers of interrupted stitches, and jejunojejunostomy between proximal, and distal loops.

He was given glucose saline on 1st, 2nd, and 3rd days to maintain fluid balance. He had penicillin and synkavit. Motion color returned, itching gradually subsided, urine color disappeared in three weeks time, and conjunctival color disappeared in 6

weeks. On the 16th postoperative day icteric index was 20 units, serum bilirubin 3.5 mgm 100 c. c. and vandensberg direct positive. November 58 we were informed he was doing well.

Comment: Whatever we do cannot be radical and is only temporarily palliative. If the infiltration spreads to the glands at porta-hepatis nothing could have been done. Palliative cholecystojejunostomy is possible only if there is an area of healthy gall bladder wall. Though anastomosis between common hepatic duct and the jejunum is anatomically more sound, technically is near to impossibility due to neoplastic infiltration around.

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Burying Live Atoms is as expensive as Burying Dead Pharaohs

By
RITCHIE CALDER

Ritchie Calder, well known British science writer, is a member of the Council of the British Association for the Advancement of Science. He was WHO Information Consultant at the United Nations Second International Conference on the Peaceful Uses of Atomic Energy held in Geneva recently.

IN the drowned landscape beneath the oceans there are great valleys, in comparison with which the Grand Canyon of Colorado, a mile deep, 200 miles long, is not so very grand. Nineteen ocean "trenches" are over four and a half miles deep and some are thousands of miles long. In the search for "burial grounds" for the disposal of radioactive wastes, which may become a problem when the atomic industry develops on a world-wide scale, those "trenches" seemed likely places. It was assumed

that they were troughs of stagnant water. There, so the argument went, the dangerous elements, in their concrete metal coffins, would lie undisturbed for centuries until their radioactivity was spent.

This glib assumption was questioned three years ago at the first International Conference on the Peaceful Uses of Atomic Energy. At the second meeting in Geneva the illusion was finally dispelled.

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In the intervening years the Russian ship "Vityaz" carried out oceanographic investigations of 12 of these trenches. The findings of the expedition have shown that the trenches are unsuitable places for the disposal of radioactive waste.

BIOLOGICAL ELEVATOR

At the conference, Dr. E. M. Kreps (USSR) reported in detail on the Tonga Trench, which extends southwards for nearly 700 miles from the Samoa Islands to the Kermadec Islands. The Russian expedition found that, by comparison with the findings of the "Galatea" expedition in 1952, the deep water temperature had risen. This showed that even at the greatest depth a change of water takes place in as brief a space as five years. The distribution of oxygen and phosphates and the presence of living organisms consuming oxygen at every depth showed that the water was actively mixing, horizontally and vertically. This means that the dangerous materials with long-lived radioactivity will be liable to break loose and escape upwards into the upper layers of water. There marine life would become radioactively infected and form a biological chain reaction which would end up in the food of human beings.

This warning was reinforced, at the conference, by Dr B. H. Ketchum, of the Woods Hole Oceanographic Institution. He showed that there was a kind of biological elevator in the sea which would be carrying radioactive materials from the deeps to the surface. Sea organisms, he showed, concentrated the fission products so that the plankton in the Bikini test area of the Pacific had 470 times more radioactivity than the water itself.

In life, the marine organisms would pick up, concentrate, and transfer the radioactivity from the contaminated layers of the ocean to the uncontaminated. In death, the organisms would sink towards the bottom and the fission products, bound up in their skeletons, would increase the radioactivity in the depths. Thus there would be an upward and downward movement of radioactivity, apart from any mixing of the upper and lower waters. This drastically changes the picture which assumed that the transfer between the deeps and the surface would take about 300 years.

NO CAUSE FOR ALARM

Both Britain and America have been dumping radioactive materials in the Atlantic trenches but of a kind and on a scale which so far gives no cause for concern. The British explained that the only materials they had so far deposited were contaminated machinery from Harwell, of a shape which made it awkward for storing them in the safety tanks in which long-lived fission products are kept. The total amount of radioactivity deposited in eight years in the deeps, by the British, amounted to about 600 curies, an insignificant amount in dilution. The Americans have carried out regular surveys of their "ocean graveyards" and have found no evidence of any increase in the radioactivity of the water.

The disposal of radioactive liquid wastes in coastal waters is another matter. The British have had a long experience of disposing of this kind of "sewage" from their atom factory at Windscale in Cumberland. A pipeline carried the effluent two miles beyond high water mark into the Irish Sea. This is very mild radioactivity, since the main fission product wastes are concentrated and stored inland. The discharging into the sea is carried out under strict supervision of government inspectors and under public health regulations already established. To inspection at source, is added strict and continual hydrographic and biological surveys of the sea and the shoreline. As part of this programme, over 35,000 fish were caught and marked and some recaptured under a planned fishing programme. These, like the edible seaweed and the sands of the shore, have given little indication whatever of any increases in radioactivity which might cause concern.

The Russians at the conference took a very strong line that no radioactivity of any kind should be disposed of in open waters, or on land, under any conditions in which it might seep into the ground water. They reported that even their mild effluent is run into concrete ditches and sealed off by concrete.

TANK STORAGE SAFEST

What was made abundantly and consistently clear was that the disposal of waste so far has not been on a scale, nor in circumstances, which constitute a present public health hazard. The insistence of the many technical papers presented on this subject was on the precautions necessary for the future. What

was emphasized was that a great deal more research must be done before any kind of "dumping" could be tolerated. The only safe method of storage is in tanks in which the radioactive substances are allowed to decay—and some of them will take centuries to do so. To the complications of storage is added the fact that in giving off their radiation the elements are producing heat which, in given circumstances, will cause the tanks to boil—and go on boiling for 100 years.

And, of course, there is always the risk, even in peaceful uses, of an accident. Again, experience so far has been reassuring. The atomic energy industry, already employing hundreds of thousands of people, is, on its record, the safest of all industries. Its accident rate, even in terms of non-radioactive accidents, is the lowest of any industry—because the preoccupation with the new kind of hazards has increased the precautions against the old kinds of hazards.

The most serious accident so far has been the "burn-out" of the British reactor at the Windscale plutonium factory. There were no casualties and no one suffered ill-effects.

PUBLIC HEALTH LESSON

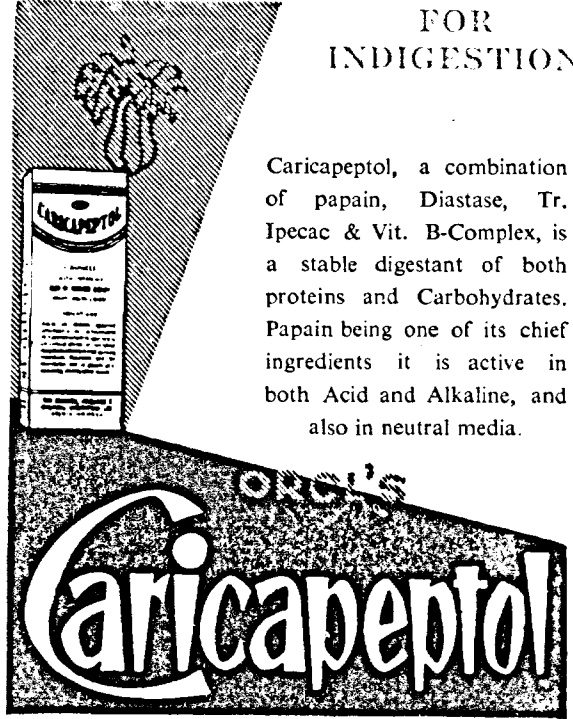
But it demonstrated a public health risk. The reactors at Windscale which had been operating since 1950 are air-cooled. Cooling air is drawn through filters from the atmosphere and then blown through the reactor core. The exhaust air is passed through a bank of filters mounted at the top of a stack 410 feet high. On the occasion of the accident these filters trapped the larger particles from the damaged reactor but finer particles and gases escaped. At the Geneva conference a detailed account was given, which will become a text book lesson for public health authorities everywhere. It included an exact record of meteorological conditions, and of the "flying squads" of radiation experts who toured the area examining the herbage, the soil and, eventually, the milk. The milk revealed the presence of radioactive iodine and the milk from farms over an area of 200 square miles was banned from use. Vegetables, eggs, meat and drinking water were also monitored but no contamination was found which would constitute a hazard. Adults and children were examined to discover if any radioiodine had been ingested and had found its way to the thyroid gland. No results were found to cause dismay.

The survey was extended to Southern Scotland, Yorkshire, Lancashire, Westmoreland and North Wales and later samples of milk were collected from the Isle of Man, Northern Ireland and the South of Scotland. The outcome of these immediate and also long-term studies showed no significant deposition of radioactivity other than radioactive iodine. For the physicists and engineers the accident emphasized the precautionary measures needed in design and in control of reactors. For the public health authorities it was an alarming but salutary experience which will be turned to account in legislation and in practice as atomic power stations develop not only in Britain but throughout the world.

INTERNATIONAL CONTROL

It underlined the appeal made by the Netherlands Royal Academy of Sciences to the conference for international measures to control the radiation risks. As Professor J. H. de Boer, the spokesman for the Academy, emphasized at the final session of the conference, radioactivity knows no frontiers. The

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hazards are particularly serious in Western Europe with its dense population and great industrial activity presently to be increased by atomic power reactors. He pointed out that the siting of reactors might be a hazard to neighbouring countries and that there must be international agreement about their location. He cited the "stationary sources of danger"—all types of reactors, fuel reprocessing plants, stores of radioactive waste and industries increasingly using radioisotopes. But he also cited mobile sources—atom-driven ships and possibly, later, aircraft; and the transport of radioactive materials by sea, air and land. The radioactive material might cross territorial frontiers in the atmosphere, the waters of the oceans, rivers, lakes, canals, etc., and by actual transport. While insisting that the problem for Western Europe is more urgent than for any other part of the world he, on behalf of the Royal Netherlands Academy, appealed for international regulation of radioactive hazards.

As a measure of the problem, consider that the United States in 14 years has accumulated 60,000,000 gallons of radioactive elements stored in more than a hundred indestructible steel tanks. The cost so far has been \$65,000,000. Some of the elements will remain dangerous for decades, others for centuries and, in the case of plutonium, for at least 24,000 years.

Forty-two years from now—on the estimates of the world's use of peaceful atomic power for 2,000 AD—the amount of waste will require 100,000 acres a year as "burial grounds"—that is, if they use the most compact methods of disposal—like fusing the fission products in glass.

As the chairman of one of the sessions commented, "The tombs of radioactive waste are becoming as elaborate and expensive as those for the mummies of the Pharaohs".



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TUBERCULOUS COXITIS

By PROF. P. KORNEV

Member of the USSR Academy of Medicine.

THE problem of tuberculous coxitis which has a long and instructive history at the present time attracts special attention due to the modern achievements in the study and therapy of this disease.

Tuberculous lesions of the hip joint have numerous variations and pertain to the most unbearable sufferings, which cause widespread destructions.

Pathologico-morphological investigations at the Leningrad Institute of Tuberculosis of Bones and Joints (M. E. Mendelshtam, A. I. Chistovin, D. M. Krylov, D. K. Khokhlov etc.) and many years of personal observations of the patients and of the changes revealed at operations convinced us, that the leading part in pathogenesis and evolution of tuberculous coxitis is played by the primary osteitis. The specific foci which appear in the spongy tissue of the epiphyseal ends of bones by hematogenous route are usually the primary source of infection of the joint with the following development of secondary arthritis. At the same time the primary osteites have a decisive influence on the form and degree of destructive changes in the joint, as well as on the outcome of the disease. The analysis of our surgical data revealed, that when the inflammatory process is improved clinically it may not yet be considered as completely liquidated. Actually, a more or less stable isolation of the remaining specific changes are found morphologically, mostly at the site of primary osteitis, which are preserved as hardened bay-formed depressions or caverns with caseation and sequestra. The abovesaid was established in case of a knee joint and was later verified on the hip joint in coxitis.

In connection with successive anatomico-pathological changes we differentiate 3 phases in the clinical course of the disease. The first is the prearthritic phase, when the isolated focus in the bone only threatens the joint, the second—the arthritic phase—is characterized by penetration of the process into the joint with development of specific clinical picture of tuberculous inflammation with 3 stages; the third—

postarthritic phase—shows anatomico-functional disturbances with unsteady stabilization and inclination to exacerbations and relapses as the result of the previous attack of the disease. It should be pointed out that the primary synovial forms have a more favourable one-phase course. However, they are exceptionally rare.

The most important problem in diagnosis, besides the establishment of the origin of the disease is the determination of the beginning and the end of the disease. The aim of the early diagnosis of tuberculous arthritis should be not only the diagnosis of inflammatory changes, but all the more of the signs of appearance of periarthritic bone focus. This gives the opportunity to administer preventive treatment, since irreversible processes appear with infection of the joint. The presence of stable improvement in the course of the disease with restoration processes and complete absence of remaining focal destruction with pathological inclusions should be considered as signs of recovery. This is why the establishment of an unhealed focus shows that the process is still active and may exacerbate at any time.

