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Poliomyelitis

A Discussion of Recent Advances in Knowledge, with Main Reference to Epidemiology

By A. J. Rhodes, M.D., F.R.C.P., Ed.

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In this paper, I shall discuss our present views regarding the epidemiology of infantile paralysis, having due regard to the research work that has been carried out on the disease in the past ten to fifteen years, mainly in North America. I shall not here quote any specific references, as I have recently given these in full in a more extensive article on the same subject, that is readily accessible to readers (Bulletin of Hygiene, London, volume 22, June 1947).

Properties of Poliomyelitis Virus

Infection of Monkeys

Monkeys are very susceptible to infection with poliomyelitis virus, especially if injected directly intracerebrally. Of particular interest is the fact that they can also be infected by nasal instillation. After such inoculation, virus ascends via the olfactory nerves that lie exposed at the roof of the nasal cavities to involve the olfactory bulbs and tracts, eventually spreading back to the brain. Infection arising from nasal inoculation can be prevented if the olfactory mucosa is first treated with chemicals such as zinc sulphate, that cause necrosis of the nerve endings.

It was hoped that by application of this technique in man, it might be possible to prevent natural infection. However, the treatment of the nasal mucosa in man has proved a complete failure. This experience has shown that it may be fallacious to apply directly to man the results of animal experiments. It is now almost certain, as will be explained, that the olfactory route is only rarely a portal of entry in man.

Monkeys can also be infected by exposure to an atomized cloud of

1Based on an address delivered in the Medical School, University of Western Ontario, on October 1st, 1947.
virus particles. It is probable that here virus invades the body both by the olfactory route, and along nerve fibres supplying the oropharynx.

Certain types of monkey and chimpanzees can be infected by the oral route. Virus may be incorporated in food stuff, or applied directly to the tongue or pharynx. Experiments have also been conducted by injecting virus directly into the intestine.

Monkeys can be infected by the intradermal route, particularly by recently isolated strains. This fact, which is often overlooked, may be of some importance as regards the method of spread of poliomyelitis in man, although hitherto there has been no evidence suggesting transmission by biting insects.

After inoculation by the various peripheral routes mentioned above, it is thought that virus invades the axons of superficial nerve fibres, mainly therefore sensory fibres, and spreading back in axons, perhaps crossing one or more synapses, eventually reaching a neuron in the central nervous system. In the central nervous system, the primary attack of the virus is on nerve cells (neurons), and the inflammatory changes that occur are regarded as secondary.

This question of the spread of virus in monkeys is of considerable importance, because there is little other way of discovering the route followed by the virus in man.

It must be realized, however, that monkeys can be infected by routes in which neural spread would not appear to operate. For example, if large doses are given, the intravenous route may secure infection. Further, it has been claimed that the intradermal route may be effective even if the skin area is separated from nerve supply.

Monkeys usually develop paralysis after an incubation similar to that in man. It is of great interest to note that virus disseminates widely in the central nervous system in the preaparalytic period, and causes histological lesions. This dissemination may give rise to signs of abortive poliomyelitis, particularly pyrexia, and the monkey may not necessarily develop paralysis. Abortive poliomyelitis occurs in the monkey, therefore, as in man.

On recovery from infection, monkeys are resistant to re-inoculation. This immunity is, however, not absolute, and is usually only operative against the homologous strain, for strains antigenically different may infect. The mechanism underlying resistance in these recovered animals is obscure, but it appears that in some way the cells previously attacked become insusceptible to further invasion. It may be that this insusceptibility is due to a local accumulation of antibody.

Some progress has been made as regards the immunization of
monkeys with vaccines. Resistance can be conferred by injections of vaccines chemically treated, but it is questionable whether there is not a small amount of live virus still present in these preparations.

INFECTION OF RODENTS

Only three or four strains of poliomyelitis virus isolated from human material, such as the Lansing strain, have been found to infect mice or cotton rats. A number of other strains of rodent-paralysing poliomyelitis-like virus have been isolated from other sources, e.g., Theiler's encephalomyelitis, an edemic infection of laboratory mice.

CULTIVATION

No real progress has been made in the cultivation of human poliomyelitis virus artificially in tissue cultures or eggs.

ANTIGENIC STRUCTURE OF POLIOMYELITIS VIRUS

Antigenic differences have been detected between freshly isolated strains of poliomyelitis virus, but it has not been possible to carry this work far, as very large numbers of monkeys would be required. It seems reasonable to suggest, on the basis of what work has already been done, and by analogy with other viruses, that various antigenic types of virus exist. It is probably theoretically possible, therefore, for repeated attacks of the infection to be caused by different virus strains.

SOME FEATURES OF POLIOMYELITIS IN MAN

DIAGNOSIS

The incubation period of poliomyelitis is usually between 7 and 14 days, but may extend from 3 to 35 days. It is evident, therefore, that it may be very difficult in any given outbreak to differentiate between cases that may have been infected from a single source and secondary cases infected from a primary case.

It is now realized that a number of cases of poliomyelitis show an illness of infection within a day or so of exposure. This is characterized by nasopharyngitis, pyrexia, and headache. The illness rapidly subsides; in some cases the infection probably goes no further, but in others after the incubation period manifestations of non-paralytic poliomyelitis develop.

Of recent years much attention has been paid to non-paralytic, pre-paralytic, or abortive illnesses. It is clear that up to 90% of all infections with poliomyelitis virus are non-paralytic. The usual clinical features of the non-paralytic illness are: fever; respiratory catarrh; frontal headaches; gastro-intestinal symptoms; pain in the head, back, and limbs; stiffness of the back; drowsiness and listlessness; and an increase in cells and protein in the C.S.F.
It will be realized that these clinical features are not very specific, and there are a number of other infections that must be considered in the differential diagnosis. As regards the virus infections that may mimic abortive poliomyelitis, the following must be excluded: lymphocytic meningitis; herpetic meningo-encephalitis; mumps meningo-encephalitis; equine encephalomyelitis, and influenza. Appropriate tests are available for the diagnosis of these conditions, but they can only be performed in a laboratory equipped for virus studies; in general, the diagnosis is made by attempting the isolation of the virus from C.S.F., and by examining acute and convalescent phase sera for an increase in antibody titre. Glandular fever, dysentery, mild enteric fever, urinary infection, and atypical pneumonia must also be excluded by appropriate tests.

**THE DISTRIBUTION OF THE VIRUS IN MAN**

Work of the last few years enables us to describe accurately the distribution of poliomyelitis virus in the human body. Virus can be found equally in abortive and paralytic cases. It is present in the secretion of the nasopharynx for the first few days after onset of pre-paralytic symptoms; it can also be recovered from the tonsil and the pharyngeal wall; apparently the nose is less commonly infected.

Virus is present in the stool in the first week of illness in practically every case, and thereafter is less commonly found; at three to four weeks after onset it is present in 50% of cases, but after two months in only about 10%; carriage for more than three months is unusual. It is probable that virus proliferates in the wall of the gut, and it has been isolated from the wall of the ileum and the colon.

It is not known whether proliferation of virus in the intestinal tract is necessarily associated with invasion of the central nervous system. But it is reasonable to suppose that invasion of nerve fibres supplying the intestine does occur.

Despite numerous tests, virus has only been isolated from the blood on a single occasion, and it does not appear that viraemia usually occurs in poliomyelitis. Virus has been isolated from lymph glands on a number of occasions, and the precise significance of this finding is not yet clear.

Virus has also been recovered from the throat secretions and stools of close contacts of cases; child contacts are more usually infected than adults. The majority of these infected contacts show no symptoms; some will develop abortive illnesses, and very few will proceed to typical paralysis.

It is generally accepted that non-contacts rarely harbour the virus. Certainly it is true that the virus tends to be distributed chiefly in the close environment of the case, abortive or paralytic.
In experimental animals, poliomyelitis virus behaves as a neurotrope. That is to say, after peripheral inoculation it invades the central nervous system and reaches its highest concentration there. In monkeys, infection can be secured by various routes, and it appears that virus usually invades nerve axons and travels along them to reach the C.N.S. It is supposed that in man, also, infection is usually secured by passage along nerve fibres.

In man, there are various possible portals of entry of the virus. At one time it was thought that the olfactory nerves, lying exposed in the roof of the nose, were the usual place of entry. Large-scale experiments were carried out in which the nasal mucosa of children was treated with astringent chemicals such as zinc sulphate. In monkeys this treatment had been found to prevent infection following nasal inoculation, but in man no benefit was found. As a further pointer to the rarity of infection by the olfactory route, I may mention that histological lesions have only rarely been found in the olfactory bulbs, contrary to what would be expected if virus passed through en route to the C.N.S.

Certain workers have carried out histological examination of fatal human cases and assessed the relative distribution of the lesions. It has been concluded that the pharynx, mouth, and nasal mucosa are common portals of entry, and that the oesophagus, bronchi, and intestines are less frequently invaded. An important part of these studies has been the examination of peripheral ganglia where there are synapses that virus passing centripetally would have to traverse. It has been assumed that histological evidence of virus attack in these ganglia indicates centripetal spread from a peripheral portal of entry that can then be reasonably definitely located. However, other workers suggest that these lesions may equally well be caused after the initial invasion of the C.N.S. by centrifugal spread outwards of virus.

It may be concluded, therefore, that further work is needed before one can state dogmatically the usual portal of entry of the virus in man. It is safe to assume, however, that the pharynx and to a lesser extent the intestine, is the commonest place of entry.

The virus of poliomyelitis attacks the anterior horn cells of the cord, but it is perhaps not generally realized that in almost every case that is thoroughly examined, lesions will also be found in the cortex, midbrain, and bulb. These lesions cannot be without some significance in the explanation of the clinical features of poliomyelitis.

From monkey experiments, it is almost certain that virus is present in the C.N.S., and causes histological changes, in the pre-paralytic period.
LABORATORY DIAGNOSIS

This can be made during life by attempting the isolation of virus from naso-pharyngeal washings or stool. Material may be inoculated nasally in the raw state and three rhesus monkeys should be used for each specimen. Alternatively, etherized extracts may be inoculated peritoneally, or if sterile, cerebrally.

It would be of great value if a serological test was available for the diagnosis of poliomyelitis, but unfortunately this is not so. The antibody response is too erratic, and in many cases there does not seem to be a rise in titre in convalescence. It is quite impossible to test for virus-neutralizing antibodies in convalescent serum by inoculating serum-virus mixtures in monkeys, owing to the expense involved. Therefore, attempts have been made to substitute mice, using the Lansing or other mouse-adapted strain. However, it does not appear that the antigenic structure of the poliomyelitis group is sufficiently homogeneous for antibodies to be necessarily detected by the use of such an heterologous strain. Further, as just mentioned, it is by no means certain that antibody increase uniformly occurs in convalescence.

THE EPIDEMIOLOGY OF POLIOMYELITIS

GEографICAL INCIDENCE

At one time it was thought that poliomyelitis was restricted to temperate countries, especially to North America, Europe (chiefly Scandinavia), and Australia. It is now known, however, that the disease enjoys a world-wide distribution. In the tropics it appears to be mainly an endemic infection, with occasional epidemics in those most susceptible—the under-five age group. During the Second World War, poliomyelitis was many times more frequent in British and American troops stationed in the Middle East, India, and Japan than it was in home commands. Of recent years, serious epidemics have occurred in South Africa, St. Helena, Mauritius, Malta, and Singapore, involving in most instances young children.

AGE INCIDENCE

Poliomyelitis has undergone a notable alteration in age incidence. When the disease was first observed as an epidemic infection, at the beginning of this century, it was truly "infantile" paralysis, attacking mainly those under five. This type of age incidence is still observed in tropical countries, but from 1916 onwards in America, Scandinavia, and Australia, there has been an increasing tendency to involve the older child. This has been attributed to improvement in social hygiene in infancy with less risk of infection, so that immunity is not acquired so commonly.
POLIOMYELITIS

DISTRIBUTION OF CASES IN RURAL AREAS

Another interesting feature of the epidemiology is a tendency to an higher incidence of the disease in rural areas. In these areas, also, there is a higher incidence in the older age groups. Both these features are attributed to the fact that in sparsely populated areas there is less human contact, and less opportunity for acquiring infection and subsequent immunity in childhood.

SEASONAL INCIDENCE

A puzzling feature of poliomyelitis is the seasonal incidence in late summer and autumn. Although cases have definitely been noted in the winter months, epidemics are unusual at this time, and it appears that the infection cannot spread widely. The warm weather must act either by facilitating spread of infection, or by lowering susceptibility in the human body.

ORIGIN OF EPIDEMICS

It is not known why serious epidemics break out year by year in America and less frequently elsewhere, but a number of factors are concerned. Undoubtedly some part is played by a recurring increase in the susceptible population. As mentioned, warm weather appears to play some part. Conditions tending to facilitate the transfer of respiratory or faecal organisms may also be concerned. For example, the recent Malta and Mauritius epidemics occurred at a time of undue overcrowding of the population in houses. It appears that usually epidemics are caused by a "flare-up" of a previous endemic infection, and presumably the same strain of virus is responsible for both types of outbreak. Sometimes, however, epidemics seem to be caused by strains "foreign" to the community. For example, a wartime outbreak on the isolated island of St. Helena, affecting mainly adults, was attributed to the introduction of a foreign strain by a carrier among the garrison. Another question to be discussed is the mechanism of survival during the winter months. Observations in America make it almost certain that a continuous series of sporadic cases occurs during the winter months, sufficient to keep the infection present in the community. Paul observed a few sporadic cases in a small town in the winter and spring, which gave rise to a spreading epidemic with the onset of the warmer weather.

METHOD OF TRANSFER OF INFECTION

There is little doubt that infection can be transferred by means of faeces and droplets of nasopharyngeal secretion. As the virus persists in the faeces for considerably longer than the nasopharynx, it is probable that faecal-spread is more important than droplet-spread. Virus in faeces could be transmitted directly by touch, or indirectly by such intermediaries as soap, towels, food, contaminated water, or flies.
There are many possible sources of infection in poliomyelitis, but it is not known which of those to be mentioned is most commonly operative.

In certain cases, infection is autogenous, the disease developing in a person who has been harbouring the virus in the nasopharynx. Infection may be precipitated in such persons by trauma, other infective conditions, fatigue, and especially tonsillectomy.

The acute case of the disease is infectious for about three to four days before and after the onset of the pre-paralytic phase. Of recent years, attention has been drawn to the fact that careful epidemiological enquiry will often reveal a case to have had prolonged and intimate contact with a previous case in the infectious period. It should be noted that the infective period appears to correspond fairly closely with the time during which the virus is known to be present in the secretions of the upper respiratory tract.

As regards carriers, there is little evidence of convalescent carriage of the virus, but healthy carriers are undoubtedly concerned. These are persons who have been in contact with a case, abortive or paralytic, but have failed to develop a clinical illness.

Recent work has shown that virus can be isolated from flies trapped in urban and rural areas at times of epidemic prevalence. The blowfly (Phormia regina) seems to be more important than the house fly. The interesting question as to whether virus may survive the winter in infected flies has not yet been answered.

Virus has been isolated from the sewage of urban communities during, and for a short time after the end of, epidemics. Quantitative examinations suggest that in an infected city a large number of healthy and unsuspected carriers must exist. Sewage-infection is of danger as it may form a source of virus for flies, and any fault in the sewerage system or in disposal might lead to infection of water supplies. The practice of using raw or only partly treated sewage to manure vegetables is highly dangerous.

Although water has been incriminated by certain observers, and may be responsible for sporadic cases in rural areas, there is no evidence that it plays an important role in urban outbreaks. In all probability the amount of chlorine generally used is enough to destroy any virus that may be present, given reasonable length of contact.

In certain explosive outbreaks milk has been definitely incriminated. The supply has presumably been infected by a human carrier or abortive case, although flies may also be a source of infection.
Food, especially fresh fruit and unwashed vegetables, has been blamed. Certainly, if such articles are handled by persons excreting the virus, or are otherwise contaminated with faecal material, they may be dangerous. In general, however, epidemiological evidence has not tended to incriminate food.

In conclusion, although much is known regarding the various ways in which poliomyelitis infection may be spread, it still remains difficult in any given case to state precisely whence the infection has derived. It is probably true to say that the bulk of the evidence points to the disease being spread usually from case to case by close contact. On the whole, there is little to suggest that extra-human agencies are concerned in the spread of the disease, apart from the evidence incriminating flies.

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Epilepsy and the Ancient Greeks

By MARY MARGARET MCQUADE, '48

The history of epilepsy is an integral part of the history of Greek medicine and Greek religion. For two thousand years this disease, which aroused peculiar interest by its dramatic physical and psychical signs, was interpreted both as a physiological process and as an effect of divine influence.

The Greeks of the third millennium B.C., the earliest of whom we have record, were farmers inhabiting the plains of Eastern Europe. They were primitive people who worshipped the sun, and revered the spirits of the rivers and mountains. Whenever disaster occurred—whether the calamity was a failure of the crops or a disturbance in their physical and mental health—they sought relief by propitiating the powers of nature with prayers and sacrifices.

Somehow they learned to forge steel into weapons that were superior to the bronze equipment possessed by their neighbours. Tribe by tribe they pushed southward. By the fourteenth century B.C. the vanguard reached the Peloponnesus. In the next four hundred years they crossed the Aegean and overran the whole East Mediterranean basin. As they advanced, they absorbed much of the culture of the Myceneans whom they conquered. They came to believe that the gods were like men, with good and evil qualities, differing only in their great stature, strength and immortality. Their physicians became members of an organized, respected profession. The healing of disease became the application of effective practical knowledge that had been gained by rough experience.

The Greeks who sacked Troy in 1183 B.C. learned from the inhabitants of Asia Minor that epilepsy had been studied by the Babylonians for a century. They were told by experts that the disease was hereditary or the result of improper behaviour during sexual intercourse.

"It is forbidden to marry a woman from an epileptic family."
"Who cohabits with a light lit will beget epileptic children."
"When a child younger than one year is lying at the feet of a couple during coition, it will become epileptic."

They observed that by the masses, however, the disease was considered to be a "sacred disease", inflicted upon individuals by evil spirits, most frequently by Labasu.

During subsequent centuries, Greek medical practitioners were hampered to an increasing degree by a popular belief that the gods caused disease when they were angry and restored health when they
were appeased. This idea had been suggested by people of Asia Minor and lately strengthened in the writings of the Greek Epic poets. Aesculapius no longer was remembered as a Thessalian king who fought at Troy and the father of two skilled physicians. He was the son of the god Apollo. Taught in his youth by Cheiron, a creature half-man and half-horse, he had become a healer who could raise the dead. As this story spread throughout the land, temples were built to which sick men came to ask the aid of Aesculapius, and to be cured by his priests.

The tendency was encouraged by an incident of the Civil War. When a Spartan army invaded Attica in 431 B.C., the inhabitants of the district abandoned their farms to crowd into Athens for protection. Plague broke out, so virulent that one-third of them perished, including their leader Pericles. The survivors, in fear, elevated Aesculapius to be God of Healing and fostered the belief that disease could be cured by one night's sleep in his temple courts. Among the credulous were victims of what the Romans later called Morbus Herculeus, who believed that they were experiencing convulsions such as Hercules once suffered through the designs of a malignant goddess. Their case histories were preserved by the priests. One, found at the temple at Epidaurus, reads as follows:

"N.N. From Argos. Epileptic. This man during his sleep in the curative chamber saw a vision; he dreamed that the god approached him, and pressed his ring upon his mouth, nostrils and ear—and he recovered."

The opposition of the medical profession to such pronouncements was led, strangely enough, by a direct descendant of Aesculapius. He was Hippocrates, physician to the plague-stricken Pericles.

"And they who first referred this disease to the gods appear to me to have been just such persons as the mountebanks and charlatans now are, who give themselves out for being excessively religious and as knowing more than other people. They have instituted a mode of treatment which is safe for themselves, namely, by applying purifications and incantations and enforcing abstinence from baths and many articles of food which are unwholesome to men in disease."

He regarded epilepsy as a hereditary disease.

"As a phlegmatic person is born of a phlegmatic and a bilious of a bilious, what is to hinder it from happening that where the father and mother were subject to this disease certain of their offspring should be affected also? As the semen comes from all parts of the body, healthy particles will come from healthy parts and unhealthy from unhealthy parts."
He maintained that the convulsions could be due to physical causes.

"Phlegm begins to be formed while the foetus is in utero by a softening of the brain substance, thus producing a secretion which, if not excreted, causes a phlegmatous condition.