It should be pointed out that the planned therapeutic and prophylactic work which has been carried out in the Soviet Union lately resulted in decrease of the incidence of tuberculosis osteoarthritis, particularly of coxitis. The initial stages of the process are now recognized more frequently, while the number of active destructive forms, as well as, purulent complications is reduced. But there are many advanced cases with remote results of coxitis. Thus the two fundamental groups of patients may be distinguished at the present time: the first with initial fresh process in the prearthritic and arthritic phases (predominantly children) and the second—adults with advanced disease in the postarthritic phase. Such subdivision of the patients stipulates the character of our therapeutic measures.

In our opinion three principles should be placed at the base of modern treatment of tuberculous coxitis.

It is to be planned, complex and active. The active treatment is aimed to affect the infectious agent directly with the aid of antibiotics, as well as, on the tuberculous focus by surgical intervention. In this disease the surgical treatment is not opposed to the conservative, but is used in conjunction with it, as a single surgical—therapeutic complex.

One of the newest active preparations—streptomycin combined with the other chemotherapeutic drugs (such as PASK, phthivacid, isoniasid) has found its stable place in the clinics of tuberculous osteoarthritis and distinctly increased the efficacy of treatment. We know that streptomycin has an antimicrobial, as well as, anti-inflammatory action. The efficacy of its antimicrobial action depends on the definite concentration of this preparation in the focal lesions with sufficient blood supply. This may be reached mostly in the early stages of the disease when the place of lesion is not yet separated by tissue barrier and has not undergone caseous necrosis. It is also important to prevent the microbes from getting used to this antibiotic.

The most important indication for streptomycin therapy are the primary synovial lesions, in which a complete recovery of the joint function is usually reached. In the secondary affection of the synovial membrane the success of streptomycin therapy becomes relative especially if the bone focus is still present. At the peak of the disease when the process involves the joint cartilage the effect of streptomycin is very insignificant, since it only helps to wall off and not to heal the process completely. Streptomycin has no effect in advanced cases. This observation is supported by histological and bacteriological examinations of surgical specimens. At the same time the significance of streptomycin therapy should be stressed in shortening the active period of the perifocal inflammatory symptoms, as well as, in prevention and treatment of dangerous complications, such as generalization and suppuration (especially of sinuses).

The most important part is played by streptomycin therapy in surgical interventions of the hip joint. The indications for these operations are now much broader in connection with the favourable conditions which are provided for post-operative treatment. With the aid of streptomycin it became possible to remove the cold abscesses and foci, to incise the joints and to perform resections within the joint

with comparative safety. Blood transfusion and the other stimulating general measures aid in success of the operation.

There are various methods of surgical interventions used in operative treatment of tuberculosis coxitis, such as radical, therapeutic-auxiliary and correcting. These operative procedures act on the tuberculosis process itself, as well as, on the recovery of the disturbed weight-bearing function of the extremity. Naturally, the most attention is attracted by the radical operations. However, the operations of therapeutic-auxiliary type, the so-called arthrodeses, are still popular among the majority of foreign and certain Soviet surgeons.

The problem of including the radical operations into the complex planned system of treatment of tuberculosis coxitis was discussed at the Leningrad Institute of Tuberculosis of Bones and Joints as early as 25 years ago.

At first the operations of resections of the hip joints were rather unpopular, but this did not hinder accumulation of practical experience of their performance. Finally, due to improvement of the operative technique and the appearance of antibiotics we have greatly extended the indications for radical operation and acknowledged its leading significance in the therapy of tuberculous coxitis. Up to the present time we have performed 600 resections of the hip joint. The total mortality rate for the last five years is almost nil (0.5%).

We distinguish 2 types of resections of the hip joint: the planned resection as the final stage of conservative treatment and late resections which are carried out for liquidation of the consequences of coxitis. The latter is performed in majority of cases in attempt to restore the working capacity of the invalids.

Technically, hypical and atypical resections should be differentiated. The first is the economical type with additional arthrodesis, which is usually performed in the presence of normal anatomical relationship of the ends of epiphysis, especially when the head of the femur is still preserved. The second type is of reconstructive character and is carried out in cases with pronounced destructions (such as the absence of the head and especially of the neck of the femur). In such cases the most important is the problem of

restoration of stable relationship between the treated destructed epiphyseal ends, which are connected by additional arthrodesis.

The radical-prophylactic interventions—necrectomies are now more widespread. They aim at the timely removal of the isolated pathological focus of the bone in order to prevent the process from involving the joint. With prescription of streptomycin, necrectomy is performed even in initial lesions of synovial membrane, before the process had time to effect the articular cartilage.

All this gave the opportunity to revise the evaluation of the surgical interventions outside the joint capsule, such as the auxiliary type, arthrodeses and the widely used correcting operations—osteotomies since they are not up to the modern standard. Thus, the indications for these operations were reduced, while the sphere of radical interventions became broader.

In conclusion it should be mentioned that the principles of complex and active treatment found reflection in differential approach in choice of the method and time limits for surgical interventions. These operations are connected with the wide administration of antibiotics together with the general orthopedic measures in sanatoria.

The antibiotic should be used with light immobilization if the tuberculous origin of the primary sinovitis is proved. The prophylactic removal of the bone focus with the following streptomycin therapy is indicated in the prearthritic phase. The complex conservative treatment should be carried out in the arthritic phase with administration of antibiotics with strict immobilization and final economical resection of the affected joint with additional arthrodesis. In the postarthritic phase the presence

of remaining foci and non-weight bearing extremity indicates the necessity for radical-correcting late resections of reconstructive type. In absence of remaining foci the operation may be limited to arthrodesis outside the joint, while in fixed wrong position, especially with ankylosis, osteotomy should be the operation of choice. In case of healed process which resulted in extensive destructions, various reconstructive and plastic procedures may be used which are being successfully developed by the Soviet surgeons and orthopedists.

Thus the complex problem of tuberculous coxitis has found a favourable solution. The actual possibility to arrest the process in its early phase and to reach the complete healing of the local process in advanced cases with irreversible changes with the aid of the final economical resection should be considered as great success in treatment of tuberculous coxitis. Complex surgical interventions of reconstructive type are of real help to patients with advanced coxitis.

Preventive treatment and measures aiming to return disabled invalids to work are important problems which are being solved by the Soviet specialists in tuberculosis of bones and joints.

A NEW CURE FOR T. B.

Soviet scientists have discovered a new preparation for curing T. B. It is called *Phtivazide*. This medicine destroys the tubercular bacillus. After using this medicine, the temperature of the patient begins to drop, he stops perspiring, eats and sleeps better, and puts on weight. People suffering from tuberculosis have found that phtivazide rids them of their racking cough. Phtivazide also lessens the pathological changes in the lungs.

Phtivazide is used only as advised by the doctor.

Tanninhaemagglutination – Immunchaemagglutination

It is well known that various serological reactions (agglutination, complement fixation, cytolysis by complement, increase of phagocytosis) can be imitated by the use of a homogeneous, non-specific substance, tannin, instead of immune serum. As a result of experiments aimed at clarifying the mechanism of effect, the author has come to the following conclusions: the macroscopic and microscopic aspects of tannin hæmagglutination differ from those of immune hæmagglutination; tannin is of type O, immune hæmagglutination of type H. Tannin exerts its agglutinant action by linkage to the red bloodcells. The agglutinative effect is independent of the specificity of the red bloodcell type and the pH of the environment. Through absorption it can be exhausted by any type of red bloodcell in respect to any kind of red bloodcell. Its affinity to red bloodcells involves a much larger group of receptors than does any one of the hæmagglutinins, but this affinity applies also to identical groups.

LEGG-PERTHES DISEASE IN SIBLINGS

A Report of Two Cases with Simultaneous Onset

By DR. HENRY BURLINGTON, M. D.
Bethlehem, Pennsylvania

THE etiology of coxa plana, or Legg-Perthes disease, remains one of the most complete enigmas in orthopedics. The radiologic and microscopic pathology of the lesion have been well described by several authors, but attempts to link the condition to hypothyroidism, Frohlich's syndrome, trauma, allergy, and various other etiologic entities have not proved to be consistent with general clinical experience.

More recently, Ponseti⁷ and Ponseti and Shepard⁸ have reported on various lesions simulating Legg-Perthes disease, epiphysiolysis, scoliosis, and other idiopathic bone and joint lesions, in experimental lathyism in rats. While these reports would not appear

to have any direct bearing on clinical practice at the present time, they should certainly stimulate the careful review of known cases, with special reference to dietary factors or possible epidemiologic relationships.

There have been several previous reports of familiar occurrence of Legg-Perthes disease. Giannestras² and Derian¹ have reported true Legg-Perthes disease, not accompanied by epiphysitis in other areas, in twins. Giannestras, Hagen,³ Hamsa and Campbell,⁴ McComas,⁵ and Mitchell⁶ have observed the condition in siblings other than twins. McComas⁵ and Slocum⁹ have reported coxa plana in fathers and sons. Only Giannestras has previously reported cases of nearly simultaneous onset.

Stephens and Kerby¹⁰ report on a group of 28 cases of Legg-Perthes disease in one family, covering a period of five generations. Of these cases however, only a few were examined personally, and only 12 were subjected to roentgen examinations. Careful perusal of the roentgenograms illustrated in their report suggests that at least several of the cases are not typical of true Legg-Perthes disease.

CASE REPORTS

CASE 1.—G. R., a white male 7 years of age, was first examined by the author on July 7, 1955. His parents gave the history of having noted a right-sided limp, painless and intermittent, over a period of approximately six months. At onset the limp had been transient and was apparently related to fatigue and over-exertion. Later the limp became somewhat more persistent, and occasionally was accompanied by low-grade pain in the right groin and medial aspect of the right thigh.

The child was admitted to St. Luke's Hospital for study. A detailed history and careful complete physical examination disclosed no history of injury other than the frequent minor traumas of all children of this age. There was no family history of hip abnormalities; the only known bone or joint abnormality in the family was that of an uncle who had limped after a fracture of the ankle. The child's prenatal and neonatal history as well as his dietary history were in no way unusual. The only previous illnesses, other than occasional mild upper respiratory infections, were measles and chickenpox, neither of

these in the preceding year. The boy had previously had a surgical procedure performed for correction of strabismus. No other significant history or symptom were elicited on detailed systemic review.

On physical examination the boy was found to be slim, well muscled, and well nourished. He was 51 inches tall and weighed 60 pounds, well within the median normal for his age. The rectal temperature, pulse, respirations, and blood pressure were all within normal limits. Dentition was normal for his age. Detailed physical examination revealed no abnormalities except in the lower extremities. There were none of the stigmas of hypothyroidism or Frohlich's syndrome.

The boy walked with a right-sided limp, and the Trendelenburg test was positive. There was visible right gluteal atrophy, and about one inch circumferential atrophy of the right thigh. Leg lengths were equal. There was about 15 degrees of restriction of motion of the right hip in both internal rotation and abduction; other motions were full and free. There was slight but definite tenderness over the femoral neck in the groin.

Laboratory studies were as follows: urinalysis complete blood count, and sedimentation rate all within normal limits; Kolmer's test negative; serum calcium 10.0 mg. per cent; phosphorus 4.9 mg. per cent; alkaline phosphatase 6.0 Bodansky units; C-reactive protein negative; serum protein-bound iodine 4.7 micrograms per cent; purified protein derivative 1:10,000 and 1:1,000 negative.

Roentgenograms of the right hip revealed density and flattening of the capital epiphysis, with widening and foreshortening of the femoral neck. The wrist bone age was the same as the chronologic age. Skeletal roentgen survey revealed no other abnormalities. The left hip appeared entirely normal.

CASE 2.—J. R., a white male 5 years of age, was first examined on the same day as G. R., his brother, and was hospitalized at the same time. The younger boy's symptoms had commenced about a month later than his brother's and had also consisted of an intermittent, painless, right-sided limp. His limp had not become persistent or painful; it also seemed to be related to fatigue or over-exertion.

Upon admission, the usual detailed work-up was

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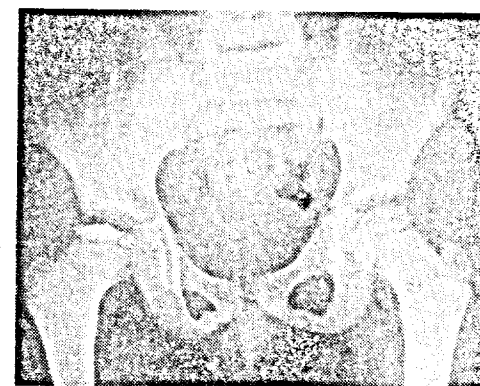


Fig. 1, Case 1 (G.R.), age 7. Right hip shows epiphyseal density and flattening and widened joint space. Femoral neck osteoporotic, foreshortened, and wide. Left hip was normal.