"When the phlegm, suddenly descending into the veins, shuts off the air and does not admit it to the brain, a man loses his speech and intellect. The hands become powerless, the blood stopping and not being diffused, as it was wont; the eyes are distorted; froth from the lungs issues by the mouth, and the bowels are evacuated in the violence of the suffocation."

He was aware of the aura.

"But such persons as are habituated to the disease know beforehand when they are about to be seized, and flee from men either to their homes or to a deserted place and cover themselves up. They do this from shame of the affection and not from fear of the divinity, as many suppose."

He believed that attacks occurred more often during changes of weather.

"Spring and severe winter are the most dangerous; spring, when the head has been exposed to the sun, winter when they have warmed themselves at the fire and gone out."

As a result of these and other observations, Hippocrates advised his epileptic patients to reduce the number of their seizures by living in an equable climate with freedom from emotional stress.

The philosopher, Plato, considered that the most divine part of man's soul revolved in the head. It appeared quite reasonable to him that, if white phlegm pervaded the veins and spread over the brain, an individual would suffer clouding of the mind.

Aristotle, Plato's famous pupil, insisted on the contrary that the seat of the intelligence was in the heart.

"Food produces evaporation into the veins which rises up, turns and descends. If much goes up, it makes the veins swell in its descent and compresses the respiratory duct."

Such an explanation of the cause of convulsions, with which no scientist is known to have agreed, is of interest only because it was proposed by the Father of Comparative Anatomy and the tutor of that distinguished epileptic, Alexander the Great.

The second period, lasting two hundred years, is remarkable in that the scientists abandoned the results of careful neurological studies and reverted to forms of treatment that savoured of superstition.
Their activity centred in Egypt. On the death of Alexander the Great, in 320 B.C., his Macedonian general, Ptolemy, had succeeded to the throne. Under his direction the Alexandrian Museum was built, endowed and made the world centre for medical research. The first group of research workers who were invited to join the staff included two Greeks, Herophile and Erasistratus.

Eventually, these men were led, by the Egyptian custom of disembowelling and embalming the bodies of the dead, to abandon their prejudice against dissecting the human body. Herophile studied the central nervous system assiduously. He is remembered for his identification of the cerebral venous sinuses, the choroid plexus and the calamus scriptorius, but, since most of his records have been lost, it is not known that he ever compounded a theory on the cause of epilepsy.

His colleague, Erasistratus, divided the nerves issuing from the brain into sensory and motor groups. He described the ventricles as full of a psychic pneuma which was conveyed by hollow nerves to the rest of the body. Then, rejecting anatomy as the chief factor in disease, he taught that all forms of sickness were caused by an excess of blood, and that diseases differed from each other according to the site of a local congestion. They could be successfully treated, he believed, by regulation of exercise, diet and bathing.

This conception of disease was developed by his pupil, Serapion. The latter, doubting his ability to find the “hidden” causes of epilepsy, confined himself to observing such “evident” causes as heat, cold and hunger. His patients were anointed with vinegar and rose oil, they engaged in mild exercise, and they drank a decoction of hyssop. One or two days previous to a convulsion, if the attacks followed a regular rhythm, they were bled or purged. Then, they ingested a mixture of camel’s hair, crocodile faeces, and blood of the sea tortoise. This regime, which combined the principles of treatment favoured by Erasistratus with those practised by the laity, was a concession to the hopes of unsatisfied patients. Many physicians adopted it in desperation as the number of cures among epileptics continued low.

While Serapion was in practice, history began to repeat itself. In 293 B.C. the Romans, having read in the Sibylline Books that a pestilence would strike their city, resolved to include in their pantheon a God of Healing. Hastily they imported Aesculapius from Greece in the form of a sacred snake, and built for him a temple on the island in the Tiber. Once again Greek scientists did what they could to discredit priest-craft. Archogathus, the physician, moved from the Peloponneseus to Rome in 219 B.C. Many other members of the profession followed in succeeding years, and with their coming the third period in the history of epilepsy began.
The Greeks discovered that the disease was not unknown to the Romans. Members of the Assembly (or Comitia) regarded it as an affliction sent by the gods, a sign of evil portent. They called it Morbus comitialis because the Comitia was adjourned for the day whenever one of their number had a convulsion. The purchase of a slave was accompanied by an agreement that the vendor would return the sum paid if within six months the slave suffered a seizure. The ineffectiveness of the remedies which the Romans applied, borrowed from the Etruscans whom they had conquered in northwest Italy, is reflected in the enthusiasm with which Greek therapy was received. After a hundred years of Greek medicine, Pliny wrote:

“This is the only one of the Greek professions which Roman dignity has not yet taken up; very few indeed of the Romans have shared in its great advantages; to tell the truth, those who know nothing of the Greek tongue have no faith in any doctor unless he does practise his calling in Greek.”

By a decree of the epileptic Emperor, Julius Caesar, all the Greek physicians were admitted to the rights of Roman citizenship in order to attract more of them to life in Rome.

One of the first to make his fortune there was Asclepiades. He believed that all diseases resulted from an alteration in the size, number and arrangement of the atoms of the body. The alteration which produced the signs of epilepsy had its origin in the corruption of retained semen. Therefore, in addition to the treatment formulated by Serapion, he prescribed coitus as a therapeutic measure.

Many of his colleagues and successors were inclined to admit the possibility of value in popular methods of preventing seizures. Some permitted the eating of specific foods such as the flesh of a goat roasted on a funeral pyre, twenty-one house flies in a liquid medium, or the ashes of a weasel. Some did not object to the application of incense soaked in the blood of a young swallow. There were others who did not scoff when the disease was referred to as Morbus lunaticus, implying by their silence that perhaps epileptic persons were “moon-struck” because they had sinned against Phoebe, the moon goddess.

Despite the many modifications in treatment, epilepsy proved resistant to cure. By 24 A.D. Celsus was prepared to recommend surgical interference.

“The last auxiliary is to make an incision in the occiput and apply the cupping instrument; also to burn in two places with a hot iron in the occiput, and below it where the first vertebra is connected with the head—that the pernicious humour may escape by them.”
A hundred years later Aretaeus had no better suggestion. His epileptic patients had not been cured by life in a warm, dry country, and the avoidance of meat, wrath and sexual intercourse. The number of their convulsive fits had not been materially decreased by venesections, cupping and emetics. Aretaeus could only try the effects of trephining the skull, cutting the arteries before and behind the ears, and applying rubefacients to the head. In such he did not place great confidence, as he recalled the meagre benefits obtained through a century of surgery, and described the gathering of epileptics at places of execution where, in a last effort to find health, they could drink the blood of beheaded criminals.

His contemporary, the great Galen, boasted upon occasion that he could cure such individuals. He would explain with condescension that their disease was caused by an accumulation of humour which soaked the root of every nerve. Their convulsions were caused by the shaking of the nerves in an effort to free themselves. Consequently, proper treatment consisted in the evacuation of the humour by purging, bleeding, and the production of copious urine.

Yet even he felt some misgivings. In one commentary he wrote:

"I know that some of our people have cured epilepsy by prescribing a drink of burned bones—the patients not knowing what they drank lest they be nauseated."

At another time he seriously investigated the case of a boy who said that he remained free from fits as long as he wore a peony root suspended from his neck.

"It was logical to assume either that certain particles of the root fell out, were sucked in by inspiration and did thus heat the affected part, or that the air itself was tempered and changed by the root."

In other words, Galen, the last of the great Greek physicians, was disturbed by uncertainties that had puzzled the warriors who burned Troy. In the year 200 A.D. he was perilously close to approving the wearing of amulets, a device popular in Asia Minor when the Greeks were uncivilized nomads. He was aware that certain of his contemporaries prescribed the chanting of incantations because no other method of checking the disease had been successful. Two thousand years of speculation and investigation had come and had gone, but epilepsy was still an enigma.

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The Pharmacology of Streptomycin

By J. Norman Wood, '48

StREPTOMYCIN is the reward of a valiant search for an antibiotic agent to supplement penicillin and the sulphonamides. In an attempt to isolate a substance capable of combating gram-negative bacteria, Waksman and his associates discovered Streptomycin. Already many agents with antibacterial properties had been found in soil fungi but proved to be too toxic for human cells. Streptothricin was the first antibiotic that seemed to fulfil the requirements but its delayed toxic effect caused it to be discarded. However, interest was stimulated and a less toxic, more effective material was obtained from the soil fungus Actinomyces Griseus. It was found that only certain strains were useful and that the ability of soil micro-organisms to produce substances lethal for bacteria depended on their cultural environment. Antibiotic production stopped with maximum fungi growth. By processes of charcoal adsorption, extraction, and concentration by dessication, a pure white crystalline powder was obtained.

Absorption

1. Intramuscularly. As in penicillin administration, this has proven to be the route of choice. It is rapidly absorbed and reaches its maximum concentration in the blood stream within thirty minutes but a reliable level can only be maintained for six hours. The average daily dose is one to three grams dissolved in sixteen ccs. of physiological saline and given in two-cc. doses every three hours. The results of streptomycin in beeswax and peanut-oil are inconclusive.

2. Intravenously. Here we get an initial blood concentration peak but a therapeutic level is not maintained. A larger dose gives a higher peak with a more prolonged blood concentration. The intravenous dose is recommended as two to three grams every six hours.

3. Orally. Streptomycin is not destroyed in the gastro-intestinal tract—neither is it absorbed. Assay shows it to be practically 100% recovered in the stools, hence one can readily see its potentialities in dealing with sensitive intestinal pathogens. It can be given, to accomplish its effect, in daily doses of four grams in orange juice.

4. Subcutaneously. Rapid absorption can be effected, yet the maximum blood concentration occurs only after forty-five minutes and persists but for a short time.

5. Intrathecally. Ordinarily no streptomycin appears in the cerebro-spinal fluid but it has been shown that one to five per cent of the blood concentration may be recovered here in meningeal irritation.
Intrathecal or intracisternal injections are effective in cases of meningitis, and the dose is 100 mgms. per day. The absorption is slow by this route and the concentration is still high after twenty-four hours. Conversely, there is no streptomycin in the blood stream after intrathecal administration, hence systemic therapy should be given concomitantly.

6. Inhalation. Streptomycin is only minimally absorbed by inhalation, with no evidence of the antibiotic in the blood stream. It may, however, prove useful in infections of the tracheo-bronchial tree.

7. Rectally. Absorption by this route is erratic and variable and is mentioned only to be condemned.

8. Topically. It has been stated that gram-negative bacteria always contaminate a chronic wound. Penicillin kills the gram-positive bacteria but is itself destroyed by penicillinase, which is produced by gram-negative organisms. Therefore the two antibiotics should be used in conjunction. By topical application, due to an osmotic effect, one can achieve a higher concentration in a wound than by parenteral administration.

**DIFFUSION**

Streptomycin diffuses well into most tissues if given by intravenous, intramuscular or subcutaneous methods.

1. Blood. Streptomycin is found wholly in the plasma and not in erythrocytes as is the case with penicillin.

2. Pleural Fluid. Pleural fluid concentration is lower than in blood, yet better sustained.

3. Peritoneal Fluid. Fifteen to thirty-three per cent of the blood concentration is found here.

4. Ocular Fluid. The secondary aqueous shows the higher concentration; this method of administration is by iontophoresis.

5. Bile. Bile recovered from the gall bladder contains only a quarter of the blood concentration. In cystic obstruction no streptomycin was recovered in this bile, indicating that parenteral administration would be ineffective in acute obstructive cholecystitis.

6. Cerebro-spinal Fluid. Neither intravenous nor intramuscular administration is effective in producing a detectable streptomycin level in the C.S.F. In meningitis some workers found a C.S.F. concentration equal to one to five per cent of the blood level. Hence intrathecal injection must be instituted for treatment of disease in the cerebrospinal system. Conversely, no streptomycin enters the blood stream after intrathecal injection. Therefore a combined I.M. and I.T. approach is advocated.
7. The Placenta. Streptomycin readily diffuses through the placenta and becomes available to the foetus. It is also recovered in the amniotic fluid. The concentration present in the umbilical cord blood is approximately half that found in the mother's blood.

**Excretion**

Studies have shown that the chief method of excretion is by the kidney—sixty to eighty per cent—and is solely a phenomenon of the glomeruli. In addition streptomycin is concentrated here.

The maximum excretory effect is accomplished in the first two hours following a single I.V. or I.M. administration, with an average of sixty-six per cent of the injected dose being eliminated. The renal clearance is thirty-eight to fifty-seven ccs. of plasma per minute. Renal damage acts as a dam so that high concentrations can be maintained in the blood for longer periods of time.

It has been demonstrated that streptomycin is excreted in bile, but only in the presence of a patent cystic duct. The liver excretes streptomycin yet does not concentrate it; hepatic bile streptomycin is only twenty-five per cent of that in the blood. An index of a normal liver is where a minimum of 1.5 units per cc. of hepatic bile is excreted within three hours after an initial dose of 100,000 units. The degree of hepatic damage seems to be proportional to the amount of antibiotic excreted.

In cystic duct obstruction no streptomycin is recovered in the bile, hence mechanical obstruction in jaundice has to be removed before antibiotics are effective.

Six per cent of streptomycin is recovered in the stools after systemic administration. After the oral route nearly one hundred per cent is found in the stools in an active form, showing that neither absorption nor destruction took place in its passage through the gastro-intestinal tract.

**Toxicity**

In the early phases of streptomycin administration many untoward toxic properties were exhibited. With the development of improved techniques in preparation, several initial impurities have been eliminated and with them many of the toxic signs.

Several of these toxic manifestations are listed:

1. Circulatory. These simulate a histamine reaction and show up as blood pressure drop, vasodilatation, flushing, headache and fainting.

In addition we see an increased gastric secretion and smooth muscle contractions, further suggesting histamine. Benadryl or histaminase
eliminates these effects, proving that streptomycin itself is not responsible.

2. **Renal.** The pathology is a glomerular and tubular degeneration of a fatty type, along with casts, albumen and hematuria. The degree is proportional to the acidity of the urine and is reversible, dependent on the cessation of the drug. Inhibition of water diuresis was also noted, with a reduced renal function and nitrogen retention as a late occurrence.

3. **Hepatic.** Fatty degeneration and focal necrosis were noted in experimental studies on monkeys with repeated streptomycin injections. The fatty metamorphosis was also reversible.

4. **Blood.** Mushell and Martland noticed only a transient normocytic anaemia, with no marrow changes, but other workers have noticed a leukopenia of 1,500 to 3,000 with a relative granulocytopenia.

5. **Local.** Such features as muscle necrosis and epidermal scaling at the site of administration, panphlebitis, pleural effusion and congestion, as well as intestinal haemorrhage, have been reported. Intrathecal administration has caused headache, vomiting, an increased number of cells, with pain over the sacrum and posterior thigh areas.

6. **Anaphylaxis.** This is shown as sustained high fever, itchy scaling dermatitis, oedema, joint pains, nausea and lymphadenitis for a period of one to three weeks. An eosinophilia of fifteen per cent occurred within four months of administration. It dropped back to normal after streptomycin cessation.

7. **Neurological.**

   (a) **Vestibular —** The signs are headache, vertigo, nystagmus, romberigsm, nausea and vomiting. They seem to be proportional to the size of the dose. Continuance of these signs results in the optic nerve assuming the gyroscopic function of the vestibular nerve. In this fashion the patient gradually is able to compensate.

   (b) **Auditory —** Deafness is preceded by a low roaring tinnitus and is generally prevented if streptomycin administration is discontinued. In experimental studies on dogs, microscopic studies of the vestibular and auditory nerves showed no pathological changes. It was suggested that the pathology might lie in the nerve endings.

There is no evidence of pathology in man and, with the exception of the neurological changes, all the other toxic manifestations can be explained on the basis of impurities. In due time the neurological signs may be attributed to contaminants and the active principle itself be exonerated.
THE PHARMACOLOGY OF STREPTOMYCIN

PROPERTIES OF STREPTOMYCIN

(a) Chemical. Streptomycin is a hydroscopic, optically active organic base, readily soluble in water and physiological saline but not in organic solvents. It is a white powder prepared as its hydrochloride and sulphate salts. Acidity decreases the action of streptomycin and it has been said that as far as the urinary tract is concerned that a Ph of 7.5 is optimum. If present in a concentration of 1,000 units in urine one may get a positive Benedict’s reaction.

In vitro NaCl, KCl, and Na₂SO₄ at a Ph 6.8, all decrease the action of streptomycin. This was not the case in vivo, as was shown by a culture in sheep’s blood and human urine. A high glucose concentration reduces its effectiveness. It is completely destroyed by potassium permanganate, potassium periodate, Vitamin C, and carbonyl.

Streptomycin is remarkably stable and will remain reliably potent as a powder at room temperature for one year. In solution it will be effective at a temperature of 28°F. (or less) and at a Ph 3-7 for sixty days.

(b) Antibacterial. The exact action of streptomycin is unknown but it is generally thought that low concentrations are bacteriostatic while high ones are bacteriocidal. Its effect depends on the sensitivity of the particular organism and their elimination before resistance is established. The development of resistance is a peculiar feature of streptomycin and is much greater than in penicillin. No morphological changes in bacteria, made artificially resistant, were noted, as opposed to changes induced by penicillin. There is a marked variation in bacterial sensitivity in different species and in different strains of the same species. Some bacteria may be sensitive, while others are quite resistant at the particular streptomycin concentration. As the streptomycin concentration goes up, the percentage resistance falls off. After knocking out the susceptible bacteria, the resultant residual resistant ones are present in relatively greater proportions; hence a much higher concentration of streptomycin is required to be effective. This weeding out helps explain the development of resistance to streptomycin. It was noted that oral administration in rats was more conducive to developing streptomycin-resistant organisms. Repeated culture of bacteria on sublethal concentrations helps to develop a resistance. In the body one needs a concentration four times that required in vitro. Bacterial sensitivity should be determined in order that an initial effective dose may be instituted.

Catheters, calculi, sequestra, infected sinuses and abscesses tend to protect bacteria and may promote the development of a resistance.

Streptomycin is highly effective against gram-negative and acid-fast bacteria as well as some gram-positive types. It is ineffective, however,
against some spores, gram-positive spore-forming anaerobic pathogens, fungi, viruses and protozoa.

No known enzyme or biological agent can destroy streptomycin.

**Bio-Assay**

Originally streptomycin was measured in units, one “S” unit being equal to the minimal amount of streptomycin in 1 cc. of media that would inhibit a growth of Eschericia Coli. Now a more uniform basis has been established and the dose is expressed as a weight of the pure base. The “S” unit is approximately equal to one micro-gram.

There are several ways of computing streptomycin strength but, like penicillin, the cylinder and paper disc methods seemed to have gained favour.

Weight for weight, streptomycin is less effective than penicillin. As yet, the disadvantage lies in the excessive cost and frequency of administration necessary to maintain an effective blood level.

**Summary**

1. The intramuscular route is the one of choice. Generally speaking, the daily dose is one to three grams in sixteen ccs. of saline, given in two-cc. doses every three hours. It must be remembered that, in the final analysis, the bacterial sensitivity determines the actual dose.

2. Intrathecal administration, along with the parenteral route, is imperative for treatment of diseases of the cerebro-spinal system.

3. The toxicity of streptomycin is negligible in the great majority of cases and should completely disappear when more improved methods of refining the extract are discovered.

4. Resistance is prone to develop, especially in subtherapeutic doses; therefore an adequate initial dose must be used.

5. Since the presence of foreign bodies and infected foci promote bacterial growth, these should be removed before streptomycin therapy in order to obviate the development of any resistance to the drug.

6. The oral route offers great potentialities in dealing with the intestinal pathogens, especially as a preoperative measure.

7. Its solubility in water and saline and its relatively good stability make it useful from a practical standpoint.

8. Topical application in open wounds in conjunction with penicillin promotes the action of the latter by preventing destruction by penicillinase.
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The Differential Diagnosis of Jaundice*

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SINCE 1847, when Virchow first demonstrated that some of the pigment crystals in old haemorrhagic areas were identical with bilirubin, suggesting the possibility of bile pigment being, in part at least, of extrahepatic origin, experimental work with bile pigment metabolism has been constantly in progress.

Jaundice is the term applied to clinical conditions in which the tissues, sclerae, skin and mucous membranes are stained yellow by bile pigment. It has been known for a long time that this occurs in a variety of conditions associated with certain diseases of the liver and biliary passages, and in certain types of anaemia. However, the accurate diagnosis of the pathological state responsible for the development of the jaundice in many cases has been very difficult, if not impossible.