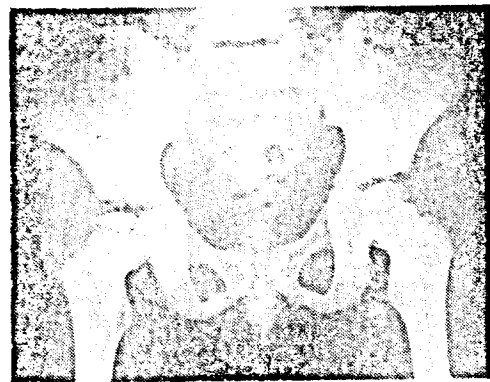


Fig. 2, Case 2 (J.R.), age 5. Right hip shows changes very similar to those of Fig. 1, but somewhat less marked.

undertaken. The patient's past history and dietary history disclosed nothing unusual. The only previous significant illness had been measles. There had been no previous hospitalization.

On physical examination, the younger boy was found to bear a distinct resemblance to his brother, both in facies and in general habitus. His height was 48 inches and his weight 52 pounds. Vital signs, dentition, and general physical examination were entirely within the normal range.

There was a barely perceptible right-sided limp. The Trendelenburg test was at first negative, but after being repeated many times over a period of a few minutes it was noted to be positive. There was definite visible gluteal atrophy, and about three-quarters of an inch of circumferential atrophy of the right thigh. Leg lengths were equal. There was no discernible restriction of hip motion, but passive internal rotation produced discomfort. There was no definite tenderness about the hip.

Laboratory findings were: urinalysis, complete blood count, and sedimentation rate entirely normal; Kolmer's test negative; serum calcium 9.8 mg. per cent; phosphorus 4.9 mg. per cent; alkaline phosphatase 5.6 Bodansky units; C-reactive protein negative; serum protein-bound iodine 6.0 micrograms per cent; purified protein derivative 1:10,000 and 1:1,000 negative.

Röntgen findings in the right hip were very similar to those described in Case 1, perhaps a little less advanced. The left hip, the other major joints, and the wrist bone age were all within normal range.

SUMMARY

Two cases of typical unilateral Legg-Perthes disease occurring in young male siblings, with almost simultaneous onset of symptoms, have been presented.

In neither case was there any evidence of endocrine disorder, growth disturbance, or multiple joint involvement.

The only unusual features of these cases were the relationship of the patients and the nearly simultaneous onset of symptoms.

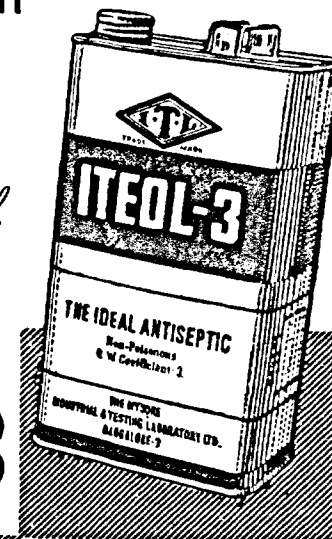
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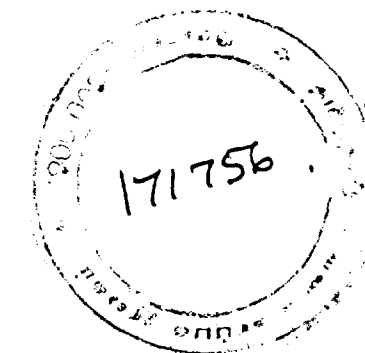
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Skin Manifestations in Parasitic Diseases

By T. V. VENKATESAN,

M.B., B.S., F.A.I.M., F.A.C.A., F.C.C.P., F.D.S., (Lond.)

Honorary Physician, Erskine Hospital, Madurai.

Human parasites may be divided into protozoa, helminths and arthropoda.

PROTOZOAL GROUP

- | | |
|--|------------------|
| (1) Rhizopoda | eg. amoeba. |
| (2) Mastigophora : | eg. Flagellates. |
| (3) Sporozoa (Protozoa without locomotor organs) | eg. Plasmodium. |
| (4) Ciliata | eg. Balantidium. |

I. RHIZOPODA GROUP

Entamoeba histolytica :—

Amoebiasis cutis: The amoebic ulceration of the skin is found adjoining the visceral organ. They are commonly in the perianal region where a granulomatous form is produced. Other sites are the area of drainage of liver abscess, and colostomy wound.

The trophozoites can be demonstrated in these lesions. The cases respond to emetine therapy.

II. FLAGELLATES

(1) *Trypanosoma gambiensi* infection :—

- At the site of infective bite of the glossina, a furuncle like swelling is produced which ulcerates producing a trypanosomal chancre.
- The posterior cervical group of lymph glands may be seen rising the skin. This is called Winter-bottom's sign.
- Hypesisthesia of the skin is produced called Kerandel's sign.
- An erythematous eruption of the skin with annular patches.

Treatment of Trypanosoma gambiensi infection :—

- Urea substituted compound called "Bayer 205" 0.5 g I. V. twice weekly for 10 injections.

- Pentamidine 4 mgm. per kilo of body weight per day I. V. for 10 injections.

(2) *Trypanosoma cruzi* infection :—

- The primary lesion at the site of bite of panstronglus (Kissingbug) is a chagoma.
- Unilateral œdema of face called Romana's sign occur.

Treatment :—Bayer 9735 Total dosage 50 cc. in divided doses I. V.

(3) *Leishmania Donavani* :—

- Pigmentation of the skin.
- Punctate rash appearing on the face described by Kirk in kala azar cases in sudan.
- Purpuric and petechial hæmorrhages as complication of kalaazar.
- Cancrum oris as a complication of kalaazar.
- Dermal Leishmanoid :— This occurs in 10% of Kalaazar patients two years after treatment in the following varieties.

- Erythematous patches having a butterfly distribution on the face
- Yellow pinkish nodules on the face.
- Hypo Pigmented patches.
- Punctate cutaneous eruption.

L. D. bodies can be demonstrated in skin clip and biopsy specimens.

Treatment of Dermal Leishmanoid :—

Three times the dosage of urea stibamine used for visceral and three or four courses at 3 weekly intervals.

(4) *Leishmania tropica* infection :—

Two types of lesions are described viz urban and

rural type, the former producing unbroken dry papules with later ulceration and the latter producing moist lesions ulcerating rapidly.

The various types of skin lesions :— The commencing lesion is an itching papule which is covered with fine pappy scales. The crusts fall leaving a shallow ulcer discharging ichorous material. The ulcer extends secondary sores appear around the parent ulcer. Later granulomatous lesions form and scar formation and unsightly deformity is produced. Associated subcutaneous nodules may occur around the primary ulcer.

Other forms : (a) Nodular or verrucose form called parasitic granuloma (b) Leishmaniasis recidiva or relapsing tuberculoid type. This is called Metaleishmaniasis of Marchionini. The nodules resemble apple jelly nodules.

The measures are :

- Local infiltration with 5% berberine sulphate.

- The general measures are neostibosan injection 8 to 10 injections an alternate days commencing with 0.1 gm. and increasing to 0.3 gm.

(5) *Leishmaniasis Americana* produces lupus like lesions around nose, pinnae of ears and punched out ulcers in the extremities.

Treatment :— (a) Esparseno 0.12 gm. I. V. once in three days for 10 injections.
(b) Local measures : 1% antimony tartrate.

III. SPOROZOA GROUP

Plasmodial infection produce pigmentation of skin and purpuric patches in the skin in septicemic type of plasmodium falciparum infection.

IV. CILIATA

Balantidium coli does not produce any skin manifestations.



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Helminthic infections :—

Helminths are divided into

- (1) Nemethy helminths.
- (2) Platyhelminths. (a) Cestodæ : Tape worms.
(b) Trematodæ : Flukes.

NEMETHYHELMINTHS : are divided into

Having no caudal chemoreceptors

- (a) Trichinella
- (b) Trichiuris Trichura.

(2) Having caudal chemoreceptors

- (a) Rhabditida.
 - (i) Strongloides.
 - (ii) Ankylostome and necator.
 - (iii) Enterobius vermicularis.
 - (iv) Ascaris lumbricoides.
- (b) Spirurida.
 - (i) Gnathostoma spinigerum.
 - (ii) Filarial group.
 - (iii) Guinea worm.

TRICHINELLA SPIRALIS

The larval forms occur in the skin, subcutaneous tissues and muscles producing pains.

The diagnosis is by biopsy

Treatment : Subcutaneous administration of carvasept has been found beneficial.

*Trichuris Trichura or Whip worm :—*Urticarial rashes may occur.

Treatment : Lechede Higueron 60 cc. followed by Saline Purge.

Strongloides Stercoralis

The filariform larva enters thro' skin causing cutaneous irritation producing prurigenic dermatitis, urticarial rash and petechial hæmorrhages.

Treatment : Gentian Violet 1 grain thrice daily before meal, for 10 days or intravenously 20 cc. of 0.5% solution of gentian violet daily for 10 days.

ANKYLOSTOMA DUODENALE AND NECATOR AMERICANUS

Infection producing ground itch due to the entry of larva thro' skin. The treatment is 3 cc. of Tetrachlor ethylene in two divided doses followed by a saline purge. For local therapy, nupercaine ointment.

Ankylostoma braziliensis.

The filariform larva producing a condition called creeping eruption. Tortuous or serpiginous tunnels are found in the stratum corneum. There is intense pruritis.

Treatment :— (a) Ethyl chloride spray locally.
(b) Diathermy needle locally.

Enterobius vermicularis :—

Enterobius vermicularis will produce pruritis ani and perini. As a result of constant irritation around the anus, an ezematous condition is produced.

The measures are application of unguentam hyd. amm. Ointment externally around anus and anti-helminthic treatment with Diphenan 1 gm. thrice daily for 7 days.

Ascaris lumbricoides infection :—

(1) Occasional cases of cutaneous and muscular lesion produced by ascaris larva has been reported.

(2) Ascaris infection has been known to produce urticaria and some cases of vitiligo.

The measures again Ascaris infection :—

Hertazen 3 mgm. per kilo of body weight twice daily for 3 days.

Gnathostoma spinigerum.

The infection is produced by ingestin of infected tissues of the second host (fish). This larva does not develop into adults in human-beings. The larva causes creeping eruption in skin.

The treatment is similar to creeping eruption produced by *Andylostoma braziliensis*.

FILARIAL GROUP**Wuchereria bancrofti**

- (a) Early allergic manifestations as fugitive swellings and Lymphangitis are produced.
- (b) Dilatation of the lymphatics will produce a silky condition of the scrotum.
- (c) Hyper plasia of the connective tissue will produce elephantiasis of the skin.

The measures during lymphangitis stage are Hertazan orally 2 mgm. perkilo of body weight per day for 11 to 22 days and sulphadiazine orally.

During the elephantoid condition, sodium floride injections 1 cc. 1% (I. M.) once weekly for 4 weeks and surgical measures.

Loa Loa

Calabar swellings are fugitive swelling in the skin and subcutaneous tissue. It is produced due to

- (1) Wanderings of the parent worm
- (2) Emission of larva
- (3) Toxins and
- (4) Allergy.

The measures are heliobrom externally hertazan orally.

Onchocerca Volvulus.

- (1) Lichenoid eruptions of the skin.
- (2) Typical nodules on the skin.

The tumours appear to be painless and may be removed by excision.

Hertazan has a specific action but should be used with caution in onchocerciasis.

Dracanculus medinensis or guinea worm infection.

A blister at the site of localisation forms. This blister ruptures. There may be secondary infection. Myriads of larva are liberated.

The measures are surgical extraction of the worm and intramuscular injection of phenothiazine 1 gm. in

olive Oil. Three or Four injections at weekly interval are given.

PLATYHELMINTHES

- (A) Tape worms.
- (B) Flukes.

(A) *Tape worms :*

- (a) Pseudophyllidæ having slit like grooves
- (b) Cyclophyllidæ (Cuplike and round suckers.)

Pseudophyllidæ :—

The larval form of *Diphyllobothrium Mansoni* is found in the subcutaneous tissues and muscles.

Two to six intravenous arsenbenzol 0.3 gm. each is helpful.

Cyclophyllidæ :—

(1) Larval Forms of *cysticercus cellulosæ* may occur in the somatic muscles and subcutaneous tissues producing pain.

Treatment :—This for cysticercosis is mainly excision. No drug therapy is helpful.

(2) Larval forms of *Tænia echinococcus* may occur in the skin and subcutaneous tissues producing hydatid cyst.

The only measure is surgical removal of the cyst.

(B) *Flukes.*

(1) *Paragonimus westermani :*

The commonest site is the lung but the skin may be an aberrant site producing a swelling.

Therapy : Carvasept subcutaneosly in 6 days. The total dosage is 0.3 gms.

(2) *Schistosomes :—*

The cercaria enter thro' skin and produces cercarial dermatitis and anaphylactoid or Toxic symptoms.

Therapy : Miracil D 0.3 gm. twice daily for 14 days.

ARTHROPODA

Classification:—

I. Crustacea. II. Arachnida. III. Hexopoda.

I. Crustacea:

(i) Cyclops.

(ii) Fresh water cray Fish.

(i) The cyclops infected with larva of guinea worm transmit infection to man when swallowed.

(ii) Fresh water cray fish may produce urticaria.

II. Arachnida:—

(i) Scorpion: The bite produces severe burning at site. The measures are local novacain and antivenin.

(ii) Spiders. (a) The black widow spider produces cramping pain in the skin and muscles due to bite.

(iii) Ticks: Tick bite may produce a sore at the site which may become gangrenous called

"tachenoire" The treatment is with broad spectrum antibiotics.

(iv) Mites.

(a) Glycophagus produces the grocer's itch.

(b) Tyroglyphus produces copraitch.

(c) The grain itch is produced by pediculoides ventricosus which is found in straw.

The eruption consists of wheals and erythematous urticarial and papular rashes.

Treatment: is (a) Prophylactic with D. D. T.

(b) Curative with benzyl benzoate emulsion.

(d) Itch mite or sarcoptes produces scabies characterised by burrows in the webs of the fingers, ulnar border of the hands, anterior axillary folds, buttocks and pubic area. The measures are to lay open burrow by preliminary bath using soap and rubber brush and the application of sulphur Ointment or Benzyl Benzoate emulsion.

(e) Onion mite dermatitis is produced by mites, indecaying onions called Acarus rhyso-glyphus Hysscanthi.

(f) Demodex folliculorum produces seborrhœic dermatitis.

The best measure is shampooing with green soap.

III. Hexapodes:—

(1) Cockroaches do not produce any skin lesion.

(2) Common Bugs of cimex lectularius produce by their bites, hives, humours and exanthemata.

Treatment is external application of spirit of Camphor and antbug measures with DDT.

(3) Panstronglus megistus or Reduid bugs or kissing bugs produce a lesion at the site of bite and transmit Trypanosoma cruzi. The lesion produced is chagoma.

(4) Fleas:

(a) Tungapenetrans orehiggerfla:

The parasite is anchored to corium. The impregnated female makes a home in the skin. There is

swelling, œdema and suppuration and in severe cases abscess formation.

Treatment: Extraction of flea and antibiotic measures.

(b) Rat fleas produce local lesion at the site of bite and transmit plague.

Louse infestation:—

Pediculus produce excoriation of the skin with intense pruritis called vagabond's diseases.

Treatment is 3 to 5% DDT.

Flies:—

(1) Sand Flies produce by their bites a condition called Hararadermatitis.

(2) Glossina by their bites at the site produced chancre like lesion.

Caterpillar Dermatitis:—

Dermatitis is induced by ulcerating caterpillars.

Treatment is Calamine Lotion externally.

Beetles produce painful blisters in the skin.

Clinical Experiences with Primycin, a New Antituberculous, in the Treatment of Urogenital Tuberculosis

In 1954 Valyi, Nagy, Uri, and Szilagyi published a report on the discovery of a new antibiotic which they named Primycin. Its empiric formula is $C_{19}H_{27}O_7N$, but the structural formula is still unknown. The authors employed the drug in operated cases of renal tuberculosis with post-operative fistulae or grave specific changes in the bladder. Primycin was used as powder or solution. Owing to its physical properties, the drug is suitable for topical application, because its power of adsorption is not inactivated even by prolonged contact with tissue fluids. High dilutions (1 : 50,000,000) have been proved effective against Gram-positive pathogens and mycobacterial strains resistant to other antituberculous agents. In the ten cases under investigation the result was favourable: improvement set in on the 2nd to 18th day. In complications of urogenital tuberculosis the topical use of Primycin brings very good results.

THE EFFECT OF HYPOXIA

ON RENAL FUNCTION IN MAN

In their previous works authors have shown that

states of hypoxia of the entire body and of the central nervous system—completely isolated in its circulation from the trunk—bring about characteristic changes in the renal function of dogs. Diuresis and sodiuresis are decreased, filtration is diminished and the volume of bloodflow streaming through the kidneys is abruptly lowered. Stagnant hypoxia being demonstrable in cardiac failure, deficient oxygenization of the central nervous system has been suggested as one of the causes responsible for sodium retention and œdema in heart disease. Authors report on investigations carried out on six healthy persons. Hypoxia induced in man by the breathing of an oxygen-nitrogen gas mixture containing a reduced amount of oxygen was found to produce the same kind of changes in the renal function of man as shown by dogs: decreased diuresis and sodiuresis, diminished glomerular filtration rate and plasma volume streaming through the kidneys. From the prompt onset of the changes in renal function and the reversibility of these changes when hypoxia has ceased the authors infer that the renal effects of hypoxia are primarily of neuro-reflex origin.

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Graphic 231

DUPUYTREN'S CONTRACTURE

BY DR. E. DOSKACH
Moscow—U.S.S.R.

AMONG the diseases the causes of which are, as yet, unknown to medicine, there is one which is not very noticeable to those around, but very serious to the patient. It is called Dupuytren's contracture after the name of the doctor who was the first to describe it. This disease develops slowly over a period of years, but causes invalidity.

Dupuytren's contracture may at times be associated with a previous trauma of the palm, but more often it occurs without any visible cause. No injury had apparently taken place but the disease, nevertheless, had begun to develop. At first a hard nodule resembling a corn appears on the palm, then it changes into a band, begins to resemble a thick metal wire protruding under the skin. It draws the 5th and the ring fingers firmly to the palm. In time, these fingers lose their ability to extend completely. The hand is gradually contracted into a fist, which the patient is unable to open.

All attempts to treat Dupuytren's contracture were of no avail for many years. First achievements in this field were attained only recently. It was noticed that certain preparations of the biologically active substances at times render softening effect on the contracture.

Two years ago, the Biochemical Laboratory of the Moscow Institute of Traumatology and Orthopedics suggested a preparation of this group which proved to be very effective in practice. It gave the Institute an opportunity to commence successful treatment not only of Dupuytren's contracture, but also of contractures occurring as a result of burns, fresh post-operative scars, hematomas (subcutaneous hemorrhages caused by injuries with poor resolving power), and even of certain diseases of the joints resulting from the pathological proliferation of connective tissue. Successful experiments are being conducted on the treatment of a number of other serious diseases with this drug.

What is the cause underlying this action?

It has long been known that the living body represents a sum total of definite chemical compounds which are in reciprocal equilibrium. In certain cases the equilibrium of a certain pair of elements becomes disturbed and then a pathological proliferation of the cells may occur upon which the liberated element exerts its action. Radical treatment of such states may consist only in creation of conditions for the re-establishment of the disturbed biochemical equilibrium or in the artificial depression of the excessive cellular growth. There are grounds to believe that the pathological proliferation of connective tissue forming the vault of the palm lies at the basis of Dupuytren's contracture. A biochemical analysis of such tissues removed surgically had demonstrated an excessive accumulation of hyaluronic acid. In working on the creation of a new preparation *rhonidase* and then *lidase* the authors of these drugs B. S. Kasavine, Doctor of Biological Sciences and G. M. Belenkaya, the chief of the microbiological laboratory, have aimed to find a substance which will neutralize hyaluronic acid. It may thus be understood why these drugs have a therapeutic effect not only on one disease, but on several, which at first glance have nothing in common. However, all these diseases have one common feature. They are characterized by an excessive accumulation of hyaluronic acid in the connective tissue.

Rhonidase, and especially, *lidase* are very active. In Dupuytren's contracture (the treatment of which has become the theme of a scientific work by I. M. Shinkarenko, a young surgeon) *rhonidase* is used as the first step of treatment. This preparation is for external use. Compresses with *rhonidase* which considerably soften the bands of contracture are applied for a certain period of time to the sick hand. The next step consists in administration of a certain dose of *lidase* by hypodermic injection. This preparation possesses an even more pronounced dissolving effect. If prompt treatment is commenced at the very beginning of the disease, this course of treatment arrests the development of the disease. In the majority of cases the nodule is completely absorbed and, consequently, the freedom of movement

(Continued on page 59)

The Application of Isotope Iodine-131 in Neurosurgical Practice

BY DR. A. N. ILNITSKAYA
(Sverdlovsk)

THE application of radioactive isotopes in medicine has made it possible to attempt to utilize some of them (iodine, arsenic, etc.) in neurosurgery for a more accurate topical diagnosis of brain tumours. In the Soviet Union iodine-131 with a half-life of 8 days is the most widely used for this purpose.

In the Nervous Diseases and Neurosurgery Clinic of the Sverdlovsk Institute of Physical Methods of Treatment a method of determining the functional activity of the thyroid gland is applied in cases of tumours of various location. The accumulation of radioactive iodine-131 was determined by applying a gamma-detector to different parts of the patient's head. Pieces of tumour tissue, brain tissue around the tumour, and the liquid from cysts taken during operations were also studied. The patient was given at first 10 microcuries of iodine-131. An hour after the introduction of the preparation the number of impulses in various parts of the head was determined with the help of a gamma-detector.

We studied 30 patients suspected of brain tumours. Nineteen persons were operated and tumours of different histological structure were removed (in 5

patients tumours of the posterior cranial fossa, in 1 patient a tumour in the lateral ventricle, in 10 patients tumours located in the hemispheres, and in 3 patients an abscess of the brain).

In analysing the preliminary data we came to the following conclusions: a) the site and the histological structure of the tumour exerts undoubted influence upon the uptake of iodine-131 by the thyroid; b) the presence of iodine-131 in the liquid of astrocytoma cysts is evidently connected with disturbances of the porosity of the vessel walls of the tumour and the brain tissue surrounding it; c) the cyst liquid of the craniopharyngiomas which contains much cholesterol was found to contain the greatest amount of iodine-131; d) in abscesses of the brain involving the development of a thick connective tissue capsule iodine-131 was not found in the walls of the abscesses; e) the function of the thyroid is heightened in cases of lesions in the posterior cranial fossa and is suppressed in cases of the protracted growth of meningiomas of the base of the brain; f) in the majority of cases in applying a gamma-detector to the patient's head the largest number of impulses was registered on the side opposite to the tumour.

(Continued from page 58)

of the hand is re-established. If the patient applies to the doctor only when the disease is already in the advanced stage combined treatment is required, i. e. both with *lidase* and operative. The rough bands which soften only partially under the effect of *lidase* have to be removed surgically. There is nothing particularly new in the idea of this operation, except that its technique and the principle of the complex

treatment used at the Institute of Traumatology are of interest. It makes it possible to avoid the danger of recurrence and the formation of new scars.

The biochemical principle in the treatment of diseases is still novel at present. However, its future is great, since it opens wide perspectives to medical science.

Dr. Grashchenkov joins W H O

New Assistant Director-General

DR. NICOLAY IVANOVICH GRASHCHENKOV, formerly Chairman of the Medical Research Council of the USSR, has been appointed Assistant Director-General of the World Health Organization, according to information received here from WHO Headquarters in Geneva. He succeeds Dr W. Aeg. Timmerman, who recently left his post, having reached retirement age.

In his position as one of the three Assistant Directors-General of WHO, Dr. Grashchenkov will advise the Director-General on major policy questions and will be responsible for the technical aspects of liaison with regional offices and other agencies. He will deal in particular with the following WHO programmes:

biology and pharmacology; health and vital statistics; editorial and reference services.

Dr. Grashchenkov was born in 1901 in a village of the Smolensk region and obtained his medical degrees at the Medical Faculty of the University of Moscow. He then devoted himself to medical research and teaching before being appointed in 1938 to the Chair of Neurology at the first Moscow Medical Institute. In 1955 he was also appointed Chairman of the Medical Research Council of the Ministry of Health of the USSR. Dr. Grashchenkov is Vice-Chairman of the Society of Soviet Neuropathologists. He has been a member of scientific missions to England and the USA and a delegate to the last two World Health Assemblies.

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CHEMICALS CLOSE IN ON CANCER

THE financial world fairly shook when word leaked out that E. R. Squibb & Sons was working on a chemical that showed promise in treating cancer. But seasoned chemical researchers took the news a lot more calmly. To them, it was merely another piece of evidence to shore up their belief that the chemical approach would be the one that would lead to the ultimate control of cancer.

NOT YET READY

Although the news of Squibb's development was enough to send Olin Mathiesons stock up briefly, Squibb itself went to great lengths to play down the development. The compound, it said, was more a palliative than a cure.

The drug is now undergoing clinical evaluation at the Sloan-Kettering Institute for Cancer Research (New York), University of Miami medical school and Jackson Memorial Hospital in Miami. Moreover, the compound will get further investigation at the studies panel of the Cancer Chemotherapy National Service Center, National Institutes of Health (Bethesda, Md).

The exact identity of the drug has not been reported. But it's believed to be related to progesterone, a female sex hormone (two possibilities: 9-a-bromo-11-ketoprogesterone or 9-a-bromo 11-oxyprogesterone). That such a compound would show anticancer activity is not surprising, for steroids have long been recognised as possible cancer weapons.