Bile pigment is formed from haemoglobin in the cells of the reticuloendothelial system, which are found chiefly in the spleen and bone marrow, and to a lesser extent in the liver (as the Kupffer cells). The bilirubin so formed is carried in the blood to the liver, where it is taken up by the polygonal cells and excreted into the bile capillaries. Thence it passes through the bile ducts to reach the intestinal tract. Here, by the action of bacteria, it is converted into urobilinogen, some of which is excreted in the faeces, and the remainder reabsorbed and carried to the liver by the portal vein, to be again taken up by the polygonal cells and excreted.

By the use of Van den Bergh's test it has been found that the blood normally contains from 0.2 to 0.4 units of bilirubin—and that if from any disturbance in the body it increases to four units, the tissues are stained yellow. Thus jaundice develops as a result of an excess of bilirubin in the blood, or bilirubinaemia.

Bilirubinaemia may result from an obstruction of the bile ducts, as from a stone in the common bile duct; from damage to the polygonal cells of the liver interfering with the secretion of the bile, as in infectious hepatitis or in various types of poisoning, or from increased destruction of red blood corpuscles, resulting in an excess formation of bilirubin, as in congenital haemolytic icterus (acholuric jaundice).

If the common bile duct is obstructed, the bile is dammed up in the bile capillaries and is reabsorbed by the vascular capillaries and enters the central vein, so resulting in an excess of bilirubin in the general circulation, and its deposition in the tissues. The polygonal cells are

normal (at least for a time) and able to secrete bile, and the bilirubin formed by the reticulo-endothelial system is normal in amount. Such bilirubin which has passed through the polygonal cells gives a prompt direct action in the qualitative Van den Bergh test.

If the polygonal cells are damaged, due to poisons carried to them by the portal vein or hepatic artery, the secretion of bilirubin is interfered with. As a result, the quantity not secreted passes directly into the central vein, causing bilirubinaemia proportional to the severity of the damage. Although the same poison may damage the red blood corpuscles and cause increased formation of bile pigment, and even obstruction to the outflow of bile from pressure on the bile capillaries in the liver by the damaged polygonal cells, the primary and essential cause in this form of jaundice is damage to the polygonal cells themselves. In such cases, one may get a biphasic reaction in the Van den Bergh test, or at times, a prompt direct reaction.

When increased blood destruction occurs, as in the crises of acholuric jaundice, there is an excessive formation of bile pigment. More is carried to the polygonal cells than they can excrete, and it is carried directly to the central vein, resulting in bilirubinaemia. In this type of jaundice the polygonal cells are normal and there is no obstruction to the outflow of bile. In such case the Van den Bergh gives an indirect reaction.

Thus it is obvious that jaundice results from:
1. obstruction to the outflow of bile;
2. damage to the polygonal cells;
3. increased destruction of red blood cells.

In 1930, Rich proposed a classification based upon the pathogenesis of jaundice as above suggested. This divided jaundice into two types, namely:
1. retention jaundice, corresponding to haemolytic jaundice; and
2. regurgitation jaundice, which includes both the obstructive and toxic jaundice of McNee.

There is much to be said for such a classification; certainly no hard and fast line can be drawn between the jaundice produced by obstruction of the common bile duct and that due to necrosis of the polygonal cells.

On the other hand, the subdivision of jaundice into three groups, as proposed by McNee, is serviceable in clinical practice and has generally been accepted. His classification is:
1. obstructive hepatic jaundice;
2. toxic or infective hepatic jaundice;
3. haemolytic jaundice.
All clinical cases of jaundice can be classified under one or more of these three varieties.

The first object in the diagnosis of a case of jaundice should be to determine from the results of clinical examination the primary cause of the jaundice—obstruction to the outflow of bile, damage to the polygonal cells of the liver, or increased blood destruction. The second object is the elucidation of the clinical cause of the variety or varieties of jaundice present.

The clinical examination obviously must include an accurate and carefully taken history, a complete physical examination, and an examination of the urine and faeces for bile and urobilin, and of the blood for anaemia. One should elicit as accurate an account as possible of the patient's symptoms at the beginning of the jaundice and up to the time of observation, recording not only the sequence of their appearance, their duration and intensity, but the time relationship between their appearance and the development of jaundice. One should enquire carefully about the colour of the urine and stools. A change in the colour of the urine may be observed before clinical jaundice is manifest. The colour of the stools is very important. They may be clay-coloured from the beginning of the jaundice, as in obstruction of the common bile duct by gall stones; normal or darker in colour in haemolytic jaundice; or normal in colour at the onset, later becoming transiently lighter or clay-coloured, in toxic or infective hepatic jaundice—such as that due to the exceedingly common infectious hepatitis.

The presence or absence of pain is of great importance in differential diagnosis. Jaundice following colicky pain is nearly always due to intrinsic obstruction of the common bile duct, usually by a gall stone, occasionally by simple stricture, or carcinoma of the wall of the duct. In this connection, one should remember that stone in the common bile duct is not invariably associated with pain. Charcot's intermittent fever due to cholangitis may accompany the jaundice in such a condition.

In obstructive jaundice due to extrinsic causes, in toxic and infective jaundice, and in haemolytic jaundice, colicky pain is usually absent, but the patient may complain of aching or soreness in the right upper quadrant of the abdomen. Other symptoms present at the onset may suggest primary disease of the liver, or disease of other organs with secondary changes in the liver or bile ducts, or disease of the blood-forming organs.

A history of anorexia, weakness, general malaise, with or without fever, followed later by nausea and vomiting, is common with hepatic disease. While these symptoms occur in other conditions, their presence before, and persistence after, the onset of jaundice is very suggestive.
of intrahepatic rather than extrahepatic disease as the cause of the jaundice—i.e., a toxic or infective hepatic type of jaundice.

In the past history, one should enquire especially into the occurrence of previous attacks of jaundice, recurring infections, upper gastrointestinal tract disturbances, and any illness suggesting disease of the liver or blood-forming organs, and should try to discover if the onset of the present attack of jaundice is or is not related to a former illness.

In the physical examination of the patient, one should pay special attention to the examination of the liver and spleen for local signs of disease, and to other regions of the body for primary disturbances, such as cardiac failure, pregnancy, etc., that might affect the liver secondarily and give rise to jaundice. In the examination of the liver, its size, and the presence or absence of tenderness, are the two points of greatest value in diagnosis. Irregularities on the surface of the liver indicate intrahepatic disease as the cause of the jaundice, but unfortunately only the gross, and not the finer irregularities more commonly present, can be determined with any degree of assurance on physical examination. Definite enlargement or the presence of local or general tenderness of the liver points to intrahepatic disease as the cause of the jaundice. Secondary cancerous deposits in the liver may cause marked enlargement, but if jaundice is present it is more often due to pressure on the common bile duct from metastases in glands, than from the lesions in the liver. The liver may be smaller than normal, as in portal cirrhosis, or in acute or subacute necrosis of the liver.

The spleen is often enlarged in liver disease and in haemolytic jaundice. Hence, one should examine this region of the abdomen very carefully to determine whether the spleen is palpable or not. Definite splenomegaly with little or no enlargement of the liver suggests that the primary cause of the jaundice is splenic or extrahepatic in origin. In the haemolytic type of jaundice, the spleen is usually palpable but rarely very large—the liver is normal in size and not tender. In biliary cirrhosis, both liver and spleen are markedly enlarged, tenderness is slight or absent, and the jaundice is persistent, and becomes more intense as the disease progresses. In portal cirrhosis, the spleen is just palpable, the liver moderately enlarged, normal, or smaller than normal in size.

If the history is suggestive of disease in regions of the body other than the liver or spleen, which may secondarily affect the liver and cause jaundice, special care should be given to the physical examination of the region affected. Valuable information is often forthcoming from the examination of the stools, urine and blood. A sample of faeces should be inspected and tested for bile pigment and the urine tested for bile pigment and urobilin. With complete obstruction of the common bile duct, the urine contains bile, rarely urobilin. When the jaundice is due
to neoplasm it is complete in ninety percent of cases; it seldom improves, and the amount of faecal urobilinogen is usually less than five mg. per day; examination of the urine reveals no urobilinogen, or traces only. When jaundice is due to stone(s) in the common bile duct, it is rarely associated with complete obstruction, and seldom shows persistent values of faecal urobilinogen below five mg. Further, the jaundice characteristically varies in intensity. Urinary urobilinogen may be absent or slightly increased except when complicating factors such as acute cholecystitis, cholangitis or cirrhosis are present. Then it may be found in increased amounts.

In toxic and infective hepatitis the urine commonly contains bile and urobilin. A phase characterized by acholic stools and lack of urinary urobilinogen and little or no faecal urobilinogen, showing the picture of complete biliary obstruction, is not uncommon, especially in toxic hepatitis. In infectious hepatitis it usually lasts but a few days and seldom longer than a fortnight, but it may last over several weeks in subacute necrosis of the liver. Watson has pointed out that in cases such as this the grossly acholic stools may still contain from ten to fifteen mg. of urobilinogen per day, and a 24-hour urinary specimen giving a negative qualitative Erhlich's test may contain as much as fifteen mg.

Repeated tests for urobilinogen and bilirubin on the urine follow a characteristic course in cases of parenchymatous jaundice with intrahepatic obstruction. The urobilinogen of the urine at first increases, then as the secretion of bile decreases it diminishes or disappears from the urine, but rises again for several days during recovery, as the flow of the bile returns, and then eventually falls to normal values; the bilirubin values are highest during the obstructive phase.

Thus, while absence of urobilinogen from the urine occurs in partial obstruction due to calculus in the common bile-duct and also in intrahepatic jaundice, though in the latter seldom for more than four to seven consecutive days, the presence of urobilinogen in the urine is very good evidence against biliary obstruction due to new growth.

In haemolytic jaundice, the urine contains urobilin or its precursor (urobilinogen) and no bile. The urinary urobilinogen is, as a rule, only slightly raised, but the faecal urobilinogen is enormously increased. If a haemolytic type of jaundice is suspected, the fragility of the red cells should be determined, and reticulocytosis and spherocytosis looked for in the blood smear.

The Van den Bergh test gives a strongly positive indirect reaction in uncomplicated cases of haemolytic jaundice. In obstructive hepatic jaundice, the result is a prompt direct reaction. At the onset of toxic
or infective hepatic jaundice a biphasic reaction commonly is present, but later a direct reaction occurs in nearly all cases, which makes the test of little value in the differential diagnosis between obstructive and toxic hepatic jaundice. The presence of a prompt direct reaction, therefore, is no indication for operative interference, unless other clinical findings indicate that the obstruction is in the extrahepatic biliary system.