Literally hundreds of steroids, turned out by a clutch of drug firms have been or are currently being screened for anticancer properties and some of these have shown promise. Upjohn's Halotestin

(9-a-fluoro-11-B-hydroxy-17-methyl testosterone), for example, has reportedly effected remission of breast cancer in some cases.

GIANT STEP

So far, anticancer chemical research has been limited by the fact that relatively few of the compounds screened have been tailored expressly for potential use as tumor-thwarters. Thousands of the compounds evaluated have originated in other forms of research, were turned over for screening on the bare hope that they might prove useful. While screening laboratories (e. g. Sloan-Kettering) welcome such compounds, relatively few of the latter have shown promise.

Now, a new contract between the Cancer Chemotherapy National Service Center and Standard Research Institute (in collaboration with Sloan-Kettering) will help alleviate this situation. First and largest of its kind, the contract will cost \$ 450,000/- year (supported mostly by the center). Under its terms, SRI will systematically seek out potentially useful cancer drugs, plan their design and synthesis. Emphasis however, will be on antimetabolites research on chemicals that block the abnormal growth of cancer cells without affecting normal cells.

OTHER IRONS

There's a massive screening programme, of course, that's sifting out all types of potential cancer drugs. And there have been any number of ones that have showed some activity in controlling it. The government's center at Bethesda which spends \$20 million of the government's \$ 46 million year Cancer Institute budget—has many chemotherapeutic irons in its fire. For example, it has had screening contracts for some time with Hazleton Laboratories (Falls Church, Va);

Arthur D. Little Inc., (Boston) Microbiological Associates (Bethesda, Md.) Southern Research Institute (Menlo Park, Calif.) and Wisconsin Alumni Research Foundation (Madison, Wis). And chances are growing that under government auspices, both the preparation and screening of potentially valuable compounds will be stepped up by drug makers and others.

The SRI programme employs 25 staffers, is headed by senior chemist Bernard Baker and group leader Leon Goodman. Its objectives:

- * To synthesize new organic chemicals that are potentially useful to the programme.

- * Analyze the new compounds to verify their composition

- * Prepare them in quantity for testing at Sloan-Kettering and other institutions participating in the broad NCI-sponsored programme. Toward this end, SRI has already built and equipped a special \$40,000 laboratory.

To date, the bulk of anticancer chemical research (excluding the cut-and-try sifting of thousands of compounds for anticancer activity) has been aimed at studying the synthesis of nucleic acids and how to block the latter's formation. Reason: formation of nucleic acids leads to formation of cells. Since one cancer trait is abnormal and uncontrolled increase of body cells, the blocking of nucleic acid formation is believed to perform a key part in controlling cancerous cell growth.

The California researchers, however, intend to concentrate on another chemical factor in cell formation—coenzymes—which, like nucleic acids also are involved in cellular reaction (e. g. fat synthesis and breakdown carbohydrate synthesis and breakdown). Their premise: studies of co-enzymes formation concern a primary effect. Nucleic acids only a secondary effect. That's because coenzymes are required for the formation of nucleic acids, but new nucleic acids aren't required for the formation of coenzymes.

THREE APPROACHES

SRI will concern itself with synthesizing three different types of compounds:

- * Coenzyme antagonists—also known as “fraudulent” coenzyme precursors—which result in coenzymes having unusual chemical composition. Such coenzymes will be incapable of synthesizing cells, are intended to slow or halt cell reproduction. The bulk of SRI's work will be in this area.

- * Nucleic acid antagonists. While Baker doesn't feel that nucleic acids play a major role in cancer chemical research he's fully aware that some other experts do. He therefore intends to spend some time on developing “fraudulent” precursors for nucleic acids. Specifically, he will seek methods of producing deoxyribose nucleosides (DRN), will attempt to replace the natural base in DRN with such compounds as 8-azaguanine.

- * SRI later on, will try to make anticoenzymes. These are different from the antagonists in that they completely block the synthesis of co-enzymes (by preventing utilization of precursors) rather than alter the coenzyme that is produced. While anticoenzymes are a logical target they're low on the SRI agenda. Reason: the compounds are extremely difficult to make, knowledge of their chemistry is not far advanced.

MAIN GOAL

Right now, SRI's approach is to vary the makeup of the nucleosides, nucleotides, B Vitamins, glutamine, and nonessential amino acids that are used in synthesizing fraudulent coenzyme precursors.

Sulfur and nitrogen-substituted forms of nucleosides will be made starting with purine. Such compounds have shown anticancer properties (e. g. Lederle's Puromycin). The trick lies in making the substitutions at the right chemical positions (the three prime positions of the nucleoside sugar's ribose group). In previous research, substitutions on the 2-and 5-positions of the ribose group gave inactive compounds.

Nucleotides of the base-ribose-phosphate type will be altered in the phosphate group. There's no evidence, yet, that this will result in anticancer activity. But that doesn't preclude an anticancer possibility, Baker feels.

Synthesis of fraudulent coenzyme precursors from B vitamins will stress riboflavin and folic acid. For

example, the SRI researchers will attempt to make a riboflavin that does not have an oxidation-reduction action, its normal role in cellular synthesis. And from folic acid and tetrahydrofolic acid they will try to make compounds that interfere with formate transfer also important in cellular synthesis.

From glutamine (an amino acid) Baker will attempt to make fraudulent coenzyme precursors in which amide nitrogen is replaced by other groupings (azaserine is an example—but there may be more effective analogs that haven't been made and evaluated).

Once SRI has learned to synthesize promising compounds, they will be screened on mice, be evaluated further for other properties (e. g. antibacterial) by pharmaceutical firms.

THORNY ROAD

Chemical treatment of malignant cells is complicated by the fact that over 300 different type of human cancer cells are known to exist. And ideal agents will have to be highly selective avoid damage to normal cells while exerting their therapeutic power. It's always possible, of course, that an entirely new route to cancer chemotherapy may turn up. Recently, such a possibility opened up in the finding (by R.A. Holman of the Welsh National School of Medicine, Cardiff) that administration of 0.45% (by weight) hydrogen peroxide in water resulted in “marked clinical improvement” in two of four humans having very advanced inoperable tumours.

LAST RESORT

Baker, himself, points out that surgery and X-ray treatment which now cure about a third of all cancer cases are approaching a limit—“the 35% asymptote”. Despite the therapeutic potential of virus, radiation and immunological treatment, he is convinced that chemicals offer the best hope for an eventual cure. Reasons Baker, “Anything that goes on in the formation of cells involves chemistry. That's why the chemical approach is so important in trying to solve this problem”.

To scores of seasoned cancer chemotherapy researchers, there's no fault to find with this philosophy.

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Untoward Reactions to Penicillin

World production of penicillin is now sufficient to provide more than 250 million courses of treatment annually. Against this staggering total, the number of severe reactions reported remains exceedingly small. Yet it is important that all users of penicillin should be fully aware of the reactions that may occur and of the precautions that should be taken to keep the risks to a minimum. With the aim of providing public health authorities with a readily accessible body of data on which to base their policies, WHO has undertaken a study of these questions, the first results of which form the subject of this article.

"PENICILLIN is the queen of drugs. It is the most satisfactory weapon known in that it does its particular task with utmost efficiency and negligible harm." This opinion was expressed in 1954 in an American textbook of pharmacology.¹ Can it still be upheld in view of the increasing number of severe and fatal reactions reported in the medical literature? The answer is of vital importance to public health programmes, for penicillin has undoubtedly become the key drug in the control of a wide range of communicable diseases. WHO has a special interest in this question, for the campaigns against treponematoses which it is sponsoring, and which involve millions of people in many parts of the world, would be impossible without penicillin. In December 1956, a questionnaire on the incidence of penicillin reactions was sent to members of the WHO Advisory Panel on Venereal Diseases and Treponematoses, and earlier this year an analysis of the answers was published in the WHO Bulletin.² The same number of the Bulletin also contained a report on penicillin-sensitivity reactions in Taiwan.³ Following up these studies, a comprehensive review of the literature has now been undertaken by T. Guthe, O. Idsøe and R. R. Willcox.⁴ It is on this review that the following discussion is mainly based.

THE PICTURE IN OUTLINE

Penicillin came into general use in 1943, but the first death from penicillin therapy was not reported until 1946, and another three years elapsed before a second fatality occurred. During the past ten years, however, severe reactions have been reported with

increasing frequency, and the number of fatal cases has multiplied rapidly. By 1955 some 560 anaphylactic reactions had been reported, 81 of them fatal, and by 1957 it was estimated that some 1000 deaths from anaphylaxis due to penicillin and occurred in the United States of America alone. To obtain a true picture, however, these figures must be set beside the phenomenal increase in the consumption of penicillin that has taken place during the past 15 years. In 1943 the first year of commercial production in the United States of America, only 29 pounds of crude penicillin were produced, whereas by 1955 the world production of penicillin exceeded 500 tons a year—enough to provide 250 million courses of treatment of 3 million units each.

The increasing frequency with which reactions have been reported in recent years is thus seen to be largely a natural consequence of the vast scale on which penicillin is now being used. Indeed, it is the general absence of untoward reactions that has encouraged such lavish use of penicillin. Unfortunately, it has also encouraged its indiscriminate use. Penicillin has been widely prescribed for all kinds of minor infections, and for conditions in which it is ineffective or not more effective than other drugs; and since it can be bought without prescription, self-medication is common. Severe reactions occur only in patients sensitized by previous exposure to the drug, and it is known that many of the fatalities that have occurred following the legitimate use of penicillin have been attributable to previous unnecessary medication. Naturally, the chances of a patient having had previous treatment with penicillin are today much greater than they were 10 or 15 years ago.

These are the main features of the present situation. In order to analyse it further, it is necessary to examine in some detail the nature of the reactions that may result from penicillin administration.

TYPES OF REACTION TO PENICILLIN

In common with most other drugs, penicillin can produce various types of untoward reaction. These are often referred to collectively as "toxic reactions", but strictly speaking this term should be reserved for quantitative, pharmacological effects experienced by every person receiving a sufficiently large dose of the drug, i. e., for effects which are inherent in the nature of the substance and the severity of which is a function of the dose.

Most modern chemotherapeutic agents have a low toxicity in relation to the therapeutic dose, and penicillin is an outstanding example of this. But these drugs can produce reactions of a different kind, by virtue of the fact that they are potential antigens; repeated administration may produce sensitization in the patient, leading to allergic skin reactions or anaphylactic shock. The majority of the reactions to antibiotics in general, and to penicillin in particular, are produced by this mechanism.

Antibacterial drugs can also produce undesirable reactions by interference with the metabolism of the microbial flora. This can result in superinfection and cross infection by organisms less affected by the drug than others, or in a temporary exacerbation of symptoms due to the release of noxious substances following microbial lysis. A more serious problem is the development of resistance in the organism against which the drug is being used.

LOCAL AND SYSTEMIC TOXIC REACTIONS

On the whole, local toxicity to penicillin has not presented an appreciable problem. The early amorphous preparations of penicillin sometimes produced thrombophlebitis when given intravenously, or pain and cellulitis on intramuscular or subcutaneous administration; and penicillin in oil-beeswax, used between 1945 and 1948, often caused local reactions of an allergic nature. Since the introduction of procaine penicillin with aluminium monostearate (PAM), however, local reactions have virtually ceased. The more recently introduced benzathine penicillin—a particularly long-acting preparation—was at first found to cause pain on injection, but improved preparations have largely overcome this difficulty.

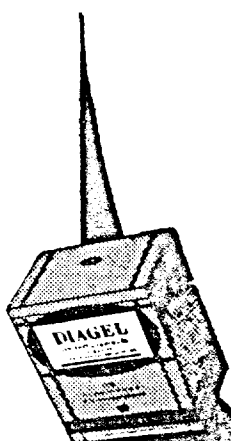
The acute toxicity of the various penicillin salts in animals is very low. Mild systemic toxic reactions were sometimes experienced with the early preparations, owing to the presence of impurities, but such reactions are practically unknown with the highly purified preparations now in use. It has been calculated that for a 70-kg man, the LD₅₀ of sodium penicillin would be more than 150 million units—a dose far in excess of what it would be practical to give. There have been isolated reports of damage to the central nervous system, peripheral neuritis, and transient psychosis following intramuscular injection. The pathogenesis of these reactions is unclear, however, and it is by no means certain that they are true toxic reactions. In any event, they are exceedingly rare. In contrast to the sulfonamides and many other drugs, penicillin does not cause damage to the bone marrow or haemopoietic system, and it can be safely given in severe anaemia. Intrathecal administration of penicillin causes meningeal irritation and serious complications have been reported, but this route of administration is seldom used today. It seems justifiable to conclude that "the toxic effects of penicillin in man are, in the broad run of

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¹ Drill, V.A. (1954) *Pharmacology in medicine: a collaborative textbook*, New York

² Willcox, R. R. (1958) *Bull. Wld. Hlth. Org.*, **18**, 457

³ Idsøe, O. & Wang, K. Y. (1958) *Bull. Wld. Hlth. Org.*, **18**, 323

⁴ Guthe, T., Idsøe, O. & Willcox, R. R. (1958) *Bull. Wld. Hlth. Org.*, **19**, (In press)

events, negligible. They certainly have detracted little from the use and usefulness of penicillin in clinical practice and public health programmes."

ALLERGIC SKIN REACTIONS

As already mentioned, allergic reactions differ from true toxic reactions in that they are not inherent in the pharmacological nature of the drug, but are due to a hypersensitivity, or altered reactivity, of the patient, usually the result of previous exposure to the drug or a related substance. Moreover, the severity of such reactions is independent of the quantity of drug administered, and they can be produced even by minute doses.

It seems that penicillin can evoke the production of two types of antibody: a skin-sensitizing antibody and an antibody responsible for anaphylactic reactions. The skin-sensitizing antibodies may produce either an eczematous reaction or an urticarial response. The most frequent form of eczema is contact dermatitis caused by local application of penicillin in the form of ointment or solution, or by prolonged handling of the

drug, as in doctors and nurses. Estimates of the frequency of contact dermatitis vary from 4% to 10% of persons exposed to contact with the drug over long periods. It is therefore advisable to avoid local applications of penicillin wherever possible, and in any case not to continue treatment for more than three to five days. Desensitization is sometimes of value for doctors and nurses.

Another form of eczema can be caused by parenteral administration of penicillin, or by its inhalation. The eruptions are of the erythematovesicular type, resembling those caused by fungal infections (trichophytosis and epidermophytosis), and are characteristically localized to the groins, the interdigital spaces, and the palms and soles. It has been suggested that a previous fungus infection may result in cross-sensitivity to penicillin, as it appears that such reactions may occur in persons not previously exposed to the drug.

Both types of eczematous reaction usually subside rapidly when penicillin is stopped and appropriate treatment given. Topical application of hydro-cortisone may be of value in prolonged cases. It is rare

for generalized eruptions or exfoliative dermatitis to develop. If they do they are generally of a mild type, although serious complications, such as anuria, have been reported, and exfoliative dermatitis may occasionally become hæmorrhagic and gangrenous.

"serum-sickness-like penicillin reactions" is a collective term which has been proposed to describe a group of allergic reactions comprising urticaria, angio-neurotic oedema, joint pains, inflammation of the lymph glands, fever, and other manifestations similar to those seen in serum sickness. Such reactions usually follow injections of penicillin, but can also occur after other forms of administration. They may appear within 30 minutes or only after several weeks. With modern preparations of penicillin, such as PAM, it has been estimated that serum-sickness-like reactions occur in 1-2% of all patients receiving the drug. Children appear to be less likely to develop such reactions than adults. Serum-sickness-like reactions are not usually dangerous, but very rarely severe and even fatal complications may develop, such as laryngeal oedema, periarteritis nodosum, purpuric lesions, or cardiovascular collapse. ACTH or cortisone may be life-saving in such cases. Mild reactions usually subside spontaneously within a few days or weeks when penicillin treatment is stopped. The antihistamines may be effective in severe or prolonged cases, but are of no value prophylactically, although an antihistamine-penicillin salt recently introduced has been claimed to obviate allergic reactions in persons sensitive to penicillin. The use of the enzyme penicillinase in cases of urticaria and angioneurotic oedema resistant to other methods is another recent development that has given promising results.

All forms of skin sensitivity to penicillin are usually transient, declining gradually over a period of 6-12 months. Nevertheless, treatment with penicillin should be avoided if possible in patients with a past history of skin reactions, since the symptoms may recur, and the possibility of systemic rather than skin sensitization has to be kept in mind.

ANAPHYLACTIC REACTIONS

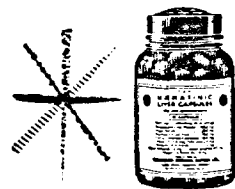
As already indicated, allergic skin reactions to penicillin rarely constitute a danger to life; most of the fatalities that have been reported have been due to reactions of the anaphylactic type. Since such reactions are only known to occur in persons sensitized

by previous exposure to the antibiotic, they were exceedingly rare during the first few years of penicillin therapy.

It is difficult to make an accurate assessment of the frequency with which anaphylactic reactions occur, as only a small proportion of them are reported in the literature, even if they end fatally. The greatest number of reports comes from the United States of America which consumes about three-fifths of the total world production of penicillin, and a survey described by Welch et al. in 1957⁵ throws some light on the frequency of anaphylactic reactions in that country. In the 827 hospitals covered by the survey, there were 2500 penicillin reactions during the three years 1954-56. Of these, about 793 were of the anaphylactic type and 72 were fatal. Since the three-year survey covered one-third of the hospitals in the United States, these figures can be considered to correspond to the annual rates for the whole country. During the same period about 260 tons of penicillin a year were used for human medicine in the United States. This is enough to provide some 300 million injections, so that there were about 25 anaphylactic reactions and 2-3 deaths for every 10 million injections given. An estimate for Denmark, based on statistics for the years 1951-55, also arrived at a figure of 3 deaths per 10 million injections.

The importance of previous exposure to penicillin is exemplified by the fact that in the mass campaigns against the treponematoses among populations not previously exposed to penicillin, several million people have received penicillin injections without anaphylactic reactions having been reported. On the other hand, in Taiwan, where the consumption of penicillin is very heavy (nearly 500,000 units per person per year), there were 74 anaphylactic reactions, including 12 deaths, between 1951 and 1955. For the same reason, anaphylactic reactions are more common in urban than in rural areas. Occasionally, a negative history of previous penicillin administration is obtained, but this can be misleading, as local applications, inhalations, etc. are not always remembered. Serious and even fatal reactions have repeatedly been reported in patients who have previously used penicillin tablets, lozenges, spray, antral instillations, and ointment. Exceedingly small quantities of penicillin seem capable of causing sensitization in susceptible persons. In one of the fatal cases reported from Taiwan, sensitization

⁵ Welch, H. et al. (1957) *Antibiot. Med.*, 4, 800

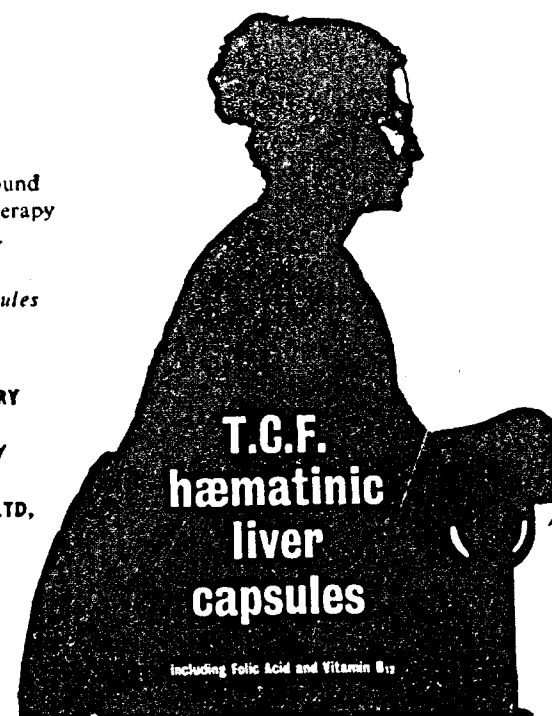


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appeared to have been induced by a single tablet of 50,000 units taken one year previously. Most of the patients, however, had previously been exposed to amounts between 0.6 and 4.8 mega-units.

The time interval between the administration of penicillin causing the anaphylactic reaction and the last previous administration can vary widely. Intervals as short as ten days and as long as eight years have been reported. The length of the interval does not appear to bear any constant relation to the severity of the reaction, which probably depends more on individual factors. It should be noted that in a sensitized patient the first subsequent administration of penicillin will bring on a reaction. Consequently, if a patient is given penicillin and no reaction occurs, it can be assumed that further administrations in the same series will be without danger, provided that the intervals between the doses are not longer than four days. From this it follows that short courses of treatment with high single doses are preferable to longer courses with smaller doses.

The type of penicillin preparation used does not appear to be important. Skin tests indicate that the common penicillin preparations are immunologically equivalent, and this is supported by clinical experience. Although most of the reactions reported have occurred with procaine-penicillin preparations, this merely reflects the fact that it is this type of preparation which is generally used; many authors have stated that procaine is unlikely to induce sensitivity, and in two cases in which aqueous penicillin was substituted because of suspected sensitivity to the procaine component, the patients died.

It seems, then, that the way in which a sensitized person will react to a subsequent exposure to penicillin is dependent largely on personal, constitutional factors. Little is known as yet about the nature of these personal factors. The reactions occur most commonly in adults between 20 and 49 years of age, but they appear to be equally distributed between the two sexes. They are rare in children under 12 years old, and the frequency decreases rapidly with increasing age after 50. Children treated with penicillin are, of course, less likely to have had a previous exposure to the drug than older persons, but there is also some evidence that they are less easily sensitized. In the older age-groups, the consumption of penicillin is presumably lower than in younger adults, but it may

also be that desensitization takes place in the course of time.

It does seem well established, however, that patients with a personal or family history of allergy are more easily sensitized than others, and that they react more severely to subsequent treatment; great caution should therefore be observed if re-treatment with penicillin is indicated in such patients.

CHANGES IN THE MICROBIAL FLORA

Of the various changes in the microbial flora brought about by the administration of penicillin, the one which has caused most concern so far is the development of resistance in staphylococci. Some organisms, such as *Escherichia coli*, show a natural resistance to penicillin, but acquired resistance has not presented a problem as yet in other than staphylococcal infections. In some studies, 50-70% of hospital patients have been found to carry antibiotic-resistant staphylococci, the type of resistance depending upon the antibiotic in current favour. Cases of complete resistance to all antibiotics have been reported. Resistant staphylococci can cause superinfection in a patient being treated with the antibiotic, or cross-infection in other patients in the same ward. The main problem has been created by staphylococcal pneumonias and urinary and wound infections. Staphylococcal enteritis may sometimes occur as the result of superinfection of the bowel with penicillin-resistant organisms from the mouth or throat, but this complication is more common with orally administered antibiotics, such as the tetracyclines.

The resistant organisms are spread by dust from clothing and bedclothes, or by hospital personnel who acquire resistant strains from penicillin-treated patients. It has been shown that the proportion of nasal carriers among student nurses entering hospital may increase in one month from around 5% to as much as 50%. Precautions which should be taken in hospital to prevent cross-infection include such measures as isolation of staphylococcal cases and carriers, barrier nursing, and the wearing of masks by hospital staff. The development of resistant strains can be minimized by restricting the use of penicillin—and, indeed, of all antibiotics—to cases where they are absolutely necessary, and by giving sufficiently large doses at the beginning of treatment to kill the organisms rapidly.

Fortunately, the acquired resistance of the staphylo-

cocci is usually lost again fairly rapidly when they are diluted with non-resistant strains in the general population, and, outside hospital, resistance has so far not been encountered on a serious scale. It has recently been reported, however, that the percentage of nasal carriers of staphylococci among blood donors in Australia was twice as high in 1955 as in 1954, and the situation must therefore be watched carefully.

Among organisms other than staphylococci which may cause superinfection during penicillin therapy, as a result either of resistance or of decreased competition, mention may be made of *Escherichia coli* and of paracolon and proteus bacilli. Overgrowth with *Candida albicans* is more common after the orally administered tetracycline antibiotics than after parenterally administered penicillin, but cases of moniliasis have been reported, usually in the mouth. It

has been suggested that the "broad spectrum" approach, in which penicillin is combined with other antibiotics, may actually increase the risk of superinfection by all types of organism.

In the treatment of syphilis with penicillin, a Herxheimer type of reaction frequently occurs. This phenomenon, also known as "therapeutic shock", is generally attributed to the release of noxious substances by the spirochaetes killed by the drug. In early acquired syphilis, it occurs in 80-90% of patients. The reaction is usually mild in such cases, and there is no need to discontinue therapy, but severe and even fatal reactions may occur in late neurosyphilis, cardiovascular syphilis, and gummatous syphilis, as well as in debilitated babies.

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cause deficiency syndromes due to disturbance of the metabolic processes in the gastro-intestinal tract and interference with the production of the vitamin B complex and vitamin K. It is believed that the symptoms, which include black tongue and lesions of the oral mucosæ, are due in part to an overgrowth of pathogenic flora.

PRECAUTIONARY MEASURES

The frequency of severe reactions to penicillin can be greatly reduced by taking a number of simple precautions, and it should be possible to eliminate fatalities almost entirely if the physician giving the injection always has at hand the necessary drugs to deal with an emergency. Before administering penicillin, the patient should be questioned carefully regarding previous exposure to the drug and any manifestations of an allergic diathesis in himself or his family. Full details of previous treatment should be noted and if a reaction occurred, renewed treatment with penicillin should be regarded as contra-indicated. Even mild reactions, such as itching, a tingling feeling in the tongue or fingers, a peculiar taste in the mouth, dizziness, or slight fever, should be taken as an indication of the probable presence of anaphylactic sensitivity, precluding re-exposure to any type of penicillin preparation. An exception is the delayed type of serum-sickness-like reaction, which does not appear to be a usual precursor of anaphylaxis.