As a general rule, liver function tests are more valuable in assessing the degree of hepatic damage and in following the patient's progress than in elucidating the cause of the jaundice. This is because of the complicated pathological changes found in the liver in many cases of icterus. Extrahepatic biliary obstruction resulting in jaundice is frequently followed by some degree of intrahepatic damage. Likewise, primary intrahepatic disease accompanied by jaundice commonly causes damage or obstruction to the biliary channels within the liver. This may be sufficient to result in suppression of the secretion of bile. It is this intrahepatic obstruction, occurring as a phase of hepatitis, which causes real difficulty in differential diagnosis. The clinical history, findings on physical examination, the course the illness has followed, together with appropriate laboratory data, obtained on repeated occasions, will usually solve the problem.

It is of paramount importance to differentiate between "medical" (intrahepatic) jaundice in the obstructive phase and "surgical" (extrahepatic) obstructive jaundice. To operate upon a case of "medical" jaundice is to invite an attendant mortality of from 35 to nearly 100 per cent, depending upon the underlying pathological state. Similarly, failure to operate upon a patient with painless jaundice due to a stone in the common bile duct is likely to result in tragedy. It is rare that a patient with jaundice presents a surgical emergency. Careful study and observation over a period of time, with serially repeated laboratory tests, will amply repay the clinician and usually lead to the correct diagnosis. Even if the jaundice has been present for a considerable period of time and associated with prolonged acholia, whether due to intrahepatic or extrahepatic biliary obstruction, the liver usually continues to function moderately well, or regains its function when the hepatic inflammation has subsided.

Generally the cause of jaundice can be determined from the history and clinical findings, along with simple qualitative urine tests for urobilin, its precursor urobilinogen, and bilirubin.

Other tests of value in the differential diagnosis of jaundice are:

1. the quantitative urobilinogen estimation on the faeces, to which certain references have already been made. Davidson, at the 6th Alumni Lectureship, described a simple test devised by Watson,
that gives a rough estimate of the amount of bile pigment present. A sample of stool is emulsified in a test tube using a saturated alcoholic solution of Zinc Acetate and examined in the dark for green fluorescence (as by shining a flashlight on it). The finding of a green fluorescent colour indicates the presence of urobilin in the faeces, and the intensity of the colour gives a rough indication of the amount of urobilin present. The test tube is then examined in the light after the addition of Ehrlich's reagent. The development of a red colour reveals the presence of urobilinogen in the sample tested. As previously pointed out, urobilinogen and urobilin are absent or nearly absent in extrahepatic obstructive jaundice and usually present in considerable amount in intrahepatic jaundice.

(2) the Van den Bergh, the limitations of which have already been discussed.

(3) the Harrison Spot Test — which is simple, sensitive, and gives a rough quantitative determination of bilirubin.

(4) the colloidal gold reaction, which is a sensitive indicator of active hepatic disease, and is consistently negative in jaundice due to extrahepatic obstruction, and positive in intrahepatic disease in a high proportion of cases.

(5) the serum alkaline phosphatase — this rises more markedly in jaundice due to extrahepatic obstruction than in parenchymatous jaundice.

Three particular combinations of (4) and (5) have diagnostic significance:

(A) A negative gold reaction with a phosphatase value above 35 King Armstrong units suggests biliary obstruction.

(B) A positive gold reaction with a phosphatase of less than 25 suggests parenchymatous hepatic disease and absence of biliary obstruction.

(C) A strongly positive gold reaction (4 or 5) has not been encountered in obstructive jaundice and appears to be diagnostic of intrahepatic disease at any phosphatase level.

(6) the thymol turbidity test which gives results very similar to the colloidal gold reaction and is probably dependent on an increase in serum gamma globulin and is related chemically to the Pandy and cephalin-cholesterol tests. The test is fairly simple to perform and has a high degree of sensitivity.

(7) the cephalin-cholesterol flocculation test of Hanger — is a very sensitive index of the activity of liver damage, but its differential diagnostic value in jaundice is lessened by the fact that it cannot
distinguish between the obstructive phase of intrahepatic jaundice and parenchymal damage secondary to extrahepatic biliary obstruction.

(8) the galactose tests — oral or intravenous methods — positive in about 70% of cases of intrahepatic jaundice, and negative in about 80% of obstructive jaundice, if done within a fortnight of the onset of jaundice, as later on parenchymatous changes may occur in extrahepatic obstructive jaundice.

(9) the plasma prothrombin level — a low prothrombin level in the patient with jaundice may be due to hepatic damage and/or poor absorption of vitamin K as a result of biliary obstruction, and the response to administration of vitamin K may give some measure of the degree of hepatic damage, and also aid in the differential diagnosis between jaundice due to extrahepatic obstruction and parenchymal liver disease. A rapid response to vitamin K indicates the absence of severe hepatic damage and suggests that the hypoprothrombinaemia is due largely to poor absorption of vitamin K as a result of the biliary obstruction. A failure to respond to vitamin K, as is frequently seen in hepatitis and cirrhosis, indicates parenchymal damage, either primary or secondary to the biliary obstruction.

In conclusion, in the differential diagnosis of jaundice isolated laboratory findings are of little value and usually not conclusive without clinical data. A careful history and physical examination, coupled with a period of observation during which simple tests are serially repeated, will usually lead to the correct diagnosis.

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Endocrine Control in Surgical Conditions of the Breast

By MARGARET MACLACHLAN, '48

In the past decade, it has been demonstrated that the growth and development of the breast is largely dependent upon the ovarian hormones — oestrogen which mediates the development of the mammary ducts, and pro-gesterone which mediates the development of the lobular alveoli. It was once thought that the influence of these hormones was a direct one, but later investigation revealed the importance of the pituitary in breast development. Now, it appears that the pituitary liberates two hormones — one, under the influence of oestrogen, stimulates mammary duct growth, and the other, under the influence of progesterone, stimulates lobule proliferation. Any alteration in this delicate imbalance may result in abnormal changes in the tissues on which they act. The adrenals, too, are thought to exert some influence on breast development, since pathological adrenal tissue is known to produce oestrogens, as dramatically demonstrated by feminizing adrenocortical tumors in males. Also oestrogens are present in the urine long after menopause, and even after surgical castration. However, these extra-ovarian oestrogens do not produce mammary or genital changes in pre-adolescent or post-menopausal women; so that their practical importance may be questioned. Androgens, the male sex hormones, are capable of producing so-called "medical" castration, and claims have been made that they may have an actually neutralizing or antagonistic effect on oestrogens.

Naturally, from this would arise the question of the effect of these hormones on tumours of mammary tissue. If endocrine glands are responsible for normal development of the breast, might they not contribute materially to its abnormal growth, also? Extensive experimentation seems to indicate that they do. Ovarian hormones, in particular, seem to influence breast tumours, both malignant and benign. Abnormal mammary proliferation was found to be the end-result of an intricate prolonged interaction and combination of at least several factors or complexes of factors. A degree of genetic susceptibility, and a degree of hormonal stimulation are considered essential and the process could be modified by numerous secondary influences of internal and external environment.

Further support of this line of reasoning lay in several clinical facts which had long been familiar to the medical profession. One was the occurrence of fibroadenoma soon after puberty when the active period of ovarian function begins. Another was the rapid development
and growth of breast cancer during pregnancy, when ovarian activity was markedly increased. Also the outlook for cure of carcinoma of the breast is much more discouraging in young women than in those in the postmenopausal period, since in the premenopausal period mammary cancer is extremely fatal.

Fear that chronic cystic mastitis is precancerous has led to much needless surgery since the possibility of such malignant change is very minor. However, a biopsy should be done and excision of large solitary cysts may be necessary. It has been demonstrated that a relative or absolute hyper-oestrogenism is present in chronic cystic mastitis. With occurrence of pregnancy and its persisting corpus luteal and later placental progesterone, chronic cystic mastitis usually disappears or markedly regresses. Similarly, with the onset of the menopause with its decreased oestrogenic activity, improvement of the mammary dysplasia ensues. In the latter instance, as illustrated by several cases, the administration of oestrogens to control climacteric symptoms, is sometimes accompanied by a recurrence of mastodynia or adenosis. In studies of sterility in women it was found that there was a high incidence of chronic cystic mastitis in these cases and endometrial biopsy revealed considerable oestrogenic but no or poor luteal stimulation. Thus it was concluded that chronic cystic mastitis depends on the same hormonal imbalance that is responsible for the non-secretory or poorly-secretory endometrium, in these infertile women. In an attempt to increase the corpus luteum and thus balance the oestrin-progesterone relationship, chorionic gonadotropin was administered for the mid-interval two weeks of the menstrual period. This produced improvement in the chronic cystic mastitis as well as producing mature secretory endometrium. One-third of the patients subsequently became pregnant.

Since ultimate results from treatment of cancer of the breast in young women were extremely disappointing, Horsley adopted the procedure of removing both ovaries whenever a radical operation was done for mammary cancer in women in the premenopausal period. This method has been suggested by Schinzinger in 1899. At approximately the same time as Horsley’s work was being done, Huggins and his co-workers had established, in their clinical and experimental work on cancer of the prostate, a definite relationship with male sex hormone. Whatever may be the explanation of the benefits of orchiectomy on cancer of the prostate, it would seem that an analogy might apply to bilateral oophorectomy in the case of tumour of the mammary gland. Numerous investigators have reported excellent results by roentgenologic or surgical castration in patients with extensive mammary carcinoma in both the pre- and post-menopausal periods. Definite regression of osseous metastases from cancer of the breast have followed X-ray sterilization. With regression of these metastases, there was also
marked relief from pain. In one series results obtained by radical 
amputation of the breast with bilateral oophorectomy in premenopausal 
cases showed 76.9% of cases living without recurrence in both 3 and 
5 year postoperative periods. Others report that ablation or suppres­
sion of ovarian function, especially in the pre-menopausal period, 
does produce regression of breast cancer but after a longer or shorter 
period of latency the growth of the cancer continued. Whether this is 
due to the properties of the neoplasm itself or to endocrine influences 
is not clear. The recurrences of mammary cancer after radical opera­
tion are doubtless due to cancer cells that have been left behind. The 
small amount that remains, however, would be stimulated by oestro­
genic substances. The effect of withdrawing oestrogenic stimuli might 
be greater if there are only a few malignant cells, than if there are 
many. Withdrawal of the stimulating effects of oestrin should be 
deletious and create an unfavourable soil for their existence. Surgical 
is preferable to roengenologic castration since even heavy doses of 
radiation may fail to produce permanent cessation of ovarian function.

The administration of androgenic hormones to produce medical 
castration of the female suffering from carcinoma of the breast has 
been given very little clinical trial. Androgens should be given with 
caution in the presence of neoplastic disease since they differ markedly 
from oestrogens in their growth-stimulating properties, and are capable 
of replacing the stimulative effect of oestrogens upon ductual growth 
in the mammary gland. The advantages of suppressing ovarian activity 
must be weighed against the possibility of stimulating the cancerous 
growth. Some striking instances of regression of metastases have been 
observed. Individual cases have shown a reduction of size of breast 
tumour itself. Bone metastases are very common and are osteolytic 
chiefly. Thus if they are observed to become sclerosed or calcified, the 
treatment may be considered as the cause of the change. By repeated 
X-rays, the benefits of therapy may be assessed. So far, testosterone 
propionate has produced no striking results when used alone and has 
been even found to accelerate metastatic growth, causing increased 
bone destruction and hypercalcaemia. Even small doses of testosterone 
propionate produce masculinization effects, such as huskiness and 
hirsutism. It may best be used in conjunction with castration, in 
which case it has been reported to have reduced skeletal metastases, 
relieved pain, and given the patient several months of fairly normal 
activity.

Gynaecomastia, an abnormal enlargement of the male breast, has 
been found in association with chorioncarcinoma of the testis. Opinion 
is not yet finally settled as to the hormonal origin of these changes, 
since not all cases of chorioncarcinoma of testis show it. Once again, 
it appears that oestrogen and progesterone which are produced by the
tumour and which act via the pituitary, are responsible. Examination of the breast tissue in these cases shows that enlargement is not due to metastases from the testicular tumour but to actual proliferation of mammary ducts and acini.

Thus it appears that the physiology of the breast and the factors which control its growth still need clarification. Androgenic substances have bisexual endocrine potentialities and should be used with caution. Surgical and irradiation castration have a limited usefulness in palliative treatment of cancer of the breast. The combination of radical mastectomy, bilateral oophorectomy, and testosterone administration may be of some value.

PERSONALITY AND ITS DEVIATIONS

By

GEORGE H. STEVENSON AND LEOLA E. NEAL


In writing this book, the authors realized that there was no one volume available discussing this subject. They have collected the information necessary to give readers a co-ordinated knowledge of medical psychology. At no time have the authors side-tracked the reader into one school of thought. The book is written to give a general knowledge of psychological principles, mentioning each discovery as it is deemed valuable. Stress is placed upon the interdependence of the physical and mental components of the individual.

Roughly, the book may be divided into two parts, the first dealing with the normal and the second with the psychopathic personality. The first section depicts the individual struggling with his environment, changing it and being changed in his development, becoming a normal adult or being too frail and falling prey to neuroses or psychoses. The second part is concerned with the psychopathic personality, the conduct of such an individual and the general principles of treatment. Two chapters on intelligence and personality tests have been written by Dr. Leola Neal.

At the present time, the knowledge of psychiatry is becoming as important as the knowledge of physical defects. Unfortunately, also at the present time we find that there is an appalling ignorance of this subject among students and graduates. The diagnosis of personality deterioration is too often unnoticed until it is too late. With this text book, one will be better able to recognize the signs of mental disease and have a fundamental knowledge of medical psychology.

I recommend that every medical student and practitioner secure this book as the time required for reading will not go unrewarded.

—JOHN C. RAWLING, '49.
BOOK REVIEWS

BIOCHEMISTRY OF CANCER
By JESSE P. GRUNDESTEIN


As the title suggests, this work is highly technical and no more than a superficial reading should be attempted by other than one familiar with the field of biochemistry. The author writes with good authority on the subject pursued, being the Head Biochemist and Chairman of the Section on Biochemistry of the National Cancer Institute.

The book is introduced with two chapters which are readily understood by the average medical reader. They afford an excellent review of tumours plus an outline of the present status of cancer research and the outstanding work which has been done in that field.

In the second section the author launches into the technicalities of tumour induction. Carcinogenic hydrocarbons and other pertinent extrinsic factors are considered in detail. In addition, the intrinsic factors (sex hormones, milk factor, virus) are as thoroughly considered. The third division deals with the control of tumour induction and tumour growth. Nutrition, endocrinology and chemotherapy are discussed at length. In the final section the author describes the biochemical properties of tumours, elaborating upon normal tissue, neoplastic tissue and the biochemistry of the tumour host. Charts, graphs, tables and microphotographs are here especially utilized as they are to a lesser degree in the preceding parts.

It is difficult for anyone other than a biochemist to assess this book. However, the abundant data and extensive reference lists contained within it impress one as being of vital interest to anyone interested in cancer research.

—J. E. MULLENS.

HENRICI'S MOULDS, YEASTS, AND ACTINOMYCETES
By SKINNER, EMMONS AND TSUCHIA

JOHN WILEY & SONS, NEW YORK; AND CHAPMAN & HALL, LONDON.

This book, originally published in 1930 by Henrici, has been revised and brought up to date by the new authors in 1947. It is intended to fill the gap between the brief and meagre discussions found in the standard text books of bacteriology and the exhausting articles that have been written about one group of organisms.
In each section there are chapters on the structure, growth, classification, cultural and other laboratory characteristics as well as a section on their pathogenicity and a brief consideration of the more salient features of their clinical picture. At the end there is a brief discussion of penicillin and streptomycin and a few similar antibiotics and their laboratory features.

The book should appeal to students especially, helping them to appreciate better, infections caused by moulds, yeasts and actinomycetes.

—R. N. BISSONNETTE, ’49.
RECENT ACCESSIONS TO THE MEDICAL SCHOOL LIBRARY

Adler: Problems of neurosis. 1930.
Barr: The structure of the brain and spinal cord in man; parts 1 and 2. 1947.
Beaumont and Dodds: Recent advances in medicine; 12th ed. 1947.
Bernard: Introduction à l'étude de la médecine expérimentale . . . part 1, 1946.
Braun-Mendenez: Renal hypertension. 1946.
Cameron: Recent advances in endocrinology; 6th ed. 1947.
Chester: Shot full. 1938.
Committee on Hospital Care: Hospital care in the U.S. 1947.
Curtis: Harvey's views on the use of the circulation of the blood. 1915.
Dingman: Risk appraisal. 1946.
Fabian: Laboratory manual of physiological bacteriology. 1945.
Fracastoro: Hieronymus Fracastor's syphilis; a translation in prose. 1911.
Freud: The future of an illusion. 1929.
Gray: Gray's anatomy, descriptive and applied; 29th ed. 1946.
Gross: Acetanilid. 1946.
Heagy: The relation of magnesium to body temperature. 1947. (M.Sc. Thesis.)
Hecht: Explaining the atom. 1947.
Jason: The thyroid gland in medical history. 1946.
Kalinowsky and Hoch: Shock treatments and other somatic procedures in psychiatry, 1946.
Lull and Hingson: Control of pain in childbirth; 2nd ed. 1945.
Major: Disease and destiny. 1936.
Morton: A histophysiological study of the effect of intra-arterial infection of acetylcholine upon the gastric mucosa of the dog. 1947. (M.Sc. Thesis.)
Naumburg: Studies of the “free” art expression of behaviour problem children and adolescents as a means of diagnosis and therapy. 1947. (Monograph Nerv. & Ment. Dis. #71.)


Pitkin: Conduction anaesthesia. 1946.

Ramon y Cajal: Recollections of my life. 2 vol. 1937.


Robinson: The patient as a person. 1946.

Ruckmick: The psychology of feeling and emotion. 1936.

Scott and Van Wyck: Essentials of obstetrics and gynecology. 1946.

Shakow: The nature of deterioration in schizophrenic conditions. 1946. (Monograph Nerv. & Ment. Dis. #70.)

Sheldon: Diseases of infancy and childhood; 5th ed. 1946.


Stevenson: Sir Frederick Banting; 2nd ed. 1947.


Sulzberger and Bae: Office immunology. 1947.

Top: Communicable diseases; 2nd ed. 1947.


Watson: The life of Sir Frederick Jones. 1934.


White and Geschickter: Diagnosis in daily practice. 1947.


Continuations
Anesthesia abstracts. v. 23. 1947.
Report of the Canadian tuberculosis association. v. 46. 1946.
Studies from the Connaught laboratories, Toronto. v. 18, 1946. 1947.
Studies of the Rockefeller Institute for medical research. v. 133. 1947
Transactions of the American neurological association. 1946.
Yearbook of endocrinology, metabolism and nutrition. 1946.

New Subscriptions
Acta chemica scandinavica.
November 12, 1947.
THE ROLE OF THE AMINO ACIDS IN MEDICINE

By J. M. Beveridge, Ph.D.

Proteins are broken down to their constituent amino acids in the gastrointestinal tract and after absorption are resynthesized into body protein. Because there is no storage mechanism for protein or amino acids, as there is for carbohydrate or fat, there must be a daily intake to prevent deficiency. A deficiency has been shown to cause a decrease in antibodies, disruption of abdominal wounds and delayed healing. In the human, there are a number of pathological conditions which prevent the ingestion, digestion or absorption of protein. In these patients, protein digests prepared by acid or enzymatic hydrolysis were found to restore nitrogen balance, antibody titre and blood protein. The digest must be prepared from a source which will give all of the essential amino acids or, failing this, the essential ones must be added.

Experimental work with both animals and humans has revealed that a lack of any one of the essential amino acids leads to a specific metabolic abnormality. A deficiency of methionine and choline will cause the development of a fatty liver and if the deficiency is prolonged will lead to portal cirrhosis. In this instance, choline is the essential factor as methionine is important only in its ability to form choline by transmethylation. A deficiency of methionine and cystine will lower the ability of the liver to withstand the effects of toxic substances such as chloroform or arsphenamine and if the deficiency is continued will eventually lead to necrosis.

—Jack Wickett, '49.