There is clear evidence that patients with a history of asthma, hay fever, rhinitis, or other allergic diseases react more easily and more severely than others. Bronchial asthma, in particular, appears to increase considerably the risk of severe anaphylactic reactions in penicillin-sensitized patients, and an asthmatic patient should not be treated with penicillin if this can possibly be avoided. As an additional precaution, a skin test can be performed, but patch tests appear to be of little value, except in contact dermatitis. On the other hand, the immediate intradermal test, although usually positive in cases of anaphylaxis, may itself produce a severe anaphylactic reaction. Moreover, a negative test does not necessarily exclude penicillin sensitivity. Routine skin testing is probably not a practical procedure for all patients, but might be considered before treatment of persons who routinely handle penicillin.

Penicillin should be injected slowly by the intramuscular route, and the patient watched carefully during

the injection for any signs of a reaction. Some authors favour giving the injection in one of the upper arms rather than in the buttock, so that a tourniquet can be applied if a reaction commences, but the efficacy of this procedure is doubtful. If possible, the patient should be allowed to remain in the consulting room for about 15 minutes after the injection. Adrenaline (1:1000) should be to hand for immediate injection if anaphylactic symptoms appear; if subcutaneous injection is ineffective, it may be given intravenously, or even directly into the heart. An antihistamine, such as diphenhydramine hydrochloride or tripeleminamine, should also be given, and aminophyllin has been recommended by some authors in cases of respiratory distress. These drugs, together with the appropriate syringes, should always be carried by a doctor giving injections of penicillin. In clinics oxygen should also be available, as well as drip-infusion set; continuous drip-infusion of *l*-arterenol or plasma has been recommended in cases of prolonged depression of the blood-pressure. Intravenous cortisone or intramuscular ACTH is also indicated in protracted cases. Recently it has been shown that penicillinase, an enzyme that inactivates penicillin, is capable of clearing the circulating antibodies from the blood. Given simultaneously, 5000 units will completely inactivate 100,000 units of crystalline penicillin. This enzyme may prove of great value in the future for arresting anaphylactic shock. The recommended dose is 800,000 units intravenously, followed by 800,000 units intramuscularly.

CONCLUSIONS

From the data at present available, it may be concluded that the inherent toxicity of penicillin is so low as to be of negligible importance, but that discretion in its use is called for on two grounds: allergic or anaphylactic reactions may occur in previously sensitized persons, and there is a risk of superinfection or cross-infection with penicillin-resistant organisms, especially staphylococci. The increasing frequency of untoward reactions to penicillin is attributable to the increasing use of the drug, and especially to its uncontrolled, indiscriminate use. Since sensitivity reactions almost always occur in patients previously exposed to the drug, it should not be given for minor ailments or for diseases in which its efficacy is doubtful or not superior to that of other drugs. If it is reserved for cases in which its use is fully justified, the chances of repeated exposures will be reduced to a minimum. Courses should be kept as short as possible

by giving high doses. This will also help to diminish the likelihood of creating resistant strains. The risks of cross-infection in hospital can be minimized by suitable hygienic measures.

Another fact that emerges clearly from this survey is that, although minor allergic reactions may occur in up to 1-2% of patients receiving penicillin, severe, anaphylactic reactions are exceedingly rare in comparison with the enormous quantities of penicillin used. It has been estimated that there are probably not more than 25 such reactions for every 10 million injections given and that only about three of these prove fatal. Moreover, it is interesting to note that, of the 12 fatalities reported from Taiwan, 10 were in patients treated by private practitioners and the other two deaths occurred after penicillin injections given in a drug store and by a herb doctor. Only one reaction was reported from a hospital. There is reason to believe, therefore, that severe reactions are much less likely to occur if proper precautions are observed.

Finally, the reactions that penicillin may cause must be set against the great powers which it possesses for the control of communicable diseases. When the entire picture is viewed in perspective, it is seen that penicillin does indeed do its task "with the utmost efficiency and negligible harm", and that there is ample justification for continuing to regard penicillin as "the queen of drugs". But, not unlike many queens of the past, she may retaliate on those who do not respect her powers. There is need for education of doctors, nurses and the general public concerning the proper use of penicillin and the risk of sensitization; and the sale of penicillin should be restricted by the introduction of regulations regarding prescription. In mass campaigns, similar tactics should be adopted to those employed to overcome the problem of insecticide-resistance in the control of insect-borne diseases: the work should be intensified so that the value of penicillin can be exploited to the full before, or in case, sensitivity or microbial resistance makes its appearance.

—(W. H. O. Chronicle)

Chemotherapy in tuberculosis. Jensen, K. A. and others, *Ugeskrift for Laeger*, Denmark, 115: 1267-1272, August 20, 1953; through: *Journal of the American Medical Association*, U. S. A., 153: 1594, December 26, 1953.

The introduction of isoniazid marks an important advance in the treatment of tuberculosis, but tubercle

bacilli rapidly become resistant to the agent when it is applied alone, and, further, there is danger of home treatment because treatment with isoniazid alone is so easily carried out. In order to prevent this valuable agent from becoming ineffective through misuse, Jensen and his associates emphasize that treatment of pulmonary tuberculosis with isoniazid alone is contra-indicated except in the case of the few patients in whom the tubercle bacilli are in advance resistant to both streptomycin and p-aminosalicylic acid (PAS) and where treatment is required. A long-continued effect of streptomycin or isoniazid can be attained by the combination of each of the substances with p-aminosalicylic acid. Combined treatment with all three substances is considered the most effective chemotherapy in tuberculosis. In treatment of patients with tubercle bacilli resistant to streptomycin the combination of isoniazid and p-aminosalicylic acid may be recommended, but it must be borne in mind that in about one-fourth of the patients with cavernous pulmonary tuberculosis, tubercle bacilli resistant to isoniazid appear after three months' treatment.



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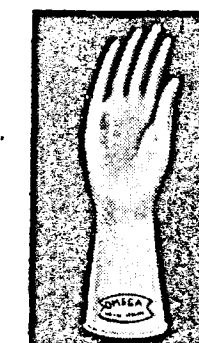
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HEY GROVES' 'A SYNOPSIS OF SURGERY'—
Fifteenth Edition—Fully Revised—Edited by Sir Cecil
P. G. Wakeley—Published by John Wright & Sons
Limited, Bristol, 1958—Price 37 s. 6 d.

To acquaint the reader of the exact scope of this book one could no better than to quote from the preface of the First Edition of this book edited by Hey Groves in 1908.

"In recent years the tendency of all surgical literature to grow in bulk and diversity has of necessity compelled authors to enlarge their textbooks more and more. Complete treatises on surgery occupy many volumes, and even the most concise require months for their perusal, so that a student often despairs of being able to revise his knowledge".

"The present volume is an attempt to make an epitome of the salient facts in surgical practice, and to place these facts in such a manner that they may most easily and rapidly be referred to or revised."

It is admitted that one cannot do without textbooks of surgery but this Synoptic volume is planned and arranged in such a manner as to enable the student to become familiar with the latest advances in surgical practice. This book will help the student when answering a question to present what he has to say in a clear and succinct manner. Anatomical and pathological facts are included only when they are essential to help understanding of clinical signs and operative measures.

The book has 650 pages and the subject is divided into 49 chapters which deal with the conventional aspects of Surgical practice. The book is by no means lacking in black and white drawings and there are 190 figures as well as 13 plates. There is a com-

prehensive index of the end of the book. Sir Cecil Wakeley's Synopsis of Surgery may with confidence be recommended to all students going up for examinations in Surgery and for all those practitioners who wish to refresh their knowledge of Surgery.

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EMERGENCY SURGERY—

Seventh Edition—Edited by Hamilton Bailey—Published by John Wright & Sons Ltd., Bristol, 1958—Price £9. 9 s.

As with all its predecessors, this is a magnificent book on Surgical Emergencies. This 1197 page book profusely illustrated with 1576 figures is divided into 8 sections namely: General Emergency Measures, The Abdomen, Genito-Urinary, The Thorax, The Spine, The Head, and the Neck, The Extremities, The Eye, Ear, Nose and Throat, and lastly Tropical Emergencies. Of the sections the first one on General Emergency Measures includes the following 14 chapters: Armamentarium, Cannulization for Infusion and Transfusion, The Establishment and Maintenance of Fluid and Electrolytic Balance, with Special Reference to Venoclysis, Replenishing the Circulating Body Fluids—Alternative Methods, Blood Transfusion, Haemophilia, The Shock Syndrome, Burns, Impending Death under Anaesthesia, Air Embolism, Acute Non-specific Infections, Acute Specific Infections, The Treatment of wounds and lastly some Post-operative complications. In this section the following features are worthy of special note. Illustrations of instruments used for surgical practice are very instructive. On page 18 beautiful colour photographs demonstrate the technique of sternal marrow infusion. The importance of fluid and electrolyte balance is adequately dealt with and the

dangers of administering excessive fluids emphasised. Useful photographs demonstrate many of the techniques of blood-transfusion which practitioners must know.

Once again excellent colour photographs show how a blood transfusion has to be put up by the bedside. Methods of treating shock including the use of nor-adrenaline by drip is included. Methods of resuscitation are described in the chapter on "Sudden death under anaesthesia". Emergency measures such as artificial respiration and a cardiac massage find a place. The principles which govern the sound management of important diseases such as tetanus and gas gangrene are emphasised. Post-operative complications are considered in one chapter.

Incidentally many of these chapters are preceded by apt quotations as for instance John Watson is quoted as follows in the chapter on post-operative complications "The more one sees of the practice of surgery the more one is impressed by the relative frequency of unforeseen complications, and when one carefully thinks out the cause of these troubles it is only to find that most of them could be prevented." The anatomical basis an understanding of which is necessary for the opening of the abdomen is enumerated. Methods of draining the peritoneal cavity, retro-peritoneal space and the abdominal wall receive a complete chapter. Six photographs on page 196 show how the stomach is aspirated.

Acute appendicitis, a very important problem in surgical practice is dealt with comprehensively and there are many excellent drawings in colour. The drawings which go to illustrate the chapter of "Some other conditions simulating acute appendicitis" are imaginatively conceived. Quoting Lord Moynihan "Perforation of a gastric or duodenal ulcer is one of the most serious and most overwhelming of catastrophes that can befall a human being" a chapter on perforation follows. The author does credit to the subject on removing foreign bodies from the oesophagus. The different types of foreign bodies which may be found in the gastro-intestinal tract are illustrated by several x-rays. Intra-abdominal injuries such as rupture of the spleen, rupture of an aneurysm of the spleen, rupture of the mesenteric artery, rupture of the liver, rupture of the small intestine, large intestine, duodenum, pancreas, and gall-bladder are all adequately dealt with, the text being illustrated by most instructive and attractive colour pictures. The

chapter on penetrating wounds of the abdomen is preceded by a quotation "It is safer to look and see than to wait and see." (Cuthbert Wallace). Detailed steps of operations for bowel anastomosis are shown with illustrations. Intestinal obstruction, an important surgical subject is extensively dealt with. There is also a most useful chapter on intestinal obstruction in the new born.

There is a special chapter on the female generative organs. Ectopic gestation, a most important and dangerous complication of pregnancy is considered as well as other emergencies such as rupture of a lutein cyst, twisted ovarian cyst, rupture of an ovarian cyst, necrobiosis of a uterine fibroid, haemotometra of one horn of a bicornuate uterus, traumatic perforation of the uterus, Hysterectomy, haematocolpos and pelvic infections. This chapter is followed by one on obstetric emergencies which require urgent surgery. Injuries of the urinary tract are dealt with, adequate stress being laid on diagnosis and methods of treatment. One chapter deals with thoracic injuries.

Magnificent colour photographs illustrate the surgery of the scalp. Modern surgical procedures in bone and joint injuries, infections, and in facio-maxillary surgery are also included. There is a chapter on the performance of urgent amputations. The surgery of the hand, a most complicated subject has a separate chapter and there is emphasis on the plastic and reconstructive aspect. Surgical complications involving the nerves, muscles and tendons are included.

The Eye and orbit, Ear, Nose and Throat are also dealt with.

A chapter which is sure to be of considerable interest to practitioners in our country is the one on surgical emergencies in the tropics. This deals with subjects such as malnutrition, dehydration, heat stroke, malaria, rupture of the spleen, worms as a source of surgical emergencies and amebic hepatitis and abscess. If one chapter is singled out for special mention it does not follow that the others are in any way lacking.

Mr. Hamilton Bailey has enrolled the help of several of his distinguished colleagues to assist him in the production of this magnificent and useful book which is a *must* on the shelf of any medical practitioner who may at any time be called upon to

perform an emergency operation. In going through the book one cannot but have praise for the great industry and the diligence with which Mr. Hamilton Bailey has gone through his professional life, which qualities alone can enable the author to write such a comprehensive and valuable book. One should meet Mr. Hamilton Bailey in person to realise the tremendous energy and capacity with which he goes through each day. It is worthwhile reiterating what he has said in the preface of the present edition.