HEMATOPOIESIS

By Dr. M. Barr

The seat of adult hematopoiesis is the red bone marrow comparable in volume to that of the liver. For satisfactory function it needs (a) all the usual constituents of cytoplasm, (b) minerals, chiefly iron, (c) the erythrocyte maturing factor of Castle. One billion erythrocytes are normally liberated into the blood stream per minute and broken down about 100 days later by the reticulo-endothelial system. The cells of the reticular connective tissue of red bone marrow resemble those of the non-specialized embryonic mesenchyme. They probably develop into blood cells extravascularly and enter the marrow sinusoids which are lined by phagocytic cells later. The earliest stage, the hemocytoblast and the same for both red and white cells, has intensely basophilic cytoplasm and a large nucleus. The prospective erythrocyte can soon be recognized by acquiring a trace of hemoglobin. With numerous mitoses taking place, successive generations gradually
lose their basophilia, acquire more hemoglobin and the nucleus becomes smaller. When, after the last mitosis, the cell has acquired the maximum amount of hemoglobin, the now dense and pyknotic nucleus is fragmented and extruded. The almost mature erythrocytes, because they contain a coarse cytoplasmic network, are called reticulocytes. They constitute one percent of the normal red count.

—P. SchneUer, '49.

HUMAN ALBUMIN THERAPY
By DR. DAVIDSON

The small molecules of albumin exert most of the osmotic pressure effect in the circulating blood. The larger globulin molecules have other purposes and uses, e.g. some part in antibody production.

When the Second World War was over the American Red Cross fractionated their large reserve stocks of human plasma to obtain the desired globulins. This left quantities of human albumin available for experimentation. It was packaged in 25% in 100-ec. bottles and released to certain groups.

The Boston researchers performed analyses and tried some laboratory and clinical studies. They found:

1. Intravenous injection of albumin does not give homologous serum reaction.
2. Albumin is deficient in glycine and tryptophane.
3. It is slowly excreted by healthy kidneys. Hence it gives an increase in total serum albumin and a positive nitrogen balance obtained.

Its chief uses are:

1. In liver disease, especially acute hepatitis.
2. Severe burns.
3. Pre-operatively in surgery.
4. “Nephrotic syndrome” where the liver fails to replace albumin as fast as the kidneys excrete it.

In all cases the chief value is in increasing the osmotic pressure of the blood.

The present cost of $10.00 to $12.00 per gram is absolutely prohibitive for general use.

—R. Whitman, '48

CARDIOVASCULAR SIGNS AND SYMPTOMS IN ANAEMIA
By G. R. Manning

Although cardiac signs and symptoms are frequent in anemias and may stimulate heart disease with failure, congestive failure seems to be uncommon. The following are present:

1. Dyspnoea is never present at rest, as often occurs in organic disease.
2. Palpitation as a result of increased rate and contraction.
3. Cardiac pain has the characteristics of angina except that it does not radiate to arms or neck and is seldom the presenting symptom. Generally, in any woman under forty without hypertension and complaining of cardiac pain, the cause may be unrecognized anemia.

Physical Signs

Moderate tachycardia, collapsing pulse and resting blood pressure below normal are common. A hypertension may be temporarily hidden by an anemia and cardiac enlargement may have been due to a previous hypertension. The severity of cardiac signs and symptoms depend also on effects of hypertension and arteriosclerosis.

The third heart sound is significant regarding the state of heart in anemia in patients over thirty years of age. Murmurs are common, usually mid-systolic with never any thrill, and are loudest in mitral area. They are caused by lowered blood viscosity.

Electrocardiographic changes include flattening or inversion of T waves, depression of S-T segment and tendency to low-voltage Q.R.S.
Circulatory adjustments include rapid circulation time, arterial vasodilatation, decreased blood volume, increased right auricular pressure, increased cardiac output and increase in percentage of utilization of arterial oxygen. Normally, the cardiac output increases with increase in right auricular pressure but, in anemia, cardiac output decreases. An increase in blood pressure coincident with falling cardiac output means increased peripheral resistance due probably to vasoconstriction. Experimentally, as R.A.P. increase, peripheral vasoconstriction occurs reflexly, resulting in high blood pressure causing mechanical blockage at left ventricle with acute pulmonary edema. Rapid transfusion may thus overload the anemic heart following the preceding pattern.

—ROBERT HUGHES, '48.

HYPOPROTEINEMIA

By Dr. R. J. ROSSITER

Dr. Rossiter first briefly outlined the possible causes of hypoproteinemiam as being due to:

1. Faulty formation:
   (a) malnutrition,
   (b) liver disease.

2. Loss of protein from the blood:
   (a) nephrotic syndrome,
   (b) burns,
   (c) haemorrhage.

3. Hydraemia.

4. Experimental methods such as plasmapharesis.

The author described a survey of chronically starved Indian soldiers immediately after their liberation from Japanese war prisons and the clinical and biological changes during their recovery. These patients exhibited many symptoms attributable to chronic starvation and avitaminoses but Dr. Rossiter dealt mainly with the oedema and other symptoms ascribable to the low plasma protein levels characteristically found.

When the normal colloid osmotic pressure of the blood, which is controlled by the plasma proteins, falls below a critical level, the resultant shift in the equilibrium between the tissue fluids and the circulating blood results in oedema.

It has long been known that albumin has a greater influence on the osmotic pressure than has globulin. The author has shown that in hypoproteinemiam of malnutrition it is not the total plasma protein but the absolute value of the albumin concentration that determines the onset of oedema, the critical value being about two grams per 100 mils of plasma. The plasma proteins were restored to normal values by the feeding of high protein, high caloric diets, and the clinical condition of the patients improved with the restored biochemical equilibrium. Throughout this study the total circulating blood volume was determined and the plasma concentrations were weighted with this information so as to be able to follow changes irrespective of shifting in fluid equilibrium.

—N. HELLER, '49.

STUDIES IN GASTRIC SECRETION

By Dr. G. W. STAVRAKY

In this paper, Dr. Stavraky showed how the physiology of the gastric secretion is related indirectly to pernicious anaemia. The stomach is really at fault in that it fails to produce the intrinsic factor. Yet, subtotal gastrectomy and vagotomy conspicuously do not result in pernicious anaemia.

The gastric secretion is produced under nervous and chemical stimuli. Impulses travel down the vagi as a result of reflex stimulation and at their terminations in the stomach liberate acetyl choline. However, the author has found that acetyl choline alone will produce no sustained secretion from the stomach but, when small amounts of histamine are added, normal gastric juice is obtained. These findings were used by Babkin for his theory of the action of the vagi in gastric secretion. At the same time he found that only when acetylcholine was injected also
Into the arteries supplying the pyloric part of the stomach was a sustained secretion produced. Enzymes sharply disappeared when the secretion turned from acid to alkaline.

Uvnas, a Scandinavian, confirmed these findings when he found that, with the pylorus removed, stimulation of the vagi had only a slight effect on the secretion but, with the pylorus present, stimulation of the vagi caused sustained secretion.

It seems, therefore, that a pyloric hormone is necessary in the circulating blood in order to have gastric secretion. Achlorhydria, with lack of the intrinsic factor, can be tentatively explained on the postulate that the intrinsic factor is an enzyme, possibly liberated at the same time as pepsin from the peptic cells, which is carried from the glands by the hydrochloric acid, simultaneously liberated by the parietal cells. Hence, traces of hydrochloric acid will perhaps make available small quantities of intrinsic factor which is necessary to prevent pernicious anaemia, provided other factors are normal.

—DON HITCH, '49.

GLYCOGEN STORAGE DISEASE
(VON GIERKE'S DISEASE)
By Dr. F. W. LUNEN

This relatively uncommon disease was first recorded by von Gierke in 1929. It is a congenital disturbance affecting infants and young children of both sexes.

Two closely related types have been described and both are characterized by an hypoglycaemia. In the first, hepato-megaly due to excessive glycogen storage is the chief pathological finding. The liver is markedly swollen and, on sectioning, a picture resembling fatty infiltration is seen. It is believed that there is a block in the conversion of liver glycogen to blood glucose. Cardiomegaly it is the prime feature of the second type. The myocardium is a virtual storehouse of glycogen; the muscle is pale. The glycogenolytic enzyme involved in the breakdown of muscle glycogen is probably disturbed in some way.

Cardiomegalics rarely live more than one year. The history usually begins with an acute infection and, indeed, many cases may go unrecognized as von Gierke's disease for this reason. Cardiac dyspnoea results in X-ray films suggestive of pneumonia or atelectasis. Cyanosis and a low fever are commonly present. Laboratory tests reveal the characteristic hypoglycaemia and secondary anaemia. In hepatomegalics, the liver is palpably enlarged in fifty percent of cases at birth. Low fever and gastric and nervous disturbances are the first symptoms. A poor feeding regime has often been recorded. Laboratory tests are confirmatory; most patients die of an acute infection within two or three years. Cardiac decompensation is the fatal factor in uncomplicated cases of both types.

There is no specific treatment for glycogen storage disease. Curiously, administration of adrenalin will not cause increase of the blood sugar level.

—DOUG. THOMPSON.

MOTION SICKNESS
By Dr. R. L. NOBLE

In 1942 the speaker determined the sensitivity of dogs to motion sickness by swinging them through ninety degrees. Of seventy dogs used, fifty-seven were made to vomit in forty-five minutes. The relative susceptibility of the dogs was determined by varying the angle of swing.

To analyze the effect of the components of the swinging motion, these were separately tested. The horizontal component was shown to be most effective in producing vomiting, while the vertical component was relatively ineffective, and the angular motion had no effect at all. No single component was as effective as the entire swing.

Later, to show that "swing sickness" was parallel to air or sea sickness,
sixteen dogs were put into a small boat on a rough lake. Ten of these vomited in forty-five minutes and many became very depressed, even trying to jump out of the boat. Four of them became carsick.

Of many barbiturates tested, the most satisfactory for prevention of motion sickness was christened V-12. This drug was found to give few side effects and almost complete protection in dogs. The most effective barbiturates were found to be “thio” compounds with unsaturated side chains—especially with substituted methyl groups.

Human trials were done, using 369 students at McGill University. Two hundred and nine of these (69.6%) were made to vomit within thirty minutes. On their first test all subjects were given placebos (these gave ten to twelve percent protection). Five grains of V-12 (in two doses) gave sixty-five percent protection, in contrast to sodium amytal, which afforded only six percent protection. A mixture of Hyoscine Hydrobromide and V-12 gave seventy percent protection.

In sea trials with the latter mixture, seventy-five percent of people were protected. Placebos gave only twenty to twenty-five percent protection.

—S. ROSEN, '48.
Amphojel is admirably suited to the management of peptic ulcer because it:
- precipitates pepsin
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