"The teachings of my masters are its foundations; practical experience gained in widely separated centres is its scaffolding; while the building material comes from my case index. Most of the sections of the text are founded upon personal experience; all are supported by a study of the literature."

No surgical library can claim to be complete without Mr. Hamilton Bailey's "Emergency Surgery".

* * * * *

THE PRESERVATION OF EYESIGHT—

By Sir Arthur Salusbury MacNalty (Prepared with the advice of a Consultative Committee) — Published by John Wright & Sons Limited, Bristol, 1958 — Price not stated.

The object of this book with 14 chapters and 102 pages is succinctly explained in the editorial preface. "The preservation of eyesight is of interest and importance to mankind in all walks of life. The structure of the eye seems complicated, and the ills to which it is subject have technical and long names. There are many books on diseases of the eye written solely for medical readers." "So far as we are aware, no comprehensive book exists which recounts in fairly simple language the care and precautions necessary to maintain and keep good eyesight. Yet the subject is an essential part of preventive medicine and public health."

"Many eyes might be saved and much anxiety and suffering avoided if people would realize how important it is to seek medical advice in the early stages of an eye malady, for example, glaucoma or the presence of a foreign body in the eye."

"The editor, over a period of years, made

inquiries into the subject and found that the need for a book of this nature was experienced by many, including ophthalmic surgeons, general practitioners, medical students, nurses, health visitors, health educators and school teachers, and others concerned with the prevention of disease and maintenance of the public health. He was so fortunate as to enlist the help of various experts who have studied eyes and eyesight from different points of view—physiological, nutritional, surgical, psychological, and in relation to environment."

It is with the aid of these experts that the editor has brought out this book.

There are 14 chapters as follows: 1. Introduction 2. The Structure and Function of the Eye 3. How we use our Eyes 4. Nutrition of the Eye 5. Defects of the Eye 6. Lighting and Eyesight 7. Common affections of the Eye 8. Diseases of the Lens, Retina, and Optic Nerve 9. Temporary loss of Sight 10. The Eye in Old Age 11. Blindness 12. The Prevention of Diseases and Injuries of the Eye in Industry 13. Eye Testing and Spectacles and 14. Care of the Eyes.

Ophthalmology is a remarkably complex specialty and many of the technical terms which are used are difficult to understand. The editor has certainly accomplished a very great feat in rendering into reasonably understandable language, the complexities of the structure of the eye and its common ailments. This book could readily be followed by an intelligent layman. That is not to say that medical students will not gain considerably by looking through this book before they commence their studies in Ophthalmology. There is a great deal of useful information knowledge of which will help the public to realise how they may protect and preserve their eyesight. The book closes with an apt quotation by a poet who knew at first hand the tragedy of blindness—Milton:

"..... why was the sight

To such a tender ball as the eye confined,

So obvious and so easy to be quenched?

O dark, dark, dark, amid the blaze of noon

Irrecoverably dark, total eclipse

Without all hope of day!

* * * * *

AN ATLAS OF SURGERY—

By Dr. Wilson Harlow — With a foreword by Sir Cecil Wakeley — William Heinemann Medical Books Ltd., London, 1958—1292 Illustrations—Price 50 s. net.

There are 363 pages to this book with 1292 illustrations. The work is an attempt to provide a pictorial aide-memoire of common and important surgical facts and procedures, primarily for the use of those working in the surgical wards, operating theatre and casualty department. It is designed as a supplement to, not a substitute for, the standard textbooks, and its objective is to help the consolidation of knowledge gained both practically and from reading and lectures. For medical students it is intended, chiefly, as an introduction to their course in clinical surgery; and for sisters and nurses as an aid to surgical training, and the understanding of the reasons underlying surgical practice.

The book is divided into eight sections as follows:

1. Abdominal Surgery 2. Urology 3. Gynecology 4. General Surgery 5. Special Surgery 6. Orthopaedics 7. Management of Operations and 8. Surgical pathology.

Commenting on this book Sir Cecil Wakeley one time President of the Royal College of Surgeons of England writes in his foreword "There can be no doubt whatever that a good picture is worth innumerable pages of the written word. Also a picture makes a more stable imprint on the memory which is so useful to the over-worked modern student and student nurse.

This picture book of surgery contains 363 pages and 1,292 illustrations, a truly remarkable feat, and what is more, many of the illustrations are original.

I can think of no better way of learning surgery than by the pictorial method. In this comprehensive atlas the reader is given the clinical picture of surgical conditions and diseases; the various pathological lesions, and the general outlines of treatment.

I have nothing but praise for this book, and I only wish such a book had been available when I was a student, as it would have been an invaluable aid to my surgical studies.

With this view no one could possibly disagree. By simply looking at the exquisitely got up pictures and reading the legend to each of them one can learn unconsciously a great deal of surgery. Printed on beautiful glossy paper the illustrations, x-ray reductions and diagrams are a pleasure to behold. The book is surely a triumph of the art of medical illustration and photography. The illustrations are well chosen and are instructive. They depict physical signs admirably. This book is worth having and is indispensable for a teacher in surgery.

The first section on Abdominal Surgery deals with the following topics: Acute Abdominal Lesions, Stomach and Duodenum, Operations on the Stomach and Duodenum, Gall-bladder and Bile-Ducts, Obstructive Jaundice, Liver and Spleen, Hernia, Acute Intestinal Obstruction, Chronic Intestinal Obstruction, Intestinal Operations, Special Diseases of the Colon, and Rectum and Anal Canal. It is not possible to comment on each illustration but we would like to single out those pictures which in our opinion is exceptionally striking. Fig. 93 is a photographic accomplishment because it outlines perfectly the external abdominal contour of a pancreatic cyst.

Section 2 on Urology deals with the following topics: Diagnostic Investigations, Renal Infections, Calculus Disease of the Kidney and Ureter, Renal Abnormalities and Injuries, Tumours of the Kidney and Ureter, Operations on the Kidneys and Ureters, Bladder, Prostatic Enlargement, Male Urethra and Penis and Testes. Fig. 204 is a photograph showing the appearance of a swelling due to a perinephric abscess. The swelling can be clearly seen although the picture and patient have not been touched. Fig. 316 is an excellent photograph of a spermatocele of the left testis.

Section 3 on Gynecology includes the following topics: Anatomy and Physiology, Anatomical Abnormalities, Clinical Examination, Diseases of the Uterus, Displacement of the Pelvic Organs, Cysts and Tumours of the Ovaries, Fallopian Tubes, Diseases of the Cervix, Vagina and Vulva, Normal Pregnancy, Complications of Pregnancy, Labour, Complications of Labour, Caesarian Section and Infertility. In Anatomy and Physiology there are the usual sort of diagrams. Although not in any way out-standing they are nevertheless instructive. The pictures dealing with clinical examinations are inadequate and could have been amplified. The instruments usually

employed for a gynecological examination are shown in Fig. 339. Fig. 348 is a pretty picture of a calcified fibroid. Figure 384 is an unusual but not a very rare picture of a dermoid cyst of the ovary. Fig. 433, 435 and 436 are diagrams of poor quality. Figure 437 on Carneous mole lacks clarity. Better pictures may have been readily obtained to show hydatidiform mole and chorionepithelioma. The figures to show labour are somewhat sketchy. A photograph to show inversion of the uterus might have been included in figure 456. The hysterosalpingograms shown in figures 469 and 470 are unsatisfactory. The pictures particularly for the section on Obstetrics could have been much more imaginatively and lavishly selected.

The section on General Surgery deals with the following subjects: Physiology and diseases of the breast, Thyroid Gland, Neck, Face and Mouth, Peripheral Vascular Lesions, Gangrene, Amputations, Skin Grafting, Pilonidal Sinus, and Adrenalectomy and Hypophysectomy. Fig. 507 is an excellent x-ray demonstrating narrowing and displacement of the trachea by a large retrosternal goitre. Fig. 599 is a good picture (infra-red photograph) of venous thrombosis of the leg. Fig. 632 is an amusing cartoon with the following legend "Tourniquet tied to the operating table." The catastrophe of failure of removal can be avoided." Fig. 635 shows quite well how the skin grafting knife is used. The section deals with Pharynx and Larynx, Nose and Ear & includes common surgical ailments of this region and is amply illustrated.

In the section on lungs and pleura, x-rays and photographs of pathological conditions of the lungs are included. The section on cardiac surgery is of great interest, and there are some composite diagrams illustrating the clinical features of Mitral stenosis (Fig. 739) and cardiac tamponade (Fig. 740). There is good coverage in the section on Neurological

Surgery. We think however that more pictures could have been included to show the technique of lumbar puncture. No Orthopaedic subject can possibly be explained without pictures. It is therefore gratifying to see several orthopaedic conditions clearly illustrated and explained.

Section 7 on "Management of Operations" deals with surgical technique, anaesthesia and analgesia and post-operative complications and treatment. The figures (1087) show how one should put on pair of surgical gloves. The methods of wound closure and healing are well explained. The photographs depicting endotracheal intubation could have been better chosen. Fig. 1204 is an interesting one of a burst abdomen. The section on surgical pathology deals with the following subjects: Ulcers, Sinuses and Fistulae, Acute Inflammation, Malignant Tumours, and Chronic Inflammation. These are the usual sort of pictures which one expects to find in surgical books. The photograph in figure 1260 must be one of the few good pictures in the world of malignant melanoma of the vulva. Any one who carefully studies Fig. 1281 should be able to unravel the mystery of the Wassermann complement fixation test. Figure 1286 summarises the clinical features of tabes dorsalis. The last picture (Figure 1292) shows actinomycosis of the liver.

On going through this book one is full of admiration for the author's achievement. Although the great majority of the figures have been taken from other books or journals they include quite a number of original pictures. We can most emphatically declare there has not as yet been an attempt to produce a picture book of surgical diseases. The Author and the publishers have in sponsoring such an attempt performed a feat in medical publishing. There is little doubt that this book has a place in all institutions which impart surgical knowledge.

DENTAL BURRS become a versatile tool in the hands of Anthony Lahongrais, a junior at the St. Louis University's School of Dentistry, who uses them for his extracurricular activity in sculpture.

Interested in this art form since childhood, Lahongrais hit on the use of dental tools when he became a student. For roughing out his figures, he uses large burrs, and the progressively finer ones for intricate detailed work. On larger projects, he works with the usual hammer and chisel, then employs the burrs for the fine points.

In addition to plastic materials such as clay, Lahongrais also sculpts in metal and ivory. At the Chautauqua, N.Y. art school last summer, he won a first prize. But this success did not change his plans to pursue the dental profession.

WORLD HEALTH DAY SUPPLEMENT

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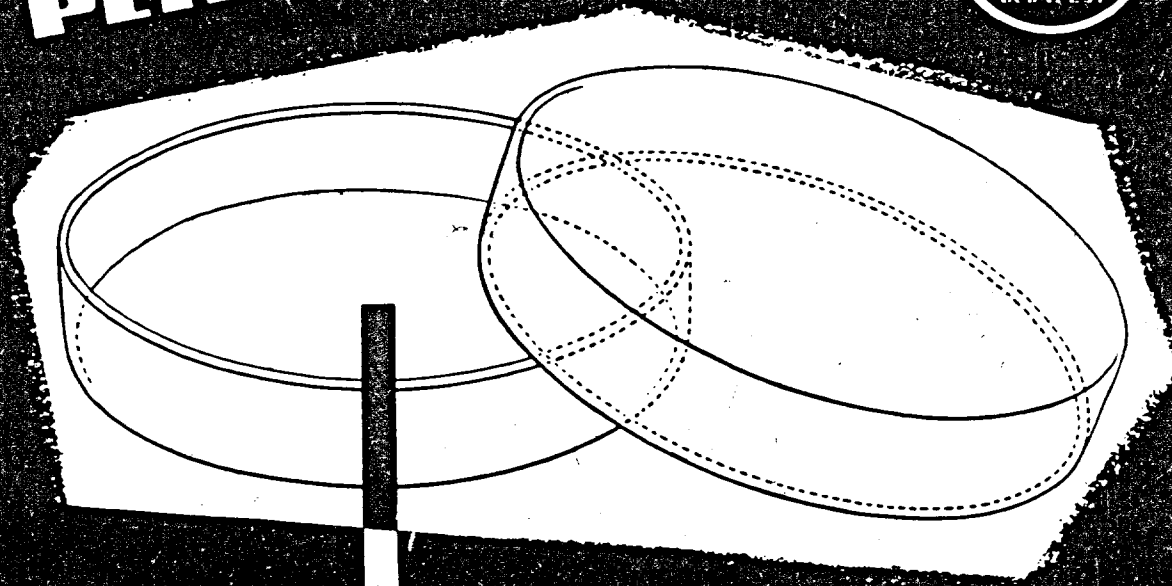
